Aedes mosquitoes in the emerging threat of urban yellow fever transmission

Gaelle Gabiane1,2 | Pei-Shi Yen1 | Anna-Bella Failloux1

1 Institut Pasteur, Université de Paris, Unit of Arboviruses and Insect Vectors, Paris, France
2 Université des Antilles, Campus de Schoelcher, Schoelcher, Martinique

Correspondence
Pei-Shi Yen and Anna-Bella Failloux, Institut Pasteur, Université de Paris, Unit of Arboviruses and Insect Vectors, F-75015 Paris, France.
Email: pei-shi.yen@pasteur.fr and anna-bella.failloux@pasteur.fr

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 contribute 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])
in 2017. 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, 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. 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. 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. In 1881, Carlos Finlay hypothesised that YF was transmitted by Aedes aegypti (which was then called Culex fasciatus). Finlay inoculated 102 healthy volunteers with YFV-infected mosquitoes, and found that volunteers could develop YF symptoms. 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. The mosquito-mediated YFV transmission was verified in 1900. Walter Reed and colleagues confirmed Finlay’s hypothesis with improved experiments: 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. 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. In these experiments, YF symptoms could be observed in the volunteers exposed to Aedes aegypti having become infected 14–25 days after feeding on symptomatic patients. 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. 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.

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. 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. 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 African genotypes are not 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. 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 YF transmissions were reported.

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
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 hemocoele. 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, with a trend of rapid expansion due to the eggs resistance to desiccation 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 strains24-27 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 1993,26 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, 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. On the field, YFV-infected Ae. albopictus was found at the edge of a forest in Brazil, 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, 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. Although the mortality rate of YF in Africa is lower than in South America, 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. In Africa, several Aedes spp. mosquito species are responsible for sylvatic, rural, and urban YFV transmission cycles, which increase the complexity of YF 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 YF to spill out of the sylvatic cycle. 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.

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, and the major source of human infections come from a YFV sylvatic transmission in Brazil. 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. Evidence suggested that humans were infected from the sylvatic cycle only 4 days after an epizootic was declared.

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. It spread to Cuba, Guadeloupe, Jamaica, Martinique, and Saint Kitts. 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. 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. 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 Haemagogus janthinomys and Sabethes chloropterus, 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. Thus, YFV circulating in Trinidad was the cause of YF epizootic in America in 1978–1980.

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. Outbreaks were reported in Spain (Barcelona, Gibraltar, Sevilla, Cadiz, Malaga), Portugal (Lisbon, Porto), France (Marseille, Brest, Saint-Nazaire, Rochefort, Bordeaux), and Italy (Livorno). More than 3500 people died in Barcelona in 1821, and
more than 6000 in Lisbon in 1857. 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 Aedes aegypti from Europe. Its last report was recorded in Italy in 1971. However, the mosquito can still be found in South Russia, West Georgia, and North Turkey, with gaining ground towards the West. Nonetheless, the estimation on the suitability of Aedes aegypti in the European region is low, as the minimum temperature and humidity do not reach the requirements of Aedes aegypti to establish sustainable populations. The risk of YFV transmission carried out by Aedes 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, 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. The history of the slave trade from Africa to Asia can be traced back to 2900 B.C. in Egypt. 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. 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. However, 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. In 2016, 11 YFV-infected workers returned to China from Angola where a YF outbreak was active. 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.

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 Aedes aegypti and Aedes albopictus are abundant. Vector competence of Asian Aedes aegypti for YFV was successfully demonstrated in laboratory conditions early in 1929. Aedes 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 Aedes aegypti mosquitoes from Cambodia and Vietnam were more susceptible than Brazilian populations to the South America genotype I, and an Aedes aegypti colony from Laos was also able to transmit the West Africa genotype I. Moreover, a more extensive study analysing Aedes spp. from the Asian-Pacific region indicated that both Aedes aegypti and Aedes albopictus were susceptible to the West Africa genotype I; the Aedes 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 Aedes aegypti from the Asia-Pacific region. On the contrary, Aedes albopictus mosquitoes from the region were less susceptible to YFV.

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, Aedes aegypti and Aedes albopictus acquire microbes vertically or from the environment, and harbour them in gut or other organs/tissues. The composition of microbiota (mainly viruses and bacteria) changes with mosquito age, probably resulting from competition among symbionts for resources or mosquito immunity 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. An example is Nhumirim virus (Flaviviridae) that was originally found in Culex chidesleri, able to reduce Zika virus (ZIKV) transmission but not chikungunya virus (CHIKV) in Aedes 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. Aedes 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. On the contrary, the impact of bacteria on mosquito vector competence has been extensively studied. Mosquito bacteria affect vector competence by inducing immune responses, competing for nutritious resources, producing secondary metabolites, and even triggering RNAi immunity. Among all mosquito symbionts, Wolbachia is the most intensively studied bacteria that suppresses YFV replication in Aedes aegypti 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 out-breaks.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,109 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.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](image-url)
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

---

**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](http://freepnglogos.com); the icons were designed by Voysla, Freepik, and kerismaker from Flaticon.
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. 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.

ORCID
Pei-Shi Yen https://orcid.org/0000-0002-2113-7394
Anna-Bella Failloux https://orcid.org/0000-0001-6890-0820

REFERENCES
1. McNeill JR. Yellow jack and geopolitics: environment, epidemics, and the struggles for empire in the American tropics, 1650–1825. QAH Mag Hist. 2004;18(3):5.
2. Chaves-Carbalo E, Carlos Finlay and yellow fever: triumph over adversity. Mil Med. 2005;170(10):881-885. https://doi.org/10.7205/milmed.170.10.881.
3. Reed W. Carroll J, Agramonte A. Experimental yellow fever. 1901. Mil Med. 2001;166(9 Suppl):55-60.
4. Ho YL, Joelsons D, Leite GFC, et al. Severe yellow fever in Brazil: clinical characteristics and management. J Trav Med. 2019;26(5). https://doi.org/10.1093/jtm/taz040.
5. Kallas EG, Wilder-Smith A. Managing severe yellow fever in the intensive care: lessons learnt from Brazil. J Trav Med. 2019;26(5). https://doi.org/10.1093/jtm/taz043.
6. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1859-1922. https://doi.org/10.1016/S0140-6736(18)32335-3
7. Holstein M. Dynamics of Aedes aegypti distribution, density and seasonal prevalence in the Mediterranean area. Bull World Health Organ. 1967;36(4):541-543.
8. Schaffner F, Mathis A. Dengue and dengue vectors in the WHO European region: past, present, and scenarios for the future. Lancet Infect Dis. 2014;14(12):1271-1280. https://doi.org/10.1016/S1473-3099(14)70834-5
9. Barrett ADT. The reemergence of yellow fever. Science. 2018;361(6405):847-848. https://doi.org/10.1126/science.aau8225.
10. Rawlins SC, Hull B, Chadee DD, et al. Sylvatic yellow fever activity in Trinidad, 1988-1989. Trans R Soc Trop Med Hyg. 1990;84(1):142-143. https://doi.org/10.1016/0035-9290(93)90411-7
11. Latalallade LG, Vazeille M, Obadia T, et al. Risk of yellow fever virus transmission in the Asia-Pacific region. Nat Commun. 2020;11(1):5801. https://doi.org/10.1038/s41467-020-19625-9.
12. Gorgas WC. Sanitation at Panama. Mil Med. 1912;58(13):3.
13. Agramonte A. The inside history of a great medical discovery. Mil Med. 2001;166(9 Suppl):68-78.
14. Mehra A. Politics of participation: Walter Reed’s yellow-fever experiments. Virtual Mentor. 2009;11(4):326-330. https://doi.org/10.1001/virtualmentor.2009.11.4.mhst1-0904.
15. Barrett AD, Higgs S. Yellow fever: a disease that has yet to be conquered. Annu Rev Entomol. 2007;52:209-229. https://doi.org/10.1146/annurev.ento.52.110405.091454.
16. Staples JE, Monath TP. Yellow fever: 100 years of discovery. JAMA. 2008;300(8):960-962. https://doi.org/10.1001/jama.300.8.960.
17. Cedillo-Barron L, Garcia-Cordero J, Shrivastava G, et al. The role of flaviviral proteins in the induction of innate immunity. Subcell Biochem. 2018;88:407-442. https://doi.org/10.1007/978-981-10-8456-0_17.
18. Mutebi JP, Wang H, Li L, Bryant JE, Barrett AD. Phylogenetic and evolutionary relationships among yellow fever virus isolates in Africa. J Virol. 2001;75(15):6999-7008. https://doi.org/10.1128/JVI.75.15.6999-7008.2001.
19. Bryant JE, Holmes EC, Barrett AD. Out of Africa: a molecular perspective on the introduction of yellow fever virus into the Americas. PLoS Pathog. 2007;3(5):e75. https://doi.org/10.1371/journal.ppat.0030075.
20. Mir D, Delatorre E, Bonaldo M, Lourenco AB. Oral susceptibility to yellow fever virus of Aedes aegypti and five South African mosquito species. Trans R Soc Trop Med Hyg. 2014;108(2):143-144. https://doi.org/10.1093/trstmh/tru083.
21. Sota T, Mogi M. Interspecific variation in desiccation survival time of Aedes (Stegomyia) mosquito eggs is correlated with habitat and egg size. Oecologia. 1992;90(3):353-358. https://doi.org/10.1007/BF00317691.
22. Jupp PG, Kemp A. Laboratory vector competence experiments with yellow fever virus and five South African mosquito species including Aedes aegypti. Trans R Soc Trop Med Hyg. 2002;96(5):493-498. https://doi.org/10.1016/S0035-9203(02)90417-7.
23. Lourenco-de-Oliveira R, Vazeille M, Bispo de Filippis AM, Failloux AB. Oral susceptibility to yellow fever virus of Aedes aegypti from
27. Vazeille M, Yebakima A, Lourenco-de-Oliveira R, et al. Oral receptivity of Aedes aegypti from Cape Verde for yellow fever, dengue, and chikungunya viruses. Vector Borne Zoonotic Dis. 2013;13(1):37-40. https://doi.org/10.1089/vbz.2012.0982

28. Couto-Lima D, Madec Y, Bersot MI, et al. Potential risk of re-emergence of urban transmission of yellow fever virus in Brazil facilitated by competent Aedes populations. Sci Rep. 2017;7(1):4848. https://doi.org/10.1038/s41598-017-01586-3

29. Johnson BW, Chambers TV, Crabtree MB, et al. Vector competence of Brazilian Aedes aegypti and Ae. albopictus for a Brazilian yellow fever virus isolate. Trans R Soc Trop Med Hyg. 2002;96(6):611-613. https://doi.org/10.1016/s0035-9203(02)90326-3

30. Peña CJ. First report of Aedes (stegomyia) albopictus (skuse) from the Dominican republic. Vector Ecol News. 1993;24(68).

31. Rodhain F. [Problems posed by the spread of Aedes albopictus]. Bull Soc Pathol Exot. 1996;89(2):137-140. discussion 140-1. Problemes poses par l’expansion d’Aedes albopictus.

32. Reiter P. Aedes albopictus and the world trade in used tires, 1988-1995: the shape of things to come? J Am Mosq Control Assoc. 1998;14(1):83-94.

33. Broche RG, Borja EM. Aedes albopictus in Cuba. J Am Mosq Control Assoc. 1999;15(4):569-570.

34. Fernández Mdel C, Jean YS, Callaba CA, Lopez LS. The first report of Aedes (Stegomyia) albopictus in Haiti. Mem Inst Oswaldo Cruz. 2012;107(2):279-281. https://doi.org/10.1590/S0074-01622012000200020

35. Ali I, Mundie M, Anzinger JJ, Sandiford SL. ‘Tiger in the sun: a report of Aedes albopictus from Trinidad, west indies.’ Science. 2012;3305:438-439.

36. Paupy C, Delatte H, Bagny L, Corbel V, Fontenille D. Aedes albopictus, an arbovirus vector: from the darkness to the light. Microbes Infect. 2009;11(14-15):1177-1185. https://doi.org/10.1016/j.micinf.2009.05.005

37. Waldock J, Chandra NL, Lelieveld J, et al. The role of environmental and anthropogenic factors which explain the global importation of yellow fever from Angola to China. Emerg Microb Infect. 2020;8(1):9. https://doi.org/10.1186/s12985-020-00674-y

38. Cintra A, Queiroz M, Abreu IP. Orião AM. Oral vaccination coverage from 1970 to 2016: an adjusted retrospective analysis. Vaccine. 2019;37:3916-3923. https://doi.org/10.1016/j.vaccine.2019.03.018

39. Gaythorpe KA, Hamlet A, Cibrelus L, Garske T, Ferguson NM. The effect of climate change on yellow fever disease burden in Africa. Elite. 9. 2020.e55619. https://doi.org/10.7554/eLife.55619

40. Kamgang B, Vazeille M, Yougang AP, et al. Potential of Stegomyia pictus, from Trinidad, west indies. Vector Borne Zoonotic Dis. 2016;16(8):566-567. https://doi.org/10.1089/vbz.2016.0231

41. Pereira Dos Santos T, Roiz D, Santos de Abreu FV, et al. Potential of Aedes albopictus to transmit yellow fever virus in urban areas in Central Africa. Emerg Microb Infect. 2019;8(1):1636-1641. https://doi.org/10.1093/iumicumni.2019.05.005

42. Silva NIO, Sacchetto L, de Rezende IM, et al. Recent sylvatic yellow fever outbreaks in Brazil. Mem Inst Oswaldo Cruz. 2013;107 (5):224-231. https://doi.org/10.1590/s0074-01622013000500010

43. Vainio J, Cutts F. Yellow Fever. World Health Organization; 1998.

44. Geggus D. Yellow fever in the 1790s: the British army in occupied Saint Domingue. Med Hist. 1979;23(1):38-58. https://doi.org/10.1017/S0025727300051012

45. Monath TP. Yellow fever: an update. Lancet Infect Dis. 2001;1(1):11-20. https://doi.org/10.1016/s1473-3099(01)00016-0

46. Vasconcelos PF, Monath TP. Yellow fever remains a potential threat to public health. Vector Borne Zoonotic Dis. 2016;16(8):566-567. https://doi.org/10.1089/vbz.2016.0231

47. Garske T, Kont SE, Grande RA, et al. Detection of Aedes aegypti, Aedes albopictus, and Aedes koreicus in the area of Sochi, Russia. Vector Borne Zoonotic Dis. 2016;16(1):58-60. https://doi.org/10.1089/vbz.2014.1761

48. WHO. Yellow Fever Rapid Field Entomological Assessment During Yellow Fever Outbreaks in Africa; 2014.

49. Cathey JT, Marr JS. Yellow fever, historical. International Encyclopedia of Public Health. 2nd ed., 2017:11.

50. Focks DA, Chadee DD. Pupal survey: an epidemiologically significant surveillance method for Aedes aegypti: an example using data from Trinidad. Am J Trop Med Hyg. 1997;56(2):159-167. https://doi.org/10.4269/ajtmh.1997.56.159

51. Dickens BL, Sun H, Jit M, Cook AR, Carrasco LR. Determining environmental and anthropogenic factors which explain the global.
distribution of *Aedes aegypti* and *Ae. albopictus*. BMJ Glob Health. 2018;3(4):e000801. https://doi.org/10.1136/bmjgh-2018-000801

66. Chotpitayasunondh T. Introduction on the global dengue epidemiological burden. *Int J Infect Dis*. 2012;16:E4. https://doi.org/10.1016/j.ijid.2012.05.014

67. Chouaia B, Rossi P, Montagna M, et al. Molecular evidence for vector competence for West Nile virus. Virolology. 2012;427(2):90-97. https://doi.org/10.1016/j.virol.2012.02.016

68. Romo H, Kenney JL, Blitvich BJ, Braut AC. Restriction of Zika virus infection and transmission in *Aedes aegypti* mediated by an insect-specific flavivirus. *Emerg Microb Infect*. 2018;7(1):1-13. https://doi.org/10.1038/s41426-018-0180-4

69. Newman CM, Cerutti F, Anderson TK, et al. *Culex flavivirus* and *West Nile virus* mosquito coinfection and positive ecological association in Chicago, United States. *Vector Borne Zoonotic Dis*. 2011;11(8):1099-1105. https://doi.org/10.1089/vbz.2010.0144

70. Crockett RK, Burkhalter K, Mead D, et al. *Culex flavivirus* and *West Nile virus* in *Culex quinquefasciatus* populations in the southeastern United States. *J Med Entomol*. 2012;49(1):165-174. https://doi.org/10.1603/me11080

71. Kuwata R, Isawa H, Hoshino K, et al. Analysis of mosquito-borne flavivirus superinfection in *Culex tritaeniorynchus* (Diptera: Culicidae) cells persistently infected with *Culex flavivirus* (Flaviviridae). *J Med Entomol*. 2015;52(2):222-229. https://doi.org/10.1093/jme/tju059

72. Hall-Mendelin S, McLean BJ, Bielefeldt-Ohmann H, Hobson-Peters J, Hall RA, van den Hurk AF. The insect-specific Palm Creek virus modulates West Nile virus infection in and transmission by Australian mosquitoes. *Parasites Vectors*. 2016;9(1):414. https://doi.org/10.1186/s13071-016-1683-2

73. Pauwloid-Corra A, Solberg O, Coutu-Lima D, et al. Nhumirim virus, a novel flavivirus isolated from mosquitoes from the Pantanal, Brazil. *Arch Virol*. 2015;160(1):21-27. https://doi.org/10.1007/s00705-014-2219-8

74. de Almeida JP, Aguilar ER, Armache JN, Olmo RP, Marques JT. The virome of vector mosquitoes. *Curr Opin Virol*. 2021;49:7-12. https://doi.org/10.1016/j.coviro.2021.04.002

75. Ruckert C, Weger-Lucarelli J, Garcia-Luna SM, et al. Impact of simultaneous exposure to arboviruses on infection and transmission by *Aedes aegypti* mosquitoes. *Nat Commun*. 2017;8:15412. https://doi.org/10.1038/ncomms15412

76. Barletta ABF, Silva TLAE, Talyuli OA, et al. Prostaglandins regulate humoral immune responses in *Aedes aegypti*. *PloS Negl Trop Dis*. 2020;14(10): e0008706. https://doi.org/10.1371/journal.pntd.0008706

77. Barletta AB, Nascimento-Silva MC, Talyuli OA, et al. *Microbiota* activates IMD pathway and limits Sindbis infection in *Aedes aegypti*. *Parasites Vectors*. 2017;10(1):103. https://doi.org/10.1186/s13071-017-2040-9

78. Xi Z, Ramirez JL, Dinopoulos G. The *Aedes aegypti* toll pathway controls dengue virus infection. *PLoS Pathog*. 2008;4(7):e1000098. https://doi.org/10.1371/journal.ppat.1000098

79. Moreira LA, Iturbe-Ormaetxe I, Jeffery JA, et al. A *Wolbachia* symbiont in *Aedes aegypti* limits infection with dengue, Chikungunya, and Plasmodium. *Cell*. 2009;139(7):1268-1278. https://doi.org/10.1016/j.cell.2009.11.042

80. Sinkins SP. *Wolbachia* and arbovirus inhibition in mosquitoes. *Future Microbiol*. 2013;8(10):1249-1256. https://doi.org/10.2217/fmb.13.95

81. Joyce JD, Nogueira JR, Bales AA, Pittman KE, Anderson JR. Interactions between La Crosse virus and bacteria isolated from the digestive tract of *Aedes albopictus* (Diptera: Culicidae). *J Med Entomol*. 2011;48(2):389-394. https://doi.org/10.1603/me09268

82. Ramírez JL, Short SM, Bahia AC, et al. *Chromobacterium* csp.P reduces malaria and dengue infection in vector mosquitoes and has entomopathogenic and in vitro anti-pathogen activities. *PLoS Pathog*. 2014;10(10):e1004398. https://doi.org/10.1371/journal.ppat.1004398

83. Mayoral JG, Etetari K, Hussain M, Khromykh AA, Asgari S. *Wolbachia* infection modifies the profile, shifting and structure of...
microRNAs in a mosquito cell line. PLoS One. 2014;9(4):e96107. https://doi.org/10.1371/journal.pone.0096107

100. Osei-Amo S, Hussain M, O’Neill SL, Asgari S. Wolbachia-induced aae-miR-12 miRNA negatively regulates the expression of MCT1 and MCM6 genes in Wolbachia-infected mosquito cell line. PLoS One. 2012;7(11):e50049. https://doi.org/10.1371/journal.pone.0050049

101. van den Hurk AF, Hall-Mendelin S, Pyke AT, et al. Impact of Wolbachia on infection with chikungunya and yellow fever viruses in the mosquito vector Aedes aegypti. PLoS Negl Trop Dis. 2012;6(11):e1892. https://doi.org/10.1371/journal.pntd.0001892

102. Rocha MN, Duarte MM, Mansur SB, et al. Pluripotency of Wolbachia against Arboviruses: the case of yellow fever. Gates Open Res. 2019;3:161. https://doi.org/10.12688/gatesopenres.12903.2

103. Cansado-Utrilla C, Zhao SY, McCall PJ, Coon KL, Hughes GL. The microbiome and mosquito vectorial capacity: rich potential for discovery and translation. Microbiome. 2021;9(1):111. https://doi.org/10.1186/s40168-021-01073-2

104. Cirimotich CM, Ramirez JL, Dimopoulos G. Native microbiota shape insect vector competence for human pathogens. Cell Host Microbe. 2011;10(4):307-310. https://doi.org/10.1016/j.chom.2011.09.006

105. Brent SE, Watts A, Cetron M, et al. International travel between global urban centres vulnerable to yellow fever transmission. Bull World Health Organ. 2018;96(5):343-354B. https://doi.org/10.2471/BLT.17.205658

106. Lai S, Huang Z, Zhou H, et al. The changing epidemiology of dengue in China, 1990-2014: a descriptive analysis of 25 years of nationwide surveillance data. BMC Med. 2015;13:100. https://doi.org/10.1186/s12916-015-0336-1

107. Daniels BC, Gaythorpe K, Imai N, Dorigatti I. Yellow fever in Asia—a risk analysis. J Trav Med. 28. 2021:taab015. https://doi.org/10.1093/jtm/taab015

108. Liu B, Gao X, Ma J, et al. Modeling the present and future distribution of arbovirus vectors Aedes aegypti and Aedes albopictus under climate change scenarios in Mainland China. Sci Total Environ. 2019;664:203-214. https://doi.org/10.1016/j.scitotenv.2019.01.301

109. Stokes A, Bauer JH, Hudson NP. Transmission of yellow fever to Macacus rhesus: preliminary note. J Am Med Assoc. 1928;90(4):253-254.

110. Davis NC. The transmission of yellow fever: experiments with the “woolly monkey” (Lagothrix lago-tricha Humboldt), the “spider monkey” (Ateleus ater F. Cuvier), and the “squirrel monkey” (Saimiri sciureus Linnaeus). J Exp Med. 1930;51(5):703-720. https://doi.org/10.1084/jem.1930.51.5.703

111. Yen PS, Failloux AB. A review: wolbachia-based population replacement for mosquito control shares common points with genetically modified control approaches. Pathogens. 2020;9(5):404. https://doi.org/10.3390/pathogens9050404

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;32(4):e2333. https://doi.org/10.1002/rmv.2333