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Review

A yellow flag on the horizon: The looming threat of yellow fever to North America

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ABSTRACT

Objectives: Yellow fever virus historically was a frequent threat to American and European coasts. Medical milestones such as the discovery of mosquitoes as vectors and subsequently an effective vaccine significantly reduced its incidence, in spite of which, thousands of cases of this deathly disease still occur regularly in Sub-Saharan Africa and the Amazonian basin in South America, which are usually not reported. An urban outbreak in Angola, consecutive years of increasing incidence near major Brazilian cities, and imported cases in China, South America and Europe, have brought this virus back to the global spotlight. The aim of this article is to underline that the preventive YFV measures, such as vaccination, need to be carefully revised in order to minimize the risks of new YFV outbreaks, especially in urban or immunologically vulnerable places. Furthermore, this article highlights the diverse factors that have favored the spread of other *Aedes* spp.-associated arboviral diseases like Dengue, Chikungunya and Zika, to northern latitudes causing epidemics in the United States and Europe, emphasizing the possibility that YFV might follow the path of these viruses unless enhanced surveillance and efficient control systems are urgently initiated.

Contents

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Introduction

During the 18th and the 19th centuries, when commercial and human trade between Europe and its American colonies was at its peak, ports were continually hit by yellow fever virus (YFV) outbreaks. In North America, the most notorious outbreak occurred in 1793 in Philadelphia, with 5000 deaths and the exile of one third of the city's population (Bryan et al., 2004). In Europe, cities like Cadiz (1701), Malaga (1741 & 1783), Barcelona (1821 & 1870), Lisbon (1723 & 1757), Livorno (1804), Marseille (1821), Saint Nazare (1861) and even Southampton (1852) and Swansea (1865) suffered the fateful consequences of YFV (Hillemand, 2006). Paramount works like the confirmation by the Reed Commission of Carlos Finlay's theory that a mosquito transmitted the virus, the effective mosquito eradication by Gorgas in La Havana, and the development of an effective vaccine in 1937 by Max Theiler led to a significant reduction in the number of cases worldwide (Figure 1). Despite these advances, YFV has never been eradicated, and thousands of cases are reported annually from Africa and the Amazonian basin. More recently, an urban outbreak in Angola, hundreds of cases identified near major Brazilian cities and the report of imported cases in Asia and Europe have brought YFV back into the spotlight. In this article, we underline the fact that the latest YFV outbreaks have evidenced flaws in the current preventive systems and analyze the factors that might favor this virus reaching the United States and Europe, just as Dengue (DENV), Chikungunya (CHIKV) and Zika (ZIKV) have recently shown.

Transmission cycles and clinical aspects of Yellow fever virus

Yellow fever virus is an enveloped, single-stranded positive RNA virus of the family *Flaviviridae*, genus *Flavivirus*. Phylogeographic studies indicate that YFV originated in Africa, and migrated to the American coasts via slave trade vessels (Bryant et al., 2007). Two major YFV clades can be identified: the first one is composed of four genotypes, two in West Africa and two in South America. The divergence between African and South American genotypes is estimated to have taken place around 470 years ago. The second clade consists of three genotypes with viruses from Central/East Africa (Bryant et al., 2007; Beck et al., 2013).

YFV has three distinct transmission cycles. In the most frequent one, the sylvatic cycle, the main hosts are non-human primates, and the vectors are mosquito species, *Aedes* spp. in Africa and *Haemagogus* spp. or *Sabethes* spp. in South America. Humans enter this cycle as end-hosts and become infected when they inhabit these areas, but also when they approach or enter these sylvatic forested areas, e.g. workers or tourists (Monath and Barrett, 2003).

In the urban cycle, the main hosts are the humans, and the vector is *Ae. aegypti (vide infra)*.

A third transmission cycle, named the Savannah or the intermediate cycle, was originally described in Africa, but certain areas in South America may also be included in this form of transmission. It occurs when humans settle in areas at the edge of the African savannahs or the Amazonian rainforests, zones of emergence, where they can become infected with the virus transmitted by a sylvatic mosquito, which may lead to small rural epidemics (Monath and Barrett, 2003).

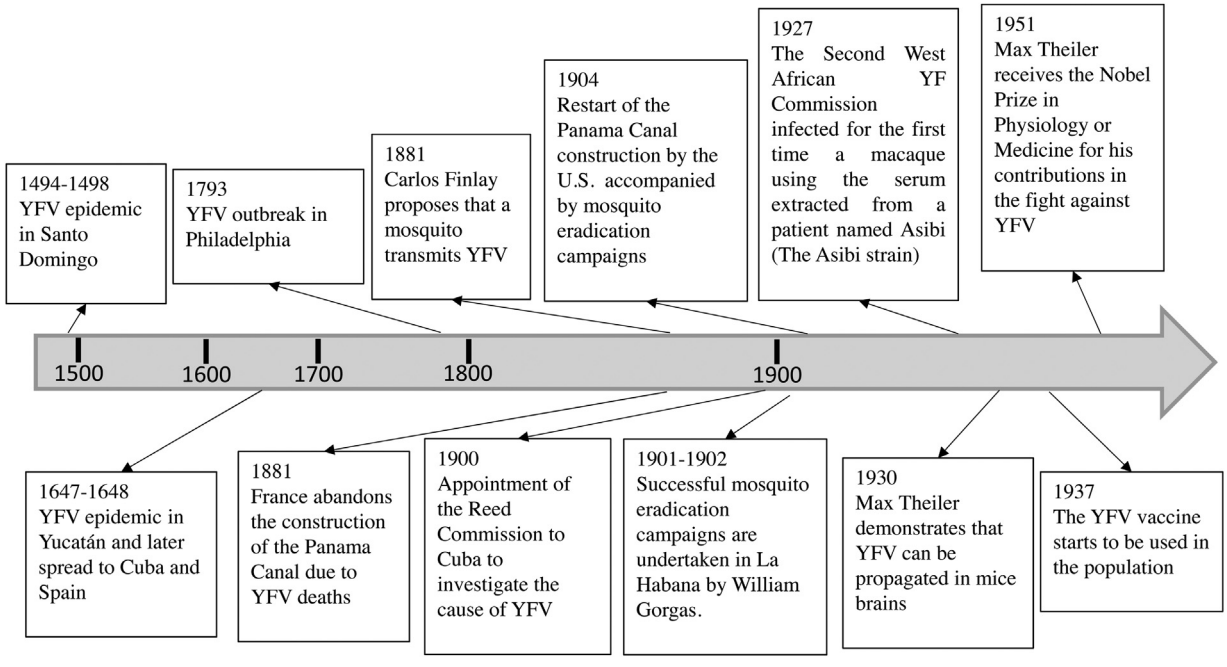

Figure 1. Yellow fever virus historic milestones.

After an incubation period of 3-6 days, most of the infected individuals (70 to 90%) remain asymptomatic or develop a flu-like illness without further complications (Tuboi et al., 2007; Paessler and Walker, 2013). The remaining patients will develop a severe infection that can lead to hemorrhagic fever and ultimately death. The natural history of YFV infection has been divided into three periods: infection, remission and intoxication (Table 1) (Monath and Barrett, 2003). The historical case fatality rate (CFR) of the patients that enter the toxic phase had been between 20 and 50%. In recent epidemics, the CFR among the confirmed cases goes from 13.5% to 35% (*vide infra*).

YFV epidemiology

Recent calculations, based on mathematical models, estimate that in Africa there is an annual burden of 51,000 – 300,000 severe YFV cases and 19,000 to 180,000 deaths (Garske et al., 2014). The number of severe cases represents only 12% of the patients (Johansonn et al., 2014), yet asymptomatic or mild cases are underreported.

The 2016 outbreak in Angola and the Democratic Republic of Congo

In December 2015, several cases of hemorrhagic fever were reported in Luanda, capital city of Angola. By mid-January 2016, laboratory tests confirmed YFV (WHO, 2016a). Between February and October 2016, the number of suspected cases was 4347 with 377 deaths, of which 884 cases and 121 deaths [Case fatality rate (CFR) 13.7%] were laboratory-confirmed (Figure 2).

In March 2016, the outbreak spread to the Democratic Republic of Congo (DRC). The number of suspected cases by October 2016 was 2987 with 121 deaths (77 cases and 16 deaths were laboratory-confirmed) (Figure 2) (WHO, 2016a). The international community responded with mass vaccination campaigns, and more than 30 million vaccine doses were administered in both countries, quickly depleting the WHO emergency vaccine stockpile. The WHO declared the end of the outbreak in December 2016 in Angola and two months later in DRC.

The 2016-2019 outbreak in Brazil

In December 2016, a YFV outbreak began in the state of Minas Gerais, Brazil. The virus migrated towards the Atlantic coast where vaccination had not previously been recommended. By May 2017, 792 cases had been confirmed (274 fatal cases, CFR - 35%) in 130 cities from eight states including Rio de Janeiro, Saô Paulo, and the Distrito Federal (Figure 2). More than 26 million emergency vaccine doses were administered in the first months of 2017. Despite the reduction in the number of human YFV cases after May 2017, there was an increase in the number of epizootics in Brazil. Between July 2017 and May 2018, over 7000 probable YFV infections in non-human primates (NHP) were reported (752 laboratory-confirmed) (OPS, 2018; Ministerio da Saude do Brasil, 2018b). In the final weeks of 2017 and the first half of 2018, the number of human YFV cases in the same country regions rose again, surpassing the number registered in 2017. Between July 2017 and May 2018, there were 1266 confirmed YFV cases (415 deaths, CFR - 32.8%) (OPS, 2018; Ministerio da Saude do Brasil, 2018b). The YFV incidence increase for the second consecutive year prompted the Brazilian authorities to expand the coverage of mass vaccination. The use of fractionated vaccine dosage and door-to-door visits reached 78.6% of the targeted population by the end of March 2018, equivalent to 17.8 million persons (Callender, 2018). Moreover, on March 20th, 2018, the Brazilian Health Minister announced that mass vaccination campaigns would expand to include the entire Brazilian population (Mendes, 2018). Phylogenetic studies have shown that the 2016-2018 human cases had a sylvatic origin, lagging behind NHP YFV cases by a few days (Moreira-Soto et al., 2018; Faria et al., 2018). The infecting virus belongs to the South American I genotype (Faria et al., 2018; Mir et al., 2017). The period between July 2018 and March 2019 has seen an important reduction in the number of human and NHPs cases compared to the two previous years (Table 2). Regarding human cases, compared to the same period in the last year, there has been a 64.2% reduction in the number of notified cases, a 93.3% reduction in the number of confirmed cases, and a 94.9% reduction in the number of deaths (Table 2). In the case of NHP, there was a 59.8% and a 94.5% reduction in the number of notified and confirmed cases, respectively (Ministerio da Saude do Brasil, 2018a, 2019; Table 2). Both the human and the NHP confirmed YFV infections have occurred in the South-Eastern states. As of April 2019, there has been no evidence of urban transmission.

YFV cases outside Angola/DRC and Brazil

Apart from the two epidemics in Angola/DRC and Southeast Brazil, YFV was simultaneously identified in neighboring regions (Figure 2). From April to June 2016, Uganda reported the presence

Table 1
YFV infection - natural history (Monath and Barrett, 2003).

	Period of infection	Period of remission	Period of intoxication	
Approximate duration	3 days	Hours to days	3 Days	
Signs and symptoms	Generalized malaise	Disappearance of symptoms	High fever	Oliguria
	Fever		Headache	Multiorgan failure
	Headache		Asthenia	Hypovolemia
	Myalgias/Arthralgias		Lumbosacral pain	Shock
	Nausea/Vomiting		Nausea/Vomiting	Confusion
	Relative bradycardia (Faget's sign)		Epigastric pain	Seizures
	Conjunctival injection		Jaundice	Coma
			Hemorrhagic diatesis	Death
			DIC[a]	
			Liver enlargement	
Laboratory tests	Leukopenia		Thrombocytopenia	
	Elevation of hepatic enzymes (mild)		Altered clotting times	
			Elevation of hepatic enzymes (severe)	
			Albuminuria	
			Elevated BUN[b] and creatinine	
			Elevated protein concentration in CSF[c]	

[a] DIC - Disseminated intravascular coagulation.
[b] BUN – Blood urea nitrogen.
[c] CSF – Cerebrospinal fluid.

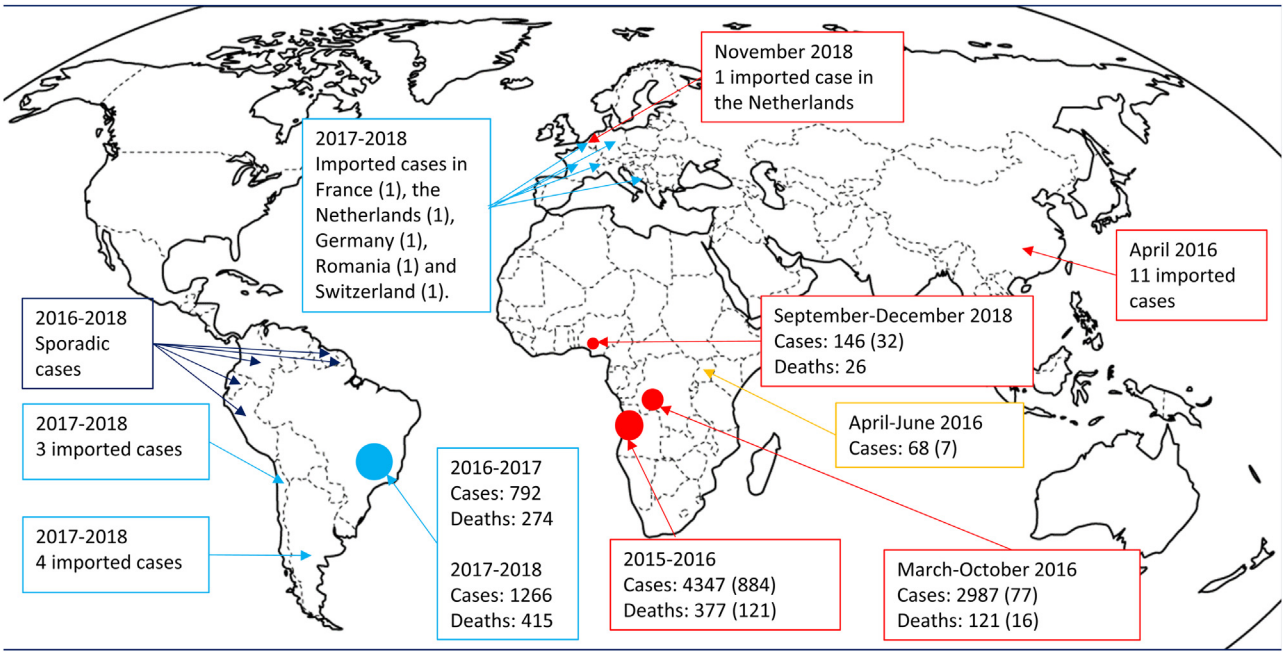

Figure 2. Recent autochthonous and imported yellow fever cases. Blue cases and arrows represent outbreaks caused by YFV clade 1 South American genotype 1. Outbreaks caused by YFV clade 2 are marked in: red - East Angola genotype, and orange – East Africa genotype 1. The numbers between parentheses in the African cases are the number of laboratory-confirmed cases.

Table 2
Comparison of the number of notified, confirmed cases and deaths in humans and non-human primates between the 2017–2018 and 2018–2019 YFV monitoring periods in Brazil.

	July 2017 - 27th March 2018	July 2018 – 29th March 2019	Reduction (%)
Humans			
Notified cases	4414	1580	64.2
Confirmed cases	1131	75	93.3
Deaths	338	17	94.9
Non-human primates			
Notified cases	5575	2237	59.8
Confirmed cases	665	36	94.5

of 68 suspect YFV cases, of which 7 were PCR-confirmed. The causative virus belonged to the East African Genotype, not the Angolan strain (Hughes et al., 2018). More recently, from September to December 2018, an unusually large YFV outbreak in Edo State, Nigeria was reported, with 146 suspected cases. Thirty-two of these cases had laboratory confirmation, and 26 of the suspected cases died (WHO, 2019). This outbreak resulted in a reactive vaccination campaign, with almost 1.5 million doses administered. In South America, during the 2016-2018 periods, YFV cases were also reported in Peru, Colombia, Bolivia, Ecuador, French Guiana, and Suriname (OPS, 2018), revealing the circulation of YFV far from the Brazilian epidemic. As of today, there is no evidence that the causative viruses are linked (Sanna et al., 2018).

In April 2016, the Chinese Centers for Disease Control and Prevention confirmed 11 imported cases of YFV in China in workers returning from Angola, setting the scenario for a possible urban transmission cycle in Asia (Cui et al., 2017), a continent where YFV is not endemic. The urban vector is highly prevalent in the South-East and Pacific regions, and their population could be immunologically vulnerable (Wasserman et al., 2016).

Importantly, during the 2017/2018 period, 19 unvaccinated tourists contracted the virus in Brazil (Figure 2). Fourteen of the infected tourists had a history of travelling to Ilha Grande, an island off Rio de Janeiro (WHO, 2018a). Finally, on November 2018, the Dutch authorities notified an imported YFV case in a man who travelled to Gambia and Senegal (WHO, 2018b; Figure 2)

Current YFV vaccination status

Today, four manufacturers are prequalified by the WHO to produce YFV vaccines with an annual yield of around 140 million doses (International Coordination Group, 2019). However, after more than 70 years of proven reliability, vaccine production remains a slow process.

The vaccine elicits an efficient immune response in 99% of the vaccinees by day 30 after the injection. Until 2013, a 10-year booster dose of the vaccine was recommended; however, the WHO declared that a single dose confers life-long immunity against YFV (WHO, 2013). The WHO recommends a vaccination coverage of 80% in the general population to prevent outbreaks in countries at risk. Moreover, after the implementation of the Yellow Fever Initiative at the beginning of the 21st century, an emergency stockpile of 6 million doses was established in case of sudden outbreaks (WHO, 2010).

The Angola/DRC epidemic highlighted several weak spots of the current vaccination system: low vaccination coverage, recurrent and frequent forgery of YFV vaccination certificates (The Economist, 2016), and the promptness with which the emergency stockpile can be outpaced by demand, especially in an urban setting (Green, 2016).

After the 2016 Angola/DRC outbreak, the WHO launched a new program called “Eliminate Yellow Fever” (EYE), targeting the elimination of YFV outbreaks by 2026. The main public health goals of this program are to protect at-risk populations, prevent the international spread of the disease, and contain epidemics rapidly (WHO, 2017a). It must be highlighted that, in order for this program to work, the participation of local and international governments is necessary, hand in hand with research and development aimed at tackling the current obstacles when diagnosing and treating YFV infections and epidemics (WHO, 2017a).

WHO regulations state that a vaccine must preferentially contain 3000 International Units (IU)/dose and no less than 1000 IU (WHO, 2017b). Martins et al. (2013) and Campi-Azevedo et al. (2016) showed that doses of 587 IU, i.e. a fifth of the required viral particles, were almost equally immunogenic as the full dosage. To maximize the vaccinated population, the WHO started administering fractionated doses equivalent to one fifth of the vaccine, (0.1 mL), in Angola and DRC as a temporary measure (WHO, 2017b). During the 2017-2018 epidemic, Brazilian authorities also implemented mass vaccination campaigns using fractional doses of the YFV vaccine to maximize the immunized population. Results by Casey et al. (2019) show that 98% of the patients who were seronegative at baseline had seroconverted one month after the administration of 0.1 mL of the standard dose. In terms of long-term effectiveness, a follow-up study by Martins et al. (2018) of patients that received fractionated doses of the vaccine has shown that 85% of the persons who received from 5% to 50% of the reference dose of 27 476 IU remained seropositive 8 years afterward. In a similar result, Roukens et al. (2018) reported that 39/40 (98%) of the patients that received one-fifth of the YFV vaccine 10 years ago, i.e. 0.1 mL, had protective levels of neutralizing antibodies. More studies are necessary to determine the effectiveness and the safety of the fractionated dose in more realistic scenarios, including different genetic backgrounds, different ages, and immunocompromised patients such as HIV-1 seropositive patients with CD4 > 200 cells/mL (Roukens and Visser, 2019).

Aedes-*transmitted arboviruses in the continental U.S. and Europe – Will YFV follow?*

This century has seen an increase in the number of DENV cases around the world, and the (re)emergence of CHIKV and ZIKV in new territories, including the United States of America. The U.S. annually receives thousands of arboviral imported cases from tourists or workers returning from countries where these viruses have become endemic. In 2014, Florida reported 272 imported Chikungunya cases (Kendrick et al., 2014). From November 2015 to September 2017, 588 travel-associated Zika cases only in California were reported, from which two thirds had come either from Mexico or Central America (Porse et al., 2018). Nevertheless, there have also been locally transmitted cases of the three diseases, albeit in smaller numbers. In 2005, there were three DENV cases in Brownsville, Texas, following a larger outbreak in the Mexican border city of Matamoros (Bouri et al., 2012). In 2009, 29 cases of locally acquired DENV infection were reported in Key West, Florida; a year later, 65 cases were reported in the same county (Bouri et al., 2012). The first autochthonous case of CHIKV in the U. S. was reported in June 2014; that year, a total of 11 locally acquired cases in Southern Florida were identified (Kendrick et al., 2014). The first local case of ZIKV was reported from Miami-Dade County during the summer of 2016. At the end of that year, 29 locally-transmitted ZIKV cases were confirmed (Likos et al., 2016). It must be underscored, that in all the above-mentioned cases, the most probable vector was *AE. aegypti*, and that the increase of imported and local cases mirrored the increased incidence in neighboring countries like Mexico (Porse et al., 2018).

Most of the *Aedes* spp.-related arboviral cases reported in Europe are imported. However, certain regions have the appropriate conditions for *Aedes* spp. to thrive. The most notorious of the recent *Ae. aegypti*-related outbreaks was the 2012-2013 DENV epidemic in Madeira, Portugal, during which 2144 locally-acquired DENV cases were identified (Alves et al., 2013). Retrospective studies indicated that the virus was introduced by tourists returning from Venezuela (Wilder-Smith et al., 2014). Additional autochthonous DENV outbreaks have been recorded in the Croatian Adriatic coast (17 cases identified in 2010) and Southern France (2 cases in 2010, 7 cases in 2015) (Schaffner and Mathis, 2014; Succo et al., 2016). In 2007, 205 autochthonous CHIKV cases were documented near Ravenna, Italy. Patient zero was identified as a man returning from India, where CHIKV was circulating (Rezza, 2018). During the summer of 2017, almost 400 cases of CHIKV were identified: 269 in Anzio, 61 in Rome and 68 in Guardavalle Marina. In France, small outbreaks of locally-transmitted CHIKV infection were documented in 2010 (2 cases), 2014 (11 cases) and 2017 (9 cases) (Kraemer et al., 2015; Calba et al., 2017). As of April 2019, no cases of ZIKV have been reported in Europe, neither imported nor locally-transmitted. Except for the DENV outbreak in Madeira 2012-2013, the recent arboviral outbreaks in Europe have been associated with transmission by *Ae. albopictus*.

Lessons from recent arboviral epidemics

Many interrelated factors come into play before an arbovirus can infect humans, and its potential spread to epidemic proportions. Some of these factors are related to the virus *per se*; in the case of YFV, its RNA genome and the extreme adaptability these biological entities have due to their high mutation rate. Some other factors are related to the vector: its efficiency to transmit a given disease, its current and potential distribution, and its capacity to migrate and invade new ecological niches. Finally, other factors are directly related to human activities that have modified the environment and favored the rapid spread of arboviruses around the world such as climate change, which results in a potential expansion of mosquito habitats; globalization and travel; and massive urbanization, that make humans more prone to interact with new vectors and their related pathogens.

Why RNA viruses?

RNA viruses must be considered one of the paramount global health threats (Carrasco-Hernández et al., 2017), since many of the most notorious outbreaks of this century have been caused by these biological entities. These viruses have evolutionary features (high mutation rates, absence of proofreading mechanisms, fast and numerous replication cycles), which confer extreme adaptability. Moreover, experience shows that RNA viruses, and Arboviruses in particular, can “easily” cross species boundaries and sometimes humans become incidental hosts (Holmes, 2013; Gould et al., 2017).

Most of the mutations that arise in a viral population are deleterious; however, occasionally, point mutations lead to an increased virulence. The mutation A226 V in Chikungunya's E protein has been associated with an increased infectivity in *Ae. albopictus*, which in turn has facilitated the spread of the disease in places where the traditional vector, *Ae. aegypti*, is not endemic (Tsetsarkin et al., 2007). ZIKV gained notoriety in the scientific community when a relationship between the infection in pregnant women and the development of microcephaly in their babies and, separately, an increase in Guillain Barré syndrome cases, became evident (Fauci and Morens, 2016; ECDC, 2015; Cao-Lormeau et al., 2016). Molecular and bioinformatic studies have shown that the lineage introduced to the American continent has differences linked to neuropathogenic features (Ramaiah et al., 2017; Yuan et al., 2017).

Mosquitoes and climate change

Aedes aegypti

Unlike the YFV sylvatic transmission cycle, in which different mosquito species can propagate the virus, the YFV urban cycle is

maintained by *Ae. aegypti*. This mosquito is well-adapted to urban settlements, it feeds indoors, mostly on humans, and its main breeding zones consist of human water containers. It can be found in almost every continent, mainly in the tropical zone (Kraemer et al., 2015). Apart from YFV, this mosquito is the main urban vector of other arboviruses like DENV, CHIKV and ZIKV. In the continental U.S., *Ae. aegypti* is restricted to the southern states: California, Arizona, Texas, Louisiana and Florida, but its sporadic presence has been reported in states like Maryland and New Jersey (Hahn et al., 2017). Local U.S. predictions suggest that Southern Florida and Texas are regions capable of supporting *Ae. aegypti*-related arboviral epidemics during the summer, and mosquito populations might be more abundant in states like Georgia, South Carolina, Louisiana, and Mississippi, increasing the risk of autochthonous transmission. However, temperatures might not be high enough to support overwintering (Butterworth et al., 2017). In Europe, *Ae. aegypti* used to be endemic in Southern countries, and frequent DENV outbreaks occurred in Greece and Turkey until the 1930s (Schaffner and Mathis, 2014). In 2001 and 2008, Russia and Georgia reported the presence of *Ae. aegypti* in the Black Sea coasts, and in 2015, Turkey also reported populations of the vector (Schaffner and Mathis, 2014; Kotsakiozi et al., 2018). Phylogenetic analyses indicated that populations of *Ae. aegypti* have persisted throughout the Black Sea coasts but had not been detected (Kotsakiozi et al., 2018). The island of Madeira, Portugal, has been populated by *Ae. aegypti* since 2005 (Seixas et al., 2018).

The risk of *Ae. aegypti* expanding its current habitats in Europe is limited. Nevertheless, the probability of this event might be higher during the summer months in places with the appropriate climate (Schaffner and Mathis, 2014), as the Madeira DENV epidemic demonstrated.

Aedes albopictus

Ae. albopictus is also an efficient urban vector of DENV, CHIKV and ZIKV. In the case of YFV, *Ae. albopictus* has only been a bystander and its role as a vector outside laboratory settings has not been demonstrated. Amraoui et al. (2016, 2018) and Couto-Lima et al. (2017), independently infected *Ae. albopictus* with YFV and showed that the virus was detected in the saliva from day 14th post-exposure. Moreover, the Evandro Chagas Institute recently detected the presence of the virus in *Ae. albopictus* mosquitoes trapped in Minas Gerais (Santos de Sousa, 2018). However, there is no proof that this species has been actively transmitting YFV during the recent outbreaks. Should its status change to an active YFV vector, then the global panorama might be more bleak. In comparison with *Ae. aegypti, Ae. albopictus* has a wider geographical range, surviving colder temperatures and higher latitudes (Kraemer et al., 2015). In the U.S., *Ae. albopictus* is widespread in the South Central, South East, and Mid-Atlantic States, as well as in California and Arizona (Hahn et al., 2017). In Europe, its current distribution includes the countries in the Mediterranean, the Adriatic, the Eastern Black Sea coasts (Javelle et al., 2018), Eastern France, Switzerland and Southwestern Germany and introductions of the vector into other countries like Austria, Belgium or the Netherlands are frequent (Scholte et al., 2008; ECDC, 2019; Schoener et al., 2019), Moreover, it has already been responsible for recent, important arboviral outbreaks in Europe (*vide supra*).

Climate change and potential Aedes spp. distribution

The main climatological factors affecting mosquitoes are temperature, precipitation and humidity. Warmer temperatures, higher rainfall and humidity are positively correlated with aspects of mosquitoes' life cycles such as hatching rate, development time, survival, and vectorial capacity (Butterworth et al., 2017). Conversely, extremely high temperatures are detrimental on mosquito development and survival (Monaghan et al., 2018). Also, cold temperatures and dryness limit mosquito distribution and prevent overwintering (Khormi and Kumar, 2014). Global predictions of the effects of climate change on *Aedes* spp. suitable habitats and populations are not homogeneous, and current models yield contradictory forecasts. Studies by Monaghan et al. (2018) and by Kraemer et al. (2019), in which they use different temperature and precipitation scenarios in comparison with historical data, and global climate models added to the current velocity with which *Ae. aegypti* and *Ae. albopictus* have been expanding their niches, respectively, predict that both species will continue to expand their habitats. Monaghan et al. (2018) predicted that by 2061-2080, there will be an 8-13% global increase of the climatically suitable *Ae. aegypti* habitat, which could lead to a significant increase in the number of persons in contact with the vector and its diseases. In both models, this vector is expected to move to regions where current conditions do not allow its survival and reproduction including areas in the United States, Africa and Europe. In the model by Kraemer et al. (2019), *Ae. aegypti* is expected to reach additional regions in Turkey and even Southern Italy, while *Ae. albopictus* is expected to have a broader habitat spread, reaching regions in Northern France and Germany. Khormi and Kumar (2014) estimated the potential future distribution of *Ae. aegypti* using two different climate models, and their results indicate that in the next few decades there will be an overall contraction in the climatically suitable areas for this mosquito such as Central and South America, Central Africa and Southern Asia, with a limited range expansion in Northern Africa, Australia and the Arabian Peninsula.

Major efforts are underway to develop innovative vector control strategies. These include the use of transgenic male mosquitoes carrying a copy of a dominant lethal gene, causing their offspring to die at the pupation stage (Marcondes et al., 2017); the release of irradiated sterile male mosquitoes leading to increased sterility in the general mosquito population (Fernández-Salas et al., 2015); and the infection by *Wolbachia* strains associated with cytoplasmic incompatibility, viral suppression or shortening of mosquitoes' life span, hampering them from transmitting more viruses (Johnson, 2015). Nevertheless, these innovations must be accompanied by massive educational campaigns aimed at preventing inappropriate water storage, effective fumigation that promotes insecticide rotation and mosaics, which diminish mosquito insecticide resistance.

Anthropogenic factors

We are witnessing a relentless process of worldwide urbanization, especially in developing countries (Neiderud, 2015; Hassell et al., 2017); however, this growth is not accompanied by suitable planning, leading to crowded, impoverished areas without a critical infrastructure, i.e. clean water supply, appropriate sewage, etc. Consequently, people obtain water whenever and wherever possible. For mosquitoes like *Ae. aegypti,* these conditions provide breeding sources. Moreover, this urban expansion leads to deforestation and land use, which in turn promotes human contact with possible viral reservoirs such as bats, rodents, non-human primates and insects. Brazil is a good example of a developing country in which these human activities have been more intense and have led to a clear increase in the incidence of diseases like leptospirosis, ZIKV infection, Hantavirus and YFV (Marcondes et al., 2017; Nava et al., 2017).

Secondly, in a globalized world any given disease might migrate to different countries/continents in a matter of hours. This was the case of ZIKV, which may have arrived at Brazil at the 2014 Soccer World Cup or an international canoeing competition in 2015 (Marcondes et al., 2017). Moreover, the vector itself can migrate and adapt to new environments (Ramasamy et al., 2011). Mosquitoes can move to new regions while travelling in human transports in the form of eggs,

which favor their survival even in harsh conditions, a situation that has occurred several times in the cases of *Ae. Aegypti* and *Ae. albopictus* (Gratz et al., 2000). Furthermore, adult mosquitoes can also survive long trips. As a vector control strategy, since 2005, the WHO (2016b) and the International Health Regulations (Hardiman and Wilder-Smith, 2007), recommend disinsecting every aircraft leaving countries where arboviral infections are present. According to WHO regulations, the flight deck, the passengers' cabin and the cargo deck should be targets for control of insects. These measures should be reinforced, after a recent report of live adult mosquitoes, most probably coming from America or Saudi Arabia, being trapped in a major international airport in the Netherlands (Ibañez-Justicia et al., 2017).

Conclusion

For centuries, YFV was an ominous companion of Trans-Atlantic travel. The existence of a safe and effective vaccine has clearly been fundamental to control the disease in recent decades. The (re) emergence of related viruses like DENV, ZIKV and CHIKV and their rapid worldwide expansion have demonstrated the ineffectiveness of vector control policies and the perils of a globalized society. The current distribution of *Ae. aegypti* limits the possibility of a YFV outbreak to very few regions in the U.S. and Europe; however, YFV could reach these regions if it becomes endemic in nearby countries like Mexico or the Eastern Mediterranean Region. Furthermore, climate change will likely continue warming the globe, probably expanding the vectors' habitats, and the possibility that YFV might also be transmitted by *Ae. albopictus* is always latent. To prevent these scenarios, it is paramount to aim globally at reinforcing the mise-en-place of WHO's EYE strategies: protect at-risk populations, prevent international spread and a rapid contention of eventual outbreaks. Nevertheless, to achieve EYE's main objectives, it is fundamental that, at a local scale, public health institutions urgently initiate enhanced surveillance and the implementation of control programs. Novel research on the molecular biology, epidemiology and clinical aspects of this virus will certainly aid in prevention and control efforts against current and future epidemics. Yellow fever is looming on the horizon in North America and Europe, and steps for controlling it should be emphasized.

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Conflict of interest statement

None of the authors of this text has any potential conflict of interest.

Ethical approval

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