Le Infezioni in Medicina, n. 4, 434-450, 2024
doi: 10.53854/liim-3204-3

Yellow Fever: Global Impact, Epidemiology, Pathogenesis, and Integrated Prevention Approaches

Shriyansh Srivastava[1,2], Shivang Dhoundiyal[3], Sachin Kumar[1], Awaneet Kaur[2], Mahalaqua Nazli Khatib[4], Shilpa Gaidhane[5], Quazi Syed Zahiruddin[6], Aroop Mohanty[7], Andres F. Henao-Martinez[8], Martin Krsak[8], Alfonso J. Rodriguez-Morales[9,10,11], Juan J. Montenegro-Idrogo[9,12], D. Katterine Bonilla-Aldana[13], Ranjit Sah[14,15,16]

[1]Department of Pharmacology, Delhi Pharmaceutical Sciences and Research University (DPSRU), Sector 3 Pushp Vihar, New Delhi 110017, India;
[2]Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida 203201, India;
[3]Department of Pharmacy, Birla Institute of Technology and Sciences, Pilani, 333031 Rajasthan, India;
[4]Division of Evidence Synthesis, Global Consortium of Public Health and Research, Datta Meghe Institute of Higher Education, Wardha, India;
[5]One Health Centre (COHERD), Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education, Wardha, India;
[6]Global Health Academy, Division of Evidence Synthesis, School of Epidemiology and Public Health and Research, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha. India;
[7]Department of Microbiology, All India Institute of Medical Sciences, Gorakhpur, India;
[8]Division of Infectious Diseases, University of Colorado Anschutz Medical Campus, Aurora, CO, USA;
[9]Master of Clinical Epidemiology and Biostatistics Program, Faculty of Health Sciences, Universidad Científica del Sur, Lima, Peru;
[10]Grupo de Investigación Biomedicina, Facultad de Medicina, Fundación Universitaria Autónoma de las Américas-Institución Universitaria Visión de las Américas, Pereira 660003, Risaralda, Colombia;
[11]Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, Lebanon;
[12]Infectious and Tropical Diseases Service, Hospital Nacional Dos de Mayo, Lima, Peru;
[13]College of Medicine, Korea University, Seoul, Republic of Korea;
[14]Department of Microbiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune 411018, Maharashtra, India;
[15]Department of Public Health Dentistry, Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pune 411018, Maharashtra, India;
[16]SR Sanjeevani Hospital, Kalyanpur-10, Siraha, Nepal

Article received 11 August 2024 and accepted 10 November 2024

SUMMARY

Yellow fever poses a substantial global health concern as one of the re-emerging diseases with pandemic potential in a scenario of the worldwide distribution of some vectors (such as *Aedes aegypti*); in the context of climatic change, an unclear knowledge about the immune behaviour of the virus, between other determinants. This review details the historical foundations, intricate evolution of geographical spread, and transmission mechanisms of the disease to understand the behaviour of outbreaks over time in a multifactorial context that could be difficult to understand. This article approaches to epidemiological, pathophysiological, immunological, social determinants, and climatic crisis by understanding possible control mechanisms and anticipating potential future epidemics. This article explores the evidence of yellow fever virus (YFV) pathogenesis and its complex interactions with the immune response in the host, the vector, and in the context of immunisation. These discussions contribute to a more comprehensive understanding of the disease's progression. Despite the global presence of the vector and other factors that could facilitate an epidemic spread, yellow fever outbreaks have remained confined to specific endemic areas. This limited distribution is not entirely understood. However, it may be influenced by the complex immune interactions between the virus, the vector, and the host, preventing its spread to other regions.

Keywords: Societal consequences, transmission mechanisms, pathogenicity, immune response, virology.

INTRODUCTION

Yellow fever (YF), an acute and potentially fatal viral illness, is an enduring testament to the intricate interplay between viruses, mosquitoes, primates and human populations and their environment [1]. YF is a disease that has not only shaped history due to relevant outbreaks worldwide, the challenges in the limited medical management of severe cases, advances, and its impact on public health interventions, with several foci of research still in development. The yellow fever virus (YFV) is a single-stranded RNA genome virus, a member of the Flaviviridae family like other viruses transmitted by a vector in this family: dengue virus (DENV), Zika virus (ZIKV), Japanese Encephalitis fever virus (JEV), among others. Both DENV and ZIKV developed epidemics with worldwide distribution. In contrast, YFV has been located exclusively in African and South American regions but has not spread in Asia regions, in contrast to JEV, which has been located mainly in these Asian regions but has not spread to other American and African regions. Thus, despite belonging to the same viral family and having a common vector involved in all cases (*Aedes* mosquito), worldwide distribution is different between them; in YFV, it is still maintained in its historical distribution [2, 3]. From its initial emergence in the sylvatic cycle involving non-human primates and forest-dwelling mosquitoes to its recent urban outbreaks, probably explained by the change in the population dynamics in tropical regions cities, where the emergence of new towns/cities near or in the middle of the forest regions to the forays into the main cities of the Americas, yellow fever has exemplified one of the enigmas around of its ecological and epidemiological dynamics in the time, with a different understanding of the transmission dynamic and its impact in contrast with other viral-borne- diseases [4].

YFV immunisation in humans was one of the main advantages of vaccines due to their excellent performance worldwide. However, this prevention mechanism became available over eighty years ago; new outbreaks have been developed within the last ten years [5, 6]. The last outbreak in South America was considered an epidemic because it had a wide distribution across the east of the continent, where mainly all regions of Brazil were affected [6, 7].

This review was developed to understand the reasons for the YFV dynamic around the world and its potential scenarios in the context of the global distribution of some vectors like *Aedes* mosquitoes since the vision of immunological basis in the vector as in the host in the context of climatic change and other potential conditions at the global level. Additionally, we will summarise the current mechanisms proposed for the management, control, and prevention of YFV [8, 9]. We conducted a literature search to find relevant articles about epidemiology, clinical aspects, prevention and vaccination, and other aspects of yellow fever. Using a controlled vocabulary thesaurus, the following databases were searched: PubMed, Scopus, Web of Science, SciELO and LILACS, focusing on articles in English, Spanish and Portuguese, particularly from the last ten years.

GEOGRAPHICAL DISTRIBUTION AND TRANSMISSION

Geographical distribution

Yellow fever, a contagious illness propagated by mosquitoes feeding primarily during daylight hours, has re-emerged outbreaks in the Americas and Africa since 2016. By 2023, around 34 nations across Africa and 13 nations in the Central and South Americas, including the Caribbean, will be considered endemic for YFV, entirely or in specific regions. This global impact underscores the gravity of the situation and the need for your involvement. In both scenarios in the Americas and African regions, the presence of the vector and a susceptible non-human primate host is necessary. These conditions have been present since the first outbreaks were reported, contrasting with other regions, such as Asia or Europe, where YFV was unavailable. However, a susceptible vector (*Ae. aegypti*) has conditioned the worldwide distribution of similar viruses like DENV and ZIKV in these other regions, independent of the urban or rural settings. In these regions, the distribution of a similar Flaviviridae virus transmitted by *Aedes* is the Japanese encephalitis fever virus.

The spread of YFV near the classical distribution zones is significantly influenced by urbanisation and habitat loss. The development of emergent cit-

Corresponding author
Alfonso J. Rodriguez-Morales
E-mail: arodriguezmo@cientifica.edu.pe

ies in these regions, with their proximity to wildlife, has led to persistent infections without disease in non-human local primates, maintaining the cycle in these zones and resulting in outbreaks. This is a serious issue that needs to be addressed [11-14]. African primate populations have not experienced significant loss, in contrast with the Americas, where there have been losses in some primate populations [13-15].

In Asia, other non-human primates could be potential hosts in an emergent YFV outbreak in this region. Nevertheless, Asia remains free of autochthonous YFV, and this behaviour was studied in a theoretical model of transmission risk based on assumptions attributed to vector availability, non-human primates' susceptibility, and other ecological predictors in Asia. This model found that Malaysia, Singapore, Indonesia, Brunei, and portions of southern India were considered high-risk zones for YFV. Still, the percentage of suitability was lower than that of endemic YFV regions. Four primate species were distributed entirely in these zones, and 44 other species were included. Thus, Asia could be a potential scenario for emerging YFV if any condition could be available to introduce in this region [12, 13].

Within urban environments, the *Aedes aegypti* mosquito is the critical carrier, thriving in still water found in human-made receptacles like old tyres, flower pots, and cisterns [16]. In rural zones, the virus is propagated by other mosquito species that reproduce in natural reservoirs such as tree holes, leaf axils, and ground puddles [17]. In South America, yellow fever is found primarily in forested areas of the Amazon Basin. The virus is transmitted by mosquitoes that breed in tree holes and other natural containers [18]. The geographical arrangement of yellow fever is influenced by a confluence of factors, including mosquito vectors, non-human primate hosts, and vulnerable human populations. Environmental elements such as temperature, precipitation, and altitude significantly influence the disease's distribution. Yellow fever correlates with altitude, precipitation, variety of non-human primate hosts, and temperature [20]. This information is crucial for understanding the distribution of yellow fever, which predominantly occurs in tropical and subtropical regions within Africa and South America [21]. The virus is propagated in these areas through mosquitoes that breed in urban and rural settings.

Yellow fever in non-human primates and vectors

Non-human primates related to the YFV outbreaks YFV had origin in Africa in a sylvatic cycle that involved 11 non-human primates (NHP) genera: baboons (*Papio spp*.), colobus monkeys (*Colobus spp*.) green and vervet monkeys (*Cercopithecus spp*.) mangabeys (*Cercocebus spp*.) chimpanzees (*Pan troglodites*), bush babies (*Galago spp*.) and others: *Erythrocebus*, *Otolemur*, *Perodicticus* and *Pilocolobus* [11, 12].

In the Americas, YFV outbreaks were related to howler monkeys (Alouatta spp.), squirrel monkeys (*Saimiri spp*.), spider monkeys (*Ateles spp*.) and owl monkeys (*Aotus spp*.) In the latest YFV outbreaks in South America (2016-2019), urban titis (*Callithrix*) were identified in São Paulo, Brazil; in addition to these NHP reports, other specimens of genera *Brachyteles*, *Callicebus*, *Leontopithecus*, and *Sapajus*, all of them inhabiting the "Mata Atlantica" (Atlantic forest of Brazil) were identified [11, 12].

In contrast with Africa, where NHPs are adapted to the endemic of YFV, in the Americas, YFV was introduced in the black slave trade, which, coming from Africa, infected and developed spreads in the New World 400 years ago. In that scenario, some genera of NHP are susceptible and well-adapted to YFV infection, and others develop diseases related to YFV. One study with neotropical primates naturally infected with YFV showed that it could be high susceptibility to YFV infection, but the development of YFV-induced lesions could be different between each genus; thus, severe hepatic lesions were described in *Alouatta sp*. (howler monkey) in contrast with *Callithrix spp*. (titis or common marmosets) who did not present hepatic lesions, it suggests that primates like *Callithrix spp*. Could be efficient as a host in these regions of the Americas [14, 15]. Unlike the NHP in Africa, NHP in the Americas is susceptible to YFV developing clinical signs and outbreaks in these groups; in this way, NHP YFV outbreaks are expected new outbreaks of YFV in humans.

In this scenario, the NHP related to YFV differs between regions, and the susceptibility and immune response differ. This could be one of the reasons for understanding the specific distribution along the time of YFV in contrast with other Flavivirus transmissions by vectors that developed epidemic outbreaks in the last decades.

Vectors related and its role in YFV transmission

The forest-dwelling mosquitoes involved in the

sylvatic cycle in Africa are *Aedes* species, mainly *Ae. africanus* (other *Ae* species: *bromeliae*, *taylori*, *furcifer, luteocephalus*, *metallicus*, *opok*, *vittatus* and *simponi* complex) [12, 22, 23]. In the Americas, this role was described on *Haemagogus* (*leucocelaenus, albomaculatus*, *spegazzini*, *janthinomys*) and *Sabethes* (*chloropterus*, *albipivus*, *glaucodaemon*, *soperi* and *cyaneus*) species [12, 22, 23]. In the urban cycle, the participation of Ae aegypti is described mainly.

YFV transmission is first made between mosquitoes by the transovarial transmission process (TOT). This step is relevant to maintain the cycle of transmission of YFV and, after that, transmission from mosquitoes to NHP in the sylvatic cycle. In Africa, during the rainy season, there is a "zone of emergence" if transmissions include humans; YFV transmission is amplified and sustainable to other humans by *Ae aegypti* in urban zones. In the Americas, humans are the eventual host who allows sustainable transmission in urban zones by *Ae. aegypti*, but in this case, without passing through a "zone of emergence". Thus, the sylvatic cycle is affected by mosquitoes and NHP in both scenarios (Africa and South America); mosquitoes must generate TOT between them to continue the YFV transmission cycle. In Africa, only the "zone of emergence" of the Savannah cycle consists of the cycle of transmission of YFV from sylvatic vectors to humans, which could develop an urban transmission cycle by *Ae. aegypti* vector (Figure 1) [10-13]. A viraemic individual initially infected in a jungle or Savannah environment typically introduces the virus into urban settings. It is essential to recognise that individuals infected with the yellow fever virus become contagious to mosquitoes shortly before the onset of fever and for up to five days after its onset [24]. This signifies that within this timeframe, an infected person can transmit the virus to mosquitoes that bite them, which can further transmit it to other individuals.

About *Ae. aegypti* is the most relevant vector studied worldwide as a universal vector, which is also related to the transmission of other viruses of the Flaviviridae family, such as DENV, ZIKV, and EJV, that developed epidemics in the last decades.

Aedes spp. African subspecies in the beginning breed in plant axils and tree holes and are zoophilic; in contrast, the urban subspecies are domestic. With the changes in the populations of mosquitoes, it is theorised that *Aedes* mosquitoes evolved from tree holes to container breeding in human settings. It is described that the behaviour

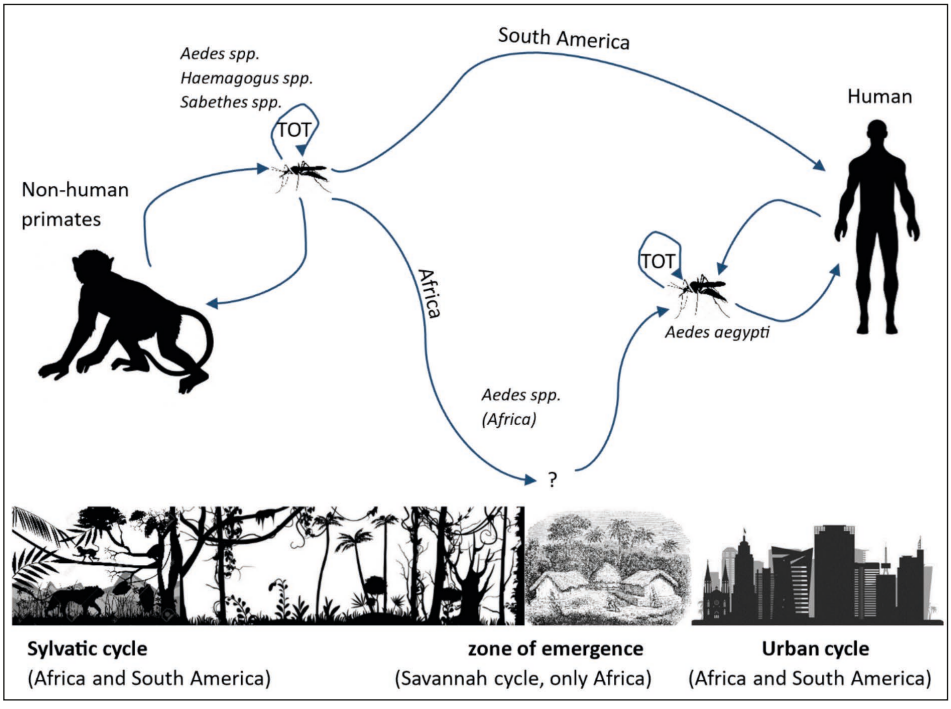

Figure 1
Transmission cycle of yellow fever virus.

of this vector could change in decades; thus, in the Indian Ocean region, the interchange between endophilic *Ae. aegypti* and exophilic *Ae. albopictus* reversed their typical habitat (to exophilic and endophilic, respectively) over decades; when the outbreak of Chikungunya virus (CHIK), this mutant was adapted to this *Ae. albopictus*.

Another scenario is the Caribbean; the last reported YFV outbreak was in 1908 and was related to the *Ae. Aegypti* vector as the primary vector; after that, the following outbreaks related to this vector were due to other viruses such as DENV and ZIKV in the last decades; one report in *Ae aegypti* populations from the Caribbean zone was analysed with five YFV genotypes (Bolivia, Ghana, Nigeria, Sudan, and Uganda) where showed good susceptibility and higher transmission success (mainly with Uganda and Bolivia strains), these finding suggest vector transmission in this region is plausible, nevertheless, at current did not report any re-emergence in the zone [25-27].

It is known that mosquitoes need clean water in household containers, but in some places in Africa, subpopulations adapted to breeding in non-clear water [28]. In addition, the *Aedes* mosquito is disseminated worldwide. Still, the activity depends on the altitude, temperature (hot seasons increase the index of mosquitoes), rains, and different behaviours related to the change in the urbanisation of rural zones. Thus, climatic change probably plays a role in facilitating some determinants to help the spread of vectors, increase the transovarial transmission between vectors, and other similar cases.

EPIDEMIOLOGY

Yellow fever is a vector-borne disease with pandemic potential in current historical zones [5, 29, 30]. Two types of outbreaks and behaviours are well-defined: YFV in Africa and the Americas. In Africa, where YFV originated, the vectors and NHP are susceptible and tolerable to the immune response to YFV. It is possible that populations in the last decades showed less mortality in comparison to previous outbreaks due to the immune response at the people level developed by the persistent exposure to these vectors infected in these zones; for that reason, only in Africa are there the Savannah cycles, in emergent zones when is expected the YFV transmission [4, 8, 10].

In the Americas region, urban cycle development is due to the eventual infection of humans and the transmission by *Aedes* species. In this region, the NHP usually had an increased immune response to YFV. Therefore, epizootic outbreaks are expected to occur in outbreaks in contrast with African settings. In both scenarios, the implementation of the YFV vaccine was a relevant factor in immune tolerance at the people level. In both scenarios, it is relevant to discuss the role of the vector as a reservoir by the transovarial transmission to continue the cycle, the NHP as host in this process, and humans, for the first time, an occasional/casual host involved in this zone [17, 22, 31-33].

In Zika and Dengue, vector adaption, climatic change (warming and precipitation) and prevalence of heterotypic serotype infections were related to these distributions by *Ae. Aegypti*, which has spread worldwide. In YFV, the transition to endemic and epidemic urban YF is due to environmental changes, such as industrialisation and urbanisation, which mainly enhance contacts between sylvatic and urban cycles that could coexist after urbanisation in these areas [32-34].

Historical patterns of yellow fever outbreaks

Yellow fever holds a significant position in human history. Its evolutionary genesis can be traced back to Africa, which likely emerged from interactions between primates, mosquitoes and humans [35]. The virus and its mosquito carrier, *Aedes aegypti*, are thought to have been transported to the western hemisphere and the Americas via slave trade ships from Africa after the initial European exploration in 1492 [36]. The earliest exported disease outbreaks, likely associated with YFV, manifested in the Caribbean's Windward Islands [36]. Notable occurrences transpired in Barbados in 1647 and Guadeloupe in 1648 (Table 1) [37]. Subsequently, a succession of significant outbreaks unfolded in North America. One such devastating event took place in 1793 in Philadelphia, where over 9% of the city's total population perished, prompting even the American government, led by President George Washington, to evacuate the capital [38]. The year 1878 witnessed a devastating epidemic, claiming approximately 20,000 lives across settlements along the Mississippi River Valley and its tributaries. Notably, the final significant outbreak in the United States transpired in 1905, centred in New Orleans (Table 1). During 88 years, New Orleans was significantly affected by yellow

Table 1 - Major yellow fever outbreaks.

Year	*Location*	*Description*	*Cases*	*Deaths*	*Case fatality rates (%)*	*References*
1647	Barbados	An outbreak, possibly yellow fever, hit Bridgetown, Barbados, killing many people.	Unknown	Unknown	Unknown	[48]
1793	Philadelphia, USA	Philadelphia saw a devastating toll, with casualties amounting to several thousand individuals, exceeding nine per cent of the city's entire population. The gravity of the situation forced the American government, including President George Washington, to evacuate the city.	50,000	5,000	10%	[49]
1817-1905	New Orleans, USA	New Orleans marked the location of the final significant outbreak within the United States.	?	41,000	?	[51]
1878	Mississippi River Valley, USA	An epidemic ravaged the settlements situated along the Mississippi River Valley and its tributaries, resulting in a staggering death toll of around 20,000 individuals.	120,000	20,000	17%	[50]
2016	Angola and the Democratic Republic of Congo	Angola experienced its worst yellow fever outbreak in 30 years, with more than 4,000 suspected cases and 376 deaths. The outbreak spread to the Democratic Republic of Congo, where there were more than 2,000 suspected cases and 95 deaths.	6,000	471	7.85%	[52]
2018	Brazil	A substantial yellow fever outbreak unfolded in Brazil, witnessing the confirmation of over 1,500 cases and a tragic toll of 500 fatalities.	1,500	500	33.3%	[53]

fever, with more than 41,000 related deaths between the years 1817 (the first year that reliable statistics are available) and 1905 (the Crescent City's last epidemic) (Figure 2) (https://nolacityarchives.org/2024/03/05/yellow-fever-deaths/). Europe also experienced yellow fever outbreaks in the 19th century, primarily linked to the arrival of sailing vessels from the Caribbean, often docking in Atlantic ports [39]. In Barcelona, Spain, outbreaks occurred in 1803, 1821, and 1870, with the latter resulting in 1,235 recorded fatalities among approximately 12,000 cases [40]. Smaller outbreaks extended to locales like Saint-Nazaire in France and Swansea in Wales, aligning with the arrivals of vessels carrying the mosquito vectors. Major yellow fever outbreaks have severely impacted North America and Europe [41]. However, since the considerable outbreak in New Orleans in 1905, the United States has managed to rein in yellow fever through vaccination campaigns and meticulous mosquito control measures [42]. Major outbreaks occurred in North America and Europe between the 18th and 20th centuries with devastating consequences [43]. In recent times, instances of yellow fever outbreaks have predominantly surfaced across Africa and South America. Angola confronted its most severe yellow fever outbreak in three decades in 2016, marked by over 4,000 suspected cases and 376 fatalities [44]. This outbreak subsequently extended its impact to the Democratic Republic of Congo, recording over 2,000 suspected cases and 95 deaths [45]. In 2018, Brazil faced a significant yellow fever outbreak, witnessing more than 1,500 confirmed cases and a

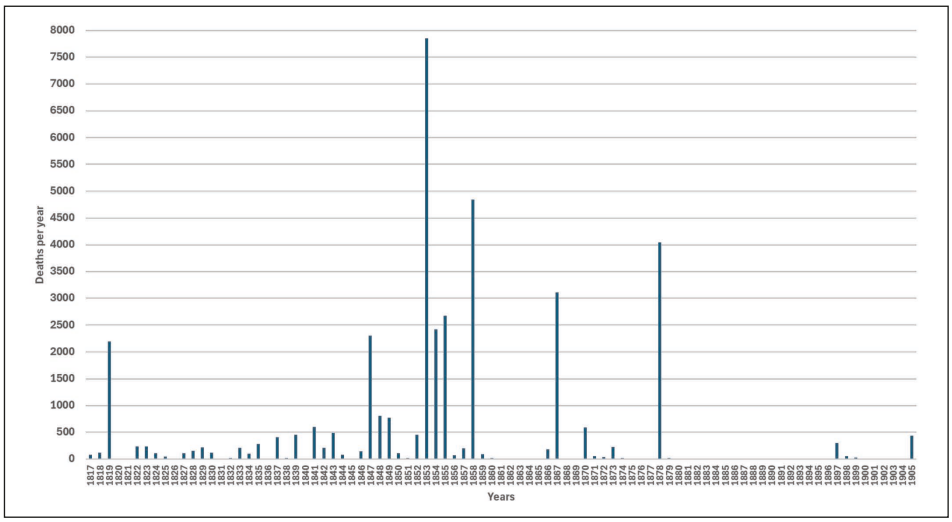

Figure 2
Deaths by yellow fever in New Orleans, USA, 1817-1905.

toll of 500 deaths [46]. Addressing these outbreaks has entailed a multifaceted approach encompassing vaccination initiatives, strategies to curb mosquito populations, and widespread public awareness campaigns about the disease. The World Health Organization (WHO) has issued recommendations advocating vaccination for individuals residing in or travelling to regions where yellow fever is endemic [47]. A solitary administration of the yellow fever vaccine guarantees lifelong protection against the ailment. Controlling these outbreaks includes vaccination campaigns, mosquito control measures, and public education about the disease. Major yellow fever outbreaks are highlighted in Table 1.

VIROLOGY AND GENETIC VARIABILITY

Viral structure and genome

YFV is classified as a single-stranded, positive-sense RNA virus and is a member of the Flavivirus genus within the Flaviviridae family [54]. The virus adopts a spherical morphology and exhibits approximately 40-50 nm diameter. Its viral envelope is derived from the host cell membrane and comprises two vital glycoproteins, namely envelope (E) and membrane (M) proteins [55]. These glycoproteins hold responsibility for instigating viral attachment and facilitating the virus's entry into host cells [56]. The genetic blueprint of YFV is about 11 kb long and codes for a singular polyprotein that is subsequently cleaved by both viral and host proteases [57]. This cleavage gives rise to three structural proteins (C, M/M, and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). The structural proteins assemble to form the virion particle, while the non-structural proteins contribute to viral replication processes and evasion of host immune responses [58]. The C protein is the viral capsid protein, which envelops the viral RNA genome. The pre/M protein serves as a precursor, undergoing cleavage to become the M protein during the maturation of the virion [59]. The E protein is pivotal in mediating viral attachment to host cells and facilitating the fusion of the viral envelope with the host cell membrane during entry. Among the non-structural proteins, the NS1 protein functions as a glycoprotein, participating in viral replication and evading immune responses. The NS2A and NS2B proteins cooperate in RNA replication and the assembly of virions [60]. The NS3 protein showcases protease, helicase, and NTPase activities central to viral replication. Additionally, the NS4A and NS4B proteins take on roles in RNA replication and modulation of host immune reactions [61]. Lastly, the NS5 protein is responsible for the viral RNA synthesis due to their possessing RNA-dependent RNA polymerase and methyl-transferase activities.

Genetic variability

Like other RNA viruses, YFV showcases a marked genetic diversity that stems from the error-prone

nature of its RNA-dependent RNA polymerase [62]. This inherent variability gives rise to novel viral strains characterized by modified antigenic attributes, levels of virulence, and transmissibility. Scientific investigations have substantiated that YFV demonstrates genetic divergence in multiple protein components, including the envelope (E) protein [63]. This protein is critical in viral attachment and facilitating the virus's entry into host cells. Genetic alterations in the E protein can influence the virus's capacity to evade the host's immune response, potentially impacting in the immunity due to vaccine [64]. In contrast, variability in non-structural proteins such as NS1, NS3, and NS5 can affect the virus's ability to replicate and evade host immune defenses [65]. These factors can influence the immune response and spread of YFV.

PATHOGENESIS AND IMMUNE RESPONSE

Immune response to YFV in host

Evidence about immune response in human in wild-type yellow fever is limited and reported in severe cases of YFV. In comparison with the non-severe cases, severe cases have increase of chemoattractant cytokines MCP-1 and IP-10 and pro-inflammatory cytokines TNF-α, IL-6 and IL-1 [66] In liver affected of severe cases were found high T cell infiltration and cell death with elevated cytokine expression at liver cells and endothelial cells. This finding suggest that immune response in severe cases of YF infection are related with increase of pro-inflammatory response innate and cellular, with the insufficient neutralizing antibody response. This could be explained in an ineffective control of YFV replication in the liver but a strongly cytolytic response that develop inflammation, damage and progression to severe disease [66-68]. Severe and hemorrhagic YF could compromise all systems, where the imbalance of the immune response with the expression of pro and anti-inflammatory cytokines developed in the tissue damage and increase destruction of resident cells in several organs such as liver, heart and kidney [68-70].

At lung level was shown in people with severe YF in comparison with people without YF the increase of the higher expression of E-selectin, P-selectin both involved in the cell migration and develop of inflammatory infiltrate; ICAM-1 and VCAM-1 both involved in the reinforce of tissue transmigration signaling; and other cytokines as TNF-α, IFN-γ which participate in the process of cell injury and viral clearance; IL-4 and TGF-β which acting in synergism in the tissue regeneration and breakdown; thus IL-4, IL-10, and IL-13 develop anti-inflammatory effect and tissue repair. According to these findings, the activation of the endothelium increases the inflammatory response with the induction of adhesion molecules and cytokines that develop in the inflammatory process in the lung parenchyma with fatal outcome of the disease [70].

At myocardial level, there was no evidence of YF-antigens or viral particles within cardiomyocytes, that suggest absence of direct YF tropism to the cardiac cells, but the myocardial injury was related to the increase inflammatory cellular infiltrate (mainly by macrophages) located in the perivascular interstitium and presence of YF antigens within endothelial cells that suggest that direct YFV invasion in endothelial cells is a main mechanism of endothelial and myocardial damage due that activation of the inflammatory response in that tissue [71].

Thus, it was described high levels of multiple cytokines in the myocardial tissue of YF cases, one of them with statistical difference in YF than sepsis control cases were CXCL-10 chemokine (it is involved in the recruitment of lymphocytes, macrophages and NK cells). Also were described in YF cases frequent endothelial abnormalities (endothelial swelling, fibrinoid necrosis) with the increase of biomarkers associated with endothelial damage related with worse prognosis in sepsis patients (angiopoietin-2, endothelin-1, syndecan-1, VCAM-1 and PAI-1) [72-75]. Angiopoietin-2 is a vascular growth factor related with capillary leakage; endothelin-1 actives pathway of IL-1, IL-6 and TNF-α; and PAI-1 is a fibrinolysis inhibitor involved in the YF-coagulopathy and subsequent hemorrhages due to role in the disseminated intravascular coagulation. In contrast to other infectious diseases, evidence of arterial thrombosis or microthrombi were rarely seen [71-125].

Thus, the progression of diseases due to YFV in severe cases is related to two compounds: hepatic injury by YFV infiltrate with exacerbated local immune response and endothelial infiltration with exacerbation of immune response at this level in non-hepatic systems, which developed in damage and organic failure.

In 1951, Max Theiler of the Rockefeller Foundation received the Nobel Prize in Physiology or Medicine for developing an effective yellow fever vaccine-first reported in the JEM 70 years earlier. This remains the only Nobel Prize awarded for a virus vaccine. Recently released Nobel archives reveal how advancements in the yellow fever vaccine were assessed over 50 years ago, leading to Theiler's recognition [126].

Immune response between YFV and vectors

At mosquito level, there are some mechanism of immune response potentially involved in *Ae. Aegypti* mosquitoes as the Thioester-containing proteins (TEPs), mainly TEP1, which was involved in the reduction of viral load when was overexpressed in contrast to TEP3; this suggest TEP1 could play a role in viral infection [76]. The Toll pathway by knockdown of the transcription factor Rel1 to attenuates the induction of Spaetzle 1A and Serpin-27A in the mosquito [77]. DENV infection of *Ae. aegypti* activates the transcription of Toll pathway-associated factors and putative effectors (Späetzle, Toll, Rel1A, and multiple AMPs) [78-80]. The Toll pathway begins to exert antiviral effects as early as 3 days after DENV infection, is able to protect against DENV infection in multiple serotypes, and remains active in different *Ae. aegypti* strains [81]. Furthermore, the symbiotic *Wolbachia* in mosquitoes can inhibit DENV replication by inducing mosquitoes to produce ROS to activate the Toll pathway and subsequently produce AMPs and DEFs [82]. The transcription of Dif, a Toll pathway transcription factor, is induced early in the infection of *Ae. aegypti* with Sindbis virus (SINV).

The JAK/STAT pathway is also important in immune response against DENV infection; thus the viral replication in the mosquito midgut was increased significantly with the inhibition by RNAi-mediated silencing of transmembrane proteins or JAK immediate homologues, this effect was reduced with the silenced of the inhibitor of STAT activated [83].

RNAi pathway involve a process of production specific small RNA molecules with different characteristics: endogenous small interfering RNAs (siRNA 18-24 nt), microRNAs (miRNAs, 18-24 nt), and Piwi protein-interacting RNAs (piRNAs); siRNAs are the main molecules involved in the antiviral response [84, 85]. In YFV, siARN pathway is mainly triggered by Dicer2, R2D2, and Ago2, this last was involved in the inhibition of the iRNA pathway. Thus, siRNA pathway inhibits the YFV and DENV2 replication, and replication increase upon the knockdown or silencing of siRNA pathway-related genes [86-88]. Thus, siRNA modules infection pathogenesis due to human flavivirus in A. aegypti.

Immune response to yellow fever vaccination

The yellow fever vaccine (YF-17D) is a live attenuated vaccine that triggers an immune response in the body to protect against future infection with the yellow fever virus. It is one of the most effective vaccines ever made in more of 80 years [69, 89]. This has two substrains: 17DD (used in South America) and 17D-204 (used in most of the rest of world) both were developed in embryonated chicken eggs The immune mechanism of immune response and attenuation of YFV there are not clear. But it is probed the good performance in the immune response after vaccination [69].

Humoral immunity was a primary protective element in previous exposed individuals, and a single vaccine could offer protection to global strains of YFV by neutralizing antibodies [68]. Over 90% of 17D immunized individuals developed antibodies, and neutralizing antibodies were detected within two weeks after vaccination, since the sixth day following vaccination with evidence of neutralizing responses for up to 60 years after vaccination [90-95].

Innate immune response way after vaccination in plasma described interferon IFN-γ levels increased after two weeks of 17D vaccination. Re-stimulation of innate immune cell cultures of natural killer cells, neutrophils, and monocytes from 17D-vaccinated humans with YF antigen results in the increase of IFN-γ, IL-1b, IL-12, TNF-α, and IL-10 with the concomitant decrease of TNF-α, IL-10 and IL-4 [68]. After vaccination virus is detected by innate immune receptor, including RIG-I (retinoic acid-inducible gene I) and MDA5 (melanoma differentiation-associated gene 5), Toll-like receptors: TLR2, TLR7, TLR8 and TLR9; this last pathway stimulates a complex and robust antiviral response with TH1 and TH2 cell profile, and other ways to B cell response [69].

It is reported the earliest induction of cytokines by interactions with dendritic cells (DC) with multiple interactions with TLRs with a consequence

downstream T cell response. However, 17D antigens are processed and presented by DCs which are most likely involved in eliciting downstream T cell responses. There is insufficient evidence about the understanding of the immune cellular response to YFV in humans, this topic is still uncertain. There is a strong immune response to 17D from T cells CD4+ and CD8+ within the first and second week after immunization, respectively; differentiated memory cells could maintain immune response for a long period of time (25 years) [68].
17D-specific CD4+ T cells develop TH1 and Th2 cytokines. TH1 T cells promote CD8+ responses due to T follicular helper (Tfh) cells (subtype of CD4+ T cell) which promote healthy B cell germinal centers, while TH2 cytokines promote B cell and neutralizing antibody response to virus. 17D-specific CD8+ T cells after re-stimulation developed a complex and multiple pro-inflammatory cytokine response, with a suggested capacity of degranulation and cytolytic effect [68, 69]. Evidence about exposure to 17D booster in comparison with individuals with only one vaccination, it did not find higher levels of memory T cell as was expected after re-exposure [69].

STRATEGIES OF PREVENTION AND CONTROL YFV SPREAD

Vector control
Vector control efforts in YFV could be limited because the dimension of the problem has been involved not only to urban vectors, but vector outdoor in the forest where mechanism to reduce populations of mosquitoes are difficult to manage despite the different interventions at local or inter-institutional level as Global Vector Control Response (GVCR) by the WHO [96]. There are common mechanisms of vector control in *Aedes spp*. in some regions of Africa due to the multiple risk of transmission of other virus (DENV, ZIKV, CHV, between others); nevertheless, insecticides mechanisms or similar are reduced to control of spread and dissemination of the forest vectors [96, 97]. This mechanism are effective in the reduction of urban mosquitos' populations, but are insufficient to cut the YFV transmission chain [22, 96, 97]. At vector level biological alternatives could be emergent options in some regions identified, for example, there is evidence on vector control based on *Wolbachia* infections in mosquitoes infected by DENV. Additionally, this infection increases the mosquito resistance to DENV, CHIKV, and YFV infection [98]. As before was mentioned the immune response of *Wolbachia* at level of innate immune response, could induce and activation of the Toll pathway that interact with the viral immune response in the mosquito, in addition to the control vector populations [76].
Nonetheless, reliable efforts in Yellow fever to control and prevention of outbreaks and worse scenarios are reduced to the most effective mechanism: YFV immunization, follow of the common behaviors as continuing prevention of bites mosquitoes by repellents, or coverage clothes, which are less effective in hyper-endemic zones.

Vaccination strategies
YF immunization have been the best and effective method in YF-prevention since their creation and use. YF vaccine is one of the aged and effective vaccines again a vector-borne virus, made and maintained around the world with high effectiveness and safety along decades for long periods in users [69]. Other characteristics that position it are a single dose, and lifelong protection in individuals immunized, and long experience in the use. Nevertheless, the good characteristics of vaccine, the efforts to cover a massive immunization in endemic regions is still a challenge (typically recommended by at least 80% of the eligible population) of high-risk and endemic regions [69, 99, 100]. One of the recommendations is the vaccination since infants at 9-12 months and synchronizing it with the administration of measles vaccine in these regions [101].
The long action of YF vaccine was shown in specific series, nonetheless, the recommendation of additional reinforce in endemic zones is a practice recommended. Several analyses about the long-term immunity was made and showed good outcomes of protection in travelers, but in people from endemic regions where they are in continuing exposure is different, in Brazil was observed lower seroprotection rates in endemic regions but in this analysis was used a higher cut-off for seroprotection [99]. Also, in people living with HIV and children (younger than 2 years) booster doses might be an alternative because lower rates of vaccines were seroprotected 10 or more years post-vaccination [102, 103]. A recommended practice involves administering the yellow fever vaccine to

Table 2 - Vaccines that WHO currently prequalifies against yellow fever.

Vaccine	*Manufacturer*	*Type*	*References*
YF-VAX®	Sanofi Pasteur Limited	Live, attenuated	[104]
Stamaril®	Sanofi Pasteur	Live, attenuated	[105]
Yellow Fever Vaccine (Bio-Manguinhos)	Bio-Manguinhos/Fiocruz	Live, attenuated	[106]
Yellow Fever Vaccine (Institut Pasteur)	Institut Pasteur de Dakar	Live, attenuated	[107]

infants at 9-12 months and synchronizing it with the administration of the measles vaccine, which is particularly pertinent in regions where yellow fever prevails [101-125]. WHO-qualified vaccines for yellow fever are listed in Table 2.

The standard yellow fever vaccine dose provides long-lasting immunity, but using fractional or half doses can extend available resources in cases of limited supply. Research has shown that smaller doses (even as low as one-fifth of a total dose) can still provide adequate protection for a certain period, although possibly shorter than a total dose. The ring vaccination strategy is also worth mentioning, focusing on vaccinating people in close contact with an infected individual and their immediate contacts. It creates a "ring" of immunised people around the infected person, which helps to contain the spread of the disease [121].

Diagnosis and surveillance

YFV surveillance is necessary in endemic regions as a One Health mechanism, where the vector control would be integrated for several other endemic diseases (within acute febrile jaundiced conditions) and the surveillance would be made at vector level, at zoonotic level, and human level; the follow in the multiple actors of the transmission chain could predict outbreak emergency and take actions to reduce they develop in the zone. Surveillance in YFV needs are active, or sentinel depends on the type of populations monitoring. Thus, current information about spreads in vector, NHP and humans could predict some behaviors at local or regional level some seasons, and updated the previous information.

Availability and effectiveness of fast processing test could warranty the optimal surveillance in the region. Laboratory diagnosis of yellow fever typically involves the examination of serum samples to detect virus-specific IgM and neutralizing antibodies [5, 108, 109]. Sometimes, the virus can be traced in blood samples obtained early during the illness. The fundamental tests pivotal for confirming yellow fever in a laboratory setting amid an

Table 3 - Diagnostic methods for detecting yellow fever.

Method	*Description*	*References*
Serological testing	Testing serum to detect virus-specific IgM and neutralizing antibodies using methods such as ELISA (Enzyme-Linked Immunosorbent Assay). It will be used as a population screening and surveillance in humans and NHP.	[109]
Molecular diagnostics	Viral RNA can be detected in serum samples during the first ten days since the onset of symptoms (viraemic phase) or even longer than ten days in severe cases, by molecular methods such as conventional (end-point) or real-time reverse transcription polymerase chain reaction (RT-PCR).	[110]
Viral isolation	Viral isolation can be performed through intracerebral inoculation in mice or cell culture (using Vero or C6/36 cells; may be performed under BSL2 containment). Because of its complexity, this methodology is rarely used as a first-line diagnostic tool, but, is useful in specific basic research models.	[111]
Histopathology	Histopathological examination of liver biopsy specimens can reveal characteristic changes in the liver, including middle-zone necrosis, Councilman bodies, and steatosis.	[112]
Immunohistochemistry	Immunohistochemical staining can detect yellow fever virus antigens in formalin-fixed, paraffin-embedded liver tissue.	[113]

outbreak encompass the deployment of enzyme-linked immunosorbent assay (ELISA) to gauge yellow fever virus IgM [108]. Different diagnostics methods for detecting yellow fever are listed in Table 3.

ROLE OF GLOBAL HEALTH ORGANIZATIONS IN YELLOW FEVER MANAGEMENT

Global health organizations play a crucial role in the management of yellow fever. The WHO is one of the key organizations involved in the global effort to control and prevent yellow fever outbreaks [114]. The WHO works with countries to strengthen their capacity to prevent, detect, and respond to yellow fever outbreaks [115]. This includes supporting vaccination campaigns, improving laboratory capacity, and enhancing surveillance systems. Also, it provides technical guidance on yellow fever prevention and control, including recommendations on vaccination, mosquito control measures, and outbreak response, and works with partners to ensure availability of yellow fever vaccines in countries with risk of outbreaks [116, 117]. In 2016, the WHO introduced the Eliminate Yellow Fever Epidemics (EYE) strategy, a comprehensive global initiative aimed at (1) protection of at risk populations, (2) preventing cross-border transmission, and (3) swiftly containing outbreaks [118]. In this case, the measures recommended depends on the risk level (a. high risk, b. moderate risk, and c. not considered at risk but potential for YF transmission). This risk level considered countries with background of outbreaks, mainly in South-America and Africa. Thus, in high risk zones the protection strategies are focused on the immunization and immunity monitoring at population level; in moderate risk zones are recommended sentinel surveillance, and it focused on fast laboratory testing, zones not considered at current risk is recommended the improvement in health services and screening/diagnostic services [119]. The inclusion of other international actors is a relevant condition to warranty more accessibility and improve in health services, immunization coverages and develop of technologies in health/One Health to improve the YF control, as the United Nations Children's Fund (UNICEF) or the International Federation of Red Cross and Red Crescent Societies (IFRC) [118-120].

CONCLUSIONS

In conclusion, in contrast with other pandemic virus-borne diseases, yellow fever still maintains specific dissemination in endemic areas in the world, especially in countries lacking appropriate vaccination in risk areas, as is the case of Venezuela and probably in other countries of Latin America and Africa [121-125]. Nonetheless, multilevel conditions could develop during a potential pandemic worldwide. For these reasons, it is relevant to reinforce the measures of prevention and control in these specific areas and immunization monitoring at the population level in high-risk zones. Despite the *Aedes* spp. mosquito, as one of the main vectors in YF outbreaks, has not triggered worldwide dissemination like other viruses transmitted by this vector (DENV, CHIK, ZIKV), probably due to the interaction and role of YF in this vector as a reservoir and the interaction with other NHP.

Another relevant condition is the early diagnostic and algorithm of response at the beginning of outbreaks, mainly based on a surveillance sentinel and differential algorithm with other similar endemic diseases (acute febrile jaundiced diseases). It is pending in the research agenda effective strategies in vector control and management of wild host in the jungle scenarios.

The WHO has introduced the Global Vector Control Response, another important cornerstone initiative that promotes vector control efficiency, affordability, ecological harmony, and long-term sustainability. In the grand scheme, the path forward hinges upon a comprehensive approach; forecasting anticipated obstacles and proactive scientific exploration.

Conflict of interest
None

Funding
None

Acknowledgement
Dr Rodriguez-Morales would like to dedicate this publication to the memory of Prof. Eloy Maceira (1945-2024), from Venezuela, a great mentor and human being who passed away in Caracas, November 2024, R.I.P.

This article has been registered in the Research Proposal Registration of the Coordination of Sci-

entific Integrity and Surveillance of Universidad Cientifica del Sur, Lima, Peru, under the number PI-50-2024-0765.

REFERENCES

[1] McMichael AJ. Environmental and social influences on emerging infectious diseases: past, present and future. *Philos Trans R Soc Lond B Biol Sci*. 2004; 359(1447): 1049-1058.
[2] Musso D, Rodriguez-Morales AJ, Levi JE, Cao-Lormeau VM, Gubler DJ. Unexpected outbreaks of arbovirus infections: lessons learned from the Pacific and tropical America. *Lancet Infect Dis*. 2018; 18(11): e355-e361.
[3] Gardner, Christina L, Ryman KD. Yellow fever: a reemerging threat. *Clin Lab Med*. 2010; 30(1): 237-60.
[4] Hanley, Kathryn A, Thomas P, et al. Fever versus fever: the role of host and vector susceptibility and interspecific competition in shaping the current and future distributions of the sylvatic cycles of dengue virus and yellow fever virus. *Infect Genet Evol*. 2013; 19: 292-311.
[5] Pan American Health Organization. Topics: Yellow fever. Available at: https://www.paho.org/en/topics/yellow-fever. [Accessed 16 November 2024].
[6] Possas C, Lourenço-de-Oliveira R, Tauil PL, et al. Yellow fever outbreak in Brazil: the puzzle of rapid viral spread and challenges for immunisation. *Mem Inst Oswaldo Cruz*. 2018; 113(10): e180278.
[7] Lacerda, AB, del Castillo Saad L, Ikefuti PV, et al. Diffusion of sylvatic yellow fever in the state of São Paulo, Brazil. *Sci Rep* 2021; 11: 16277.
[8] Hussain-Alkhateeb L, Rivera Ramírez T, Kroeger A, Gozzer E, Runge-Ranzinger S. Early warning systems (EWSs) for chikungunya, dengue, malaria, yellow fever, and Zika outbreaks: What is the evidence? A scoping review. *PLoS Negl Trop Dis*. 2021; 15(9): e0009686.
[9] National Academies of Sciences, Engineering, and Medicine. Global health impacts of vector-borne diseases: workshop summary. 2016. Available at: https://nap.nationalacademies.org/catalog/21792/global-health-impacts-of-vector-borne-diseases-workshop-summary. Accessed 16 November 2024.
[10] Abdullahi IN, Anka AU, Emeribe AU, et al. The interplay between environmental factors, vector competence and vaccine immunodynamics as possible explanation of the 2019 yellow fever re-emergence in Nigeria. *New Microbes New Infect*. 2021; 41: 100858.
[11] Aliaga-Samanez A, Real R, Segura M, Marfil-Daza C, Olivero J. Yellow fever surveillance suggests zoonotic and anthroponotic emergent potential. *Commun Biol*. 2022; 5(1): 530.
[12] Valentine MJ, Murdock CC, Kelly PJ. Sylvatic cycles of arboviruses in non-human primates. *Parasit Vectors*. 2019; 12(1): 463.
[13] Bicca-Marques, J.C., Rabelo, R.M., de Almeida, M.A.B. et al. The Risks of Yellow Fever to Asian Primates. *Int J Primatol*. 2022; 43: 74-91.
[14] Mares-Guia MAMM, Horta MA, Romano A, et al. Yellow fever epizootics in non-human primates, Southeast and Northeast Brazil (2017 and 2018). *Parasit Vectors*. 2020; 13(1): 90.
[15] Santos DOD, de Oliveira AR, de Lucena FP, et al. Histopathologic Patterns and Susceptibility of Neotropical Primates Naturally Infected With Yellow Fever Virus. *Vet Pathol*. 2020; 57(5): 681-686.
[16] Reinhold JM, Lazzari CR, Lahondère C. Effects of the Environmental Temperature on Aedes aegypti and Aedes albopictus Mosquitoes: A Review. *Insects*. 2018; 9(4): 158.
[17] McGregor BL, Connelly CR. A Review of the Control of Aedes aegypti (Diptera: Culicidae) in the Continental United States. *J Med Entomol*. 2021; 58(1): 10-25.
[18] Powell JR, Tabachnick WJ. History of domestication and spread of Aedes aegypti--a review. *Mem Inst Oswaldo Cruz*. 2013; 108 (Suppl 1): 11-7.
[19] Beck AS, Barrett AD. Current status and future prospects of yellow fever vaccines. *Expert Rev Vaccines*. 2015; 14(11): 1479-92.
[20] Jácome R, Carrasco-Hernández R, Campillo-Balderas JA, et al. A yellow flag on the horizon: The looming threat of yellow fever to North America. *Int J Infect Dis*. 2019; 87: 143-150.
[21] Cathey JT, Marr JS. Yellow fever, Asia and the East African slave trade. *Trans R Soc Trop Med Hyg*. 2014; 108(5): 252-257.
[22] Hanley KA, Monath TP, Weaver SC, Rossi SL, Richman RL, Vasilakis N. Fever versus fever: the role of host and vector susceptibility and interspecific competition in shaping the current and future distributions of the sylvatic cycles of dengue virus and yellow fever virus. *Infect Genet Evol*. 2013; 19: 292-311.
[23] Vasilakis N, Weaver SC. Flavivirus transmission focusing on Zika. *Curr Opin Virol*. 2017; 22: 30-35.
[24] Johansson MA, Arana-Vizcarrondo N, Biggerstaff BJ, Gallagher N, Marano N, Staples JE. Assessing the risk of international spread of yellow fever virus: a mathematical analysis of an urban outbreak in Asuncion, 2008. *Am J Trop Med Hyg*. 2012; 86(2): 349.
[25] Gabiane G, Bohers C, Mousson L, et al. Evaluating vector competence for Yellow fever in the Caribbean. *Nat Commun*. 2024; 15(1): 1236.
[26] 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.
[27] Amraoui F, Pain A, Piorkowski G, et al. Experimental adaptation of the yellow fever virus to the mosquito Aedes albopictus and potential risk of urban epidemics in Brazil, South America. *Sci Rep*. 2018; 8(1): 14337.
[28] Kuno G. Mechanisms of yellow fever transmission:

gleaning the overlooked records of importance and identifying problems, puzzles, serious issues, surprises and research questions. *Viruses*. 2024; 16(1): 84.
[29] Nwaiwu AU, Musekiwa A, Tamuzi JL, Sambala EZ, Nyasulu PS. The incidence and mortality of yellow fever in Africa: a systematic review and meta-analysis. *BMC Infect Dis*. 2021; 21: 1-11.
[30] Rosser JI, Nielsen-Saines K, Saad E, Fuller T. Reemergence of yellow fever virus in southeastern Brazil, 2017–2018: What sparked the spread? *PLoS Negl Trop Dis*. 2022; 16(2): e0010133.
[31] Hamrick PN, Aldighieri S, Machado G, et al. Geographic patterns and environmental factors associated with human yellow fever presence in the Americas. *PLoS Negl Trop Dis*. 2017; 11(9): e0005897.
[32] Walsh JF, Molyneux DH, Birley MH. Deforestation: effects on vector-borne disease. *Parasitology*. 1993; 106 Suppl: S55-75.
[33] Braack L, Gouveia de Almeida AP, Cornel AJ, Swanepoel R, de Jager C. Mosquito-borne arboviruses of African origin: review of key viruses and vectors. *Parasit Vectors*. 2018; 11(1): 29.
[34] Yang B, Yang KD. Immunopathogenesis of different emerging viral infections: evasion, fatal mechanism, and prevention. *Front Immunol*. 2021; 12: 690976.
[35] Sall AA, Faye O, Diallo M, Firth C, Kitchen A, Holmes EC. Yellow fever virus exhibits slower evolutionary dynamics than dengue virus. *J Virol*. 2010; 84(2): 765-772.
[36] McNeill JR. Mosquito empires: ecology and war in the Greater Caribbean, 1620-1914. Cambridge University Press; 2010.
[37] Tuells J, Henao-Martínez AF, Franco-Paredes C. Yellow fever: a perennial threat. *Arch Med Res*. 2022; 53(7): 649-657.
[38] Watson RP. America's first plague: the deadly 1793 epidemic that crippled a young nation. Rowman & Littlefield; 2023.
[39] Kotar SL, Gessler JE. Yellow fever: a worldwide history. McFarland; 2017.
[40] Fong IW, Fong IW. Climate change: impact on health and infectious diseases globally. Current Trends and Concerns in Infectious Diseases (book). 2020; 165-190.
[41] Monath TP, Vasconcelos PFC. Yellow fever. *J Clin Virol*. 2015; 64: 160-173.
[42] Jusino MA. Nursing imperialism: Clara Maass, yellow fever and US ambitions in Cuba, 1898-1901 [PhD dissertation]. Newark, NJ: Rutgers University-Graduate School-Newark; 2012.
[43] Centers for Disease Control and Prevention. History of Yellow Fever [Internet]. Available at: https://www.cdc.gov/yellowfever/resources/training/mod-1/files-b/History_Yellow_Fever_document.pdf [Accessed 24 June 2024].
[44] Torresi J, Kollaritsch H. Recommended/required travel vaccines. In: Travel Medicine (book). Elsevier; 2019; 101-124.
[45] Makiala-Mandanda S, Ahuka-Mundeke S, Abbate JL, et al. Identification of dengue and chikungunya cases among suspected cases of yellow fever in the Democratic Republic of the Congo. *Vector-Borne Zoonotic Dis*. 2018; 18(7): 364-370.
[46] Gonzalez JP, Souris M, Valdivia-Granda W. Global spread of hemorrhagic fever viruses: predicting pandemics. Hemorrhagic Fever Viruses: Methods and Protocols (book). 2018:3-31.
[47] World Health Organization. A global brief on vector-borne diseases. Geneva, Switzerland: World Health Organization; 2014. Report No.: WHO/DCO/WHD/2014.1.
[48] Rodhain F. Yellow fever: a brief history of a tropical virosis. *Presse Med*. 2022; 51(3):104132.
[49] Murphy J. An American plague: the true and terrifying story of the yellow fever epidemic of 1793. Boston, MA: Houghton Mifflin Harcourt; 2014.
[50] Ellis JH. Yellow fever and public health in the New South. Lexington, KY: University Press of Kentucky; 2014.
[51] Saucier HDL. From Dago to White: the story of Sicilian ethnic evolution in New Orleans amidst the yellow fever epidemic of 1905 [Master's thesis]. Hattiesburg, MS: University of Southern Mississippi; 2018.
[52] World Health Organization. Weekly bulletin on outbreaks and other emergencies: week 32: 05–11 August 2017. *Wkly Bull Outbreaks Emerg*. 2017; 1-14.
[53] de Alencastro LF. The trade in the living: the formation of Brazil in the South Atlantic, sixteenth to seventeenth centuries. Albany, NY: SUNY Press; 2018.
[54] Bollati M, Alvarez K, Assenberg R, Baronti C, Canard B, Cook S, Coutard B, et al. Structure and functionality in flavivirus NS-proteins: perspectives for drug design. *Antiviral Res*. 2010; 87(2): 125-148.
[55] Kinnear C, Moore TL, Rodriguez-Lorenzo L, Rothen-Rutishauser B, Petri-Fink A. Form follows function: nanoparticle shape and its implications for nanomedicine. *Chem Rev*. 2017; 117(17): 11476-11521.
[56] Xu K, Rajashankar KR, Chan YP, Himanen JP, Broder CC, Nikolov DB. Host cell recognition by the henipaviruses: crystal structures of the Nipah G attachment glycoprotein and its complex with ephrin-B3. *Proc Natl Acad Sci U S A*. 2008; 105(29): 9953-9958.
[57] Gebhard LG, Iglesias NG, Byk LA, Filomatori CV, De Maio FA, Gamarnik AV. A proline-rich N-terminal region of the dengue virus NS3 is crucial for infectious particle production. *J Virol*. 2016; 90(11): 5451-5461.
[58] Chen S, Wu Z, Wang M, Cheng A. Innate immune evasion mediated by flaviviridae non-structural proteins. *Viruses*. 2017; 9(10): 291.
[59] De Wispelaere M, Khou C, Frenkiel MP, Desprès P, Pardigon N. A single amino acid substitution in the M

protein attenuates Japanese encephalitis virus in mammalian hosts. *J Virol*. 2016; 90(5): 2676-2689.
[60] Jones CT, Patkar CG, Kuhn RJ. Construction and applications of yellow fever virus replicons. *Virology*. 2005; 331(2): 247-259.
[61] Caetano-Anollés K, Hernandez N, Mughal F, Tomaszewski T, Caetano-Anollés G. The seasonal behaviour of COVID-19 and its galectin-like culprit of the viral spike. In: Methods in Microbiology. Academic Press; 2022: 27-81.
[62] Collins ND, Beck AS, Widen SG, Wood TG, Higgs S, Barrett ADT. Structural and nonstructural genes contribute to the genetic diversity of RNA viruses. *MBio*. 2018; 9(5): e01871-18.
[63] Dos Santos WG. Impact of virus genetic variability and host immunity for the success of COVID-19 vaccines. *Biomed Pharmacother*. 2021; 136: 111272.
[64] Beck AS. Population Structure of Yellow Fever Virus: Influence of Viral Diversity on Vaccine Attenuation [dissertation]. 2016.
[65] Diamond MS. Evasion of innate and adaptive immunity by flaviviruses. *Immunol Cell Biol*. 2003; 81(3): 196-206.
[66] ter Meulen J, Sakho M, Koulemou K, et al. Activation of the cytokine network and unfavorable outcome in patients with yellow fever. *J Infect Dis*. 2004; 190(10): 1821-1827.
[67] Quaresma JA, Barros VL, Pagliari C, et al. Hepatocyte lesions and cellular immune response in yellow fever infection. *Trans R Soc Trop Med Hyg*. 2007; 101(2): 161-168.
[68] Watson AM, Klimstra WB. T Cell-Mediated Immunity towards Yellow Fever Virus and Useful Animal Models. *Viruses*. 2017; 9(4): 77.
[69] Pulendran B. Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology. *Nat Rev Immunol*. 2009; 9: 741-747.
[70] Vasconcelos DB, Falcão LFM, da Ponte LCT, et al. New insights into the mechanism of immune-mediated tissue injury in yellow fever: the role of immunopathological and endothelial alterations in the human lung parenchyma. *Viruses*. 2022; 14(11): 2379.
[71] Giugni FR, Aiello VD, Faria CS, et al. Understanding yellow fever-associated myocardial injury: an autopsy study. *EBioMedicine*. 2023; 96: 104810.
[72] Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of angiopoietin-2 in vascular physiology and pathophysiology. *Cells*. 2019; 8: 471.
[73] Amalakuhan B, Habib SA, Mangat M, et al. Endothelial adhesion molecules and multiple organ failure in patients with severe sepsis. *Cytokine*. 2016; 88: 267-273.
[74] Puerta-Guardo H, Glasner DR, Harris E. Dengue virus NS1 disrupts the endothelial glycocalyx, leading to hyperpermeability. *PLoS Pathog*. 2016; 12(7): e1005738.
[75] Sun T, Wang Y, Wu X, Cai Y, Zhai T, Zhan Q. Prognostic value of syndecan-1 in the prediction of sepsis-related complications and mortality: a meta-analysis. *Front Public Health*. 2022; 10: 870065.
[76] Li M, Zhou Y, Cheng J, Wang Y, Lan C, Shen Y. Response of the mosquito immune system and symbiotic bacteria to pathogen infection. *Parasit Vectors*. 2024; 17(1): 69.
[77] Bian G, Shin SW, Cheon HM, Kokoza V, Raikhel AS. Transgenic alteration of Toll immune pathway in the female mosquito *Aedes aegypti*. *Proc Natl Acad Sci U S A*. 2005; 102: 13568-13573.
[78] Xi Z, Ramirez JL, Dimopoulos G. The Aedes aegypti Toll pathway controls dengue virus infection. *PLoS Pathog*. 2008; 4(7): e1000098.
[79] Sim S, Ramirez JL, Dimopoulos G. Dengue virus infection of the *Aedes aegypti* salivary gland and chemosensory apparatus induces genes that modulate infection and blood-feeding behavior. *PLoS Pathog*. 2012; 8(3): e1002631.
[80] Luplertlop N, Surasombatpattana P, Patramool S, et al. Induction of a peptide with activity against a broad spectrum of pathogens in the *Aedes aegypti* salivary gland following infection with dengue virus. *PLoS Pathog*. 2011; 7(1): e1001252.
[81] Ramirez JL, Dimopoulos G. The Toll immune signaling pathway controls conserved anti-dengue defenses across diverse Aedes aegypti strains and against multiple dengue virus serotypes. *Dev Comp Immunol*. 2010; 34(6): 625-629.
[82] Pan X, Zhou G, Wu J, et al. Wolbachia induces reactive oxygen species (ROS)-dependent activation of the Toll pathway to control dengue virus in the mosquito *Aedes aegypti*. *Proc Natl Acad Sci U S A*. 2012; 109(1): E23-31.
[83] Souza-Neto JA, Sim S, Dimopoulos G. An evolutionarily conserved function of the JAK-STAT pathway in anti-dengue defense. *Proc Natl Acad Sci U S A*. 2009; 106: 17841-17846.
[84] Deshpande G, Calhoun G, Schedl P. Drosophila argonaute-2 is required early in embryogenesis for the assembly of centric/centromeric heterochromatin, nuclear division, nuclear migration, and germ-cell formation. *Genes Dev*. 2005; 19: 1680-1685.
[85] Liu Q, Rand TA, Kalidas S, et al. R2D2, a bridge between the initiation and effector steps of the Drosophila RNAi pathway. *Science*. 2003; 301: 1921-1925.
[86] Samuel GH, Wiley MR, Badawi A, Adelman ZN, Myles KM. Yellow fever virus capsid protein is a potent suppressor of RNA silencing that binds double-stranded RNA. *Proc Natl Acad Sci U S A*. 2016; 113: 13863-13868.
[87] Sánchez-Vargas I, Scott JC, Poole-Smith BK, et al. Dengue virus type 2 infections of Aedes aegypti are modulated by the mosquito's RNA interference pathway. *PLoS Pathog*. 2009; 5(2): e1000299.

[88] Keene KM, Foy BD, Sanchez-Vargas I, et al. RNA interference acts as a natural antiviral response to O'nyong-nyong virus (Alphavirus; Togaviridae) infection of *Anopheles gambiae*. *Proc Natl Acad Sci U S A*. 2004; 101: 17240-17245.
[89] Amanna IJ, Slifka MK. Questions regarding the safety and duration of immunity following live yellow fever vaccination. *Expert Rev Vaccines*. 2016; 15(12): 1519-1533.
[90] Gotuzzo E, Yactayo S, Cordova E. Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. *Am J Trop Med Hyg*. 2013; 89: 434-444.
[91] Theiler M, Smith HH. The use of yellow fever virus modified by in vitro cultivation for human immunization. *J Exp Med*. 1937; 65: 787-800.
[92] Niedrig M, Lademann M, Emmerich P, Lafrenz M. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. *Trop Med Int Health*. 1999; 4: 867-871.
[93] Poland JD, Calisher CH, Monath TP, et al. Persistence of neutralizing antibody 30–35 years after immunization with 17D yellow fever vaccine. *Bull World Health Organ*. 1981; 59: 895-900.
[94] Wieten RW, Jonker EFF, van Leeuwen EM, et al. A single 17D yellow fever vaccination provides lifelong immunity; characterization of yellow-fever-specific neutralizing antibody and T-cell responses after vaccination. *PLoS One*. 2016; 11(3): e0149871.
[95] Bodilis HC, Benabdelmoumen G, Gergely A, et al. Persistance à long terme des anticorps neutralisants de la fièvre jaune chez les personnes âgées de 60 ans et plus. *Bull Soc Pathol Exot*. 2011; 104: 260-265.
[96] Velayudhan R. Brief overview of the World Health Organization Vector Control Global Response 2017-2030 and Vector Control Advisory Group activities. *Area-Wide Integr Pest Manage*. 2021: 633-644.
[97] Smith LB, Kasai S, Scott JG. Pyrethroid resistance in Aedes aegypti and Aedes albopictus: important mosquito vectors of human diseases. *Pestic Biochem Physiol*. 2016; 133: 1-12.
[98] 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.
[99] Schnyder JL, de Jong HK, Bache BE, et al. Long-term immunity following yellow fever vaccination: a systematic review and meta-analysis. *Lancet Glob Health*. 2024; 12(3): e445-e456.
[100] DeWitt WS, Emerson RO, Lindau P, et al. Dynamics of the cytotoxic T cell response to a model of acute viral infection. *J Virol*. 2015; 89(8): 4517-4526.
[101] Okonko IO, Nkang AO, Udeze AO, et al. Global eradication of measles: a highly contagious and vaccine-preventable disease-what went wrong in Africa. *J Cell Anim Biol*. 2009; 3(8): 119-140.
[102] Domingo C, Fraissinet J, Ansah P, et al. Long-term immunity against yellow fever in children vaccinated during infancy: a longitudinal cohort study. *Lancet Infect Dis*. 2019;19: 1363-1370.
[103] Lopez A, Mariette X, Bachelez H, et al. Vaccination recommendations for the adult immunosuppressed patient: a systematic review and comprehensive field synopsis. *J Autoimmun*. 2017; 80: 10-27.
[104] Piras-Douce F, Raynal F, Raquin A, et al. Next generation live-attenuated yellow fever vaccine candidate: safety and immuno-efficacy in small animal models. *Vaccine*. 2021; 39(13): 1846-1856.
[105] Cottin P, Niedrig M, Domingo C. Safety profile of the yellow fever vaccine Stamaril®: a 17-year review. *Expert Rev Vaccines*. 2013; 12(11): 1351-1368.
[106] de Menezes Martins R, de S. Maia ML, dos Santos EM, et al. Yellow fever vaccine post-marketing surveillance in Brazil. *Procedia Vaccinol*. 2010; 2(2): 178-183.
[107] Michel R, Berger F, Ravelonarivo J, et al. Observational study on immune response to yellow fever and measles vaccines in 9- to 15-month-old children. Is it necessary to wait 4 weeks between two live attenuated vaccines? *Vaccine*. 2015; 33(20): 2301-2306.
[108] Madewell ZJ. Risk factors and surveillance for arboviruses and their vectors in Guatemala and Puerto Rico [dissertation]. San Diego State University; 2020.
[109] Adungo F, Yu F, Kamau D, et al. Development and characterization of monoclonal antibodies to yellow fever virus and application in antigen detection and IgM capture enzyme-linked immunosorbent assay. *Clin Vaccine Immunol*. 2016; 23(8): 689-697.
[110] Davis EH, Velez JO, Russell BJ, et al. Evaluation of Whatman FTA cards for the preservation of yellow fever virus RNA for use in molecular diagnostics. *PLoS Negl Trop Dis*. 2022; 16(6): e0010487.
[111] Souza RP, Petrella S, Coimbra TL, et al. Isolation of yellow fever virus (YFV) from naturally infected Haemagogus (Conopostegus) leucocelaenus (Diptera, Culicidae) in São Paulo State, Brazil, 2009. *Rev Inst Med Trop Sao Paulo*. 2011; 53: 133-139.
[112] Quaresma JA, Barros VL, Fernandes ER, et al. Reconsideration of histopathology and ultrastructural aspects of the human liver in yellow fever. *Acta Trop*. 2005; 94(2): 116-127.
[113] Andrus JK, Aguilera X, Oliva O, Aldighieri S. Global health security and the International Health Regulations. *BMC Public Health*. 2010; 10(1): 1-4.
[114] André AM, Lopez A, Perkins S, et al. Frontline field epidemiology training programs as a strategy to improve disease surveillance and response. *Emerg Infect Dis*. 2017; 23(13): S166-S173.
[115] World Health Organization. Yellow fever: strategic response plan, June-August 2016. WHO. 2016.

[116] Walldorf JA, Date KA, Sreenivasan N, Harris JB, Hyde TB. Lessons learned from emergency response vaccination efforts for cholera, typhoid, yellow fever, and Ebola. *Emerg Infect Dis*. 2017; 23(13): S210-S216.
[117] World Health Organization. A WHO report of the eliminate yellow fever epidemics (EYE) strategy annual partners' meeting 2018: Dakar, Senegal, 11-13 September 2018. Geneva: World Health Organization; 2019. Report No.: WHO/WHE/IHM/2019.7.
[118] WHO. A global strategy to eliminate yellow fever epidemics 2017–2026. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789241513661 [Accessed 24 June 2024].
[119] World Health Organization. Review of the international coordination group on vaccine provision (2006-2016). Geneva: World Health Organization; 2016. Report No.: WHO/WHE/IHM/16.1.
[120] Reno E, Quan NG, Franco-Paredes C, Chastain DB, Chauhan L, Rodriguez-Morales AJ, Henao-Martínez AF. Prevention of yellow fever in travellers: an update. *Lancet Infect Dis*. 2020; 20(6): e129-e137.
[121] Rodríguez-Morales AJ, Bonilla-Aldana DK, Suárez JA, et al. Yellow fever reemergence in Venezuela-Implications for international travelers and Latin American countries during the COVID-19 pandemic. *Travel Med Infect Dis*. 2021; 44: 102192.
[122] Chaves TDSS, Orduna T, Lepetic A, et al. Yellow fever in Brazil: epidemiological aspects and implications for travelers. *Travel Med Infect Dis*. 2018; 23: 1-3.
[123] Ortiz-Martínez Y, Patiño-Barbosa AM, Rodriguez-Morales AJ. Yellow fever in the Americas: the growing concern about new epidemics. *F1000Res*. 2017; 6: 398.
[124] Rifakis PM, Benitez JA, De-la-Paz-Pineda J, Rodriguez-Morales AJ. Epizootics of yellow fever in Venezuela (2004-2005): an emerging zoonotic disease. *Ann N Y Acad Sci*. 2006; 1081: 57-60.
[125] Norrby E. Yellow fever and Max Theiler: the only Nobel Prize for a virus vaccine. *J Exp Med*. 2007; 204(12): 2779-2784.