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Yellow Fever Encephalitis: An Emerging and Resurging Global Public Health Threat in a Changing Environment

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1. Introduction

Emergence and re-surgence of vector-borne diseases still constitute an important threat to human health in the 21st century, causing over a million death and considerable mortality and morbidity worldwide. Vector-borne diseases are linked to the environment by the ecology of the vectors and of their hosts, including humans. In the recent decades, climate change is a global phenomenon which has greatly influenced the emergence and resurgence of several infectious diseases such as malaria, dengue fever, plague, filariasis, trypanosomiasis, leishmaniasis and arbo-viral diseases, particularly yellow fever. Indeed, arbo-viruses will represent a threat for the coming century too. The resource constrained developing countries are the foremost sufferer and the major victims of several vector-borne diseases [1], including yellow fever.

Yellow fever (YF) is one of the great infectious scourges of humankind. It is a zoonosis indigenous to some tropical regions of South America and Africa which has caused numerous epidemics with high mortality rates throughout history [2]. Approximately 200,000 cases of YF occur annually, resulting in about 30 000 deaths; 90% of cases occur in Africa. Large epidemics, with over 100,000 cases, have been recorded repeatedly in Sub-Saharan Africa, and multiple outbreaks have occurred in the Americas. The virus has never appeared in Asia or in the Indian subcontinent [3].

YFV is endemically transmitted in forests and savannas of South America and Africa, periodically emerging from enzootic cycles to cause epidemics of hemorrhagic fever [2], with reported fatality rates ranging from 20% to 80% due to two principal syndromes: YEL-AND (yellow-fever associated neurologic disease, which includes encephalitis, myelitis or myelo-

encephalitis [ADEM]), and YEL-AVD (yellow-fever associated viscerotropic disease, which usually involves multi-organ failure including liver, renal and circulatory failure) [4].

Although YF has undoubtedly been endemic in tropical Africa for thousands of years, it was only after the arrival of the European migrants in the New World at the end of the fifteenth century that this scourge emerged in the form of devastating epidemics. The term 'vomito-negro' was used in those days to describe clinical aspects of this pathological condition, because death was frequently preceded by black vomit or by partially digested blood. Other terms used to designate yellow fever included 'Yellow Jack' and 'Safran scourge,' with reference to the jaundice observed in many patients [5].

Griffin Hughes was the first to use the term "yellow fever" to describe the disease in his book in 1750 [6]. At different stages of human development, YF has caused untold hardship and indescribable misery among different populations in the Americas, Europe, and Africa. Hundreds of thousands of people have been affected by the disease throughout ages among which tens of thousands have died. YF brought economic disaster in its wake, constituting a stumbling block to development too [7].

YF is known for bringing on a characteristic yellow tinge to the eyes and skin, and for the terrible "black vomit" caused by bleeding into the stomach [8,9]. It was one of the most feared lethal diseases before the development of effective vaccine. Today the disease still affects as many as 200,000 persons annually in the tropical regions of Africa and South America, and poses a significant hazard to unvaccinated travellers to these areas [10]. Recent increases in the density and distribution of the urban mosquito vector, *Ae. aegypti*, as well as the rise in air travel has increased the risk of introduction and spread of yellow fever to North and Central America, the Caribbean and Asia [10].

In East Africa, yellow fever remains as a disease of increasing epidemic risk. The most recent yellow fever outbreak in the region was reported by the WHO in the late 2010 and included the first human cases reported in Uganda in almost 50 years [11]. Prior to this, outbreaks occurred in Sudan (2003 and 2005) and were the first reports of yellow fever from that country in approximately 50 years. These events were preceded by the first outbreak ever reported in Kenya (1992–1993), which were the first reported human cases in East Africa for close to 25 years [11].

Over the last 20 years the number of yellow fever epidemics has risen and more countries are reporting cases. Mosquito numbers and habitats are increasing. Nevertheless, in both Africa and the Americas, there is a large susceptible, unvaccinated population. Changes in the world's environment, such as deforestation and urbanization, have increased contact with the mosquito/virus. Widespread international travel plays an important role in spreading the disease. The priorities are vaccination of exposed populations, improved surveillance and epidemic preparedness [12]. During the 20th century yellow fever has reemerged as a cause of human suffering. The recent epidemics are clearly indicating the vulnerability and potentiality of the YF as a global public health threat in the changing environment. In this context, the present chapter becomes more significant and pertains.

2. Global public health impact

The virus is endemic in tropical areas of Africa and Latin America, with a combined population of over 900 million people [13]. During the past decade, official reports of YF incidence (50-120 cases a year from South America and 200–1200 cases a year from Africa) probably underestimate the true number of cases. Many cases of jaundice and fever (a surveillance definition of yellow fever) are not assessed, unexplained deaths go unreported, symptoms suggest alternative diagnoses, and, in some countries, surveillance systems for yellow fever are not in place [14]. The case-fatality rate ranges from 20% to 50% and is partly dependent on case recognition and testing practices [15,16]. The continued presence and epidemic potential of yellow fever virus make it a global health threat. The growth of international travel to endemic areas annually has increased the number of travelers potentially exposed to the virus and consequently it has increased the risk of introduction into other new areas where competent vectors are present [10].

3. A brief history of YF

The cause of YF was unknown, but it was thought to be contracted either by coming into contact with “effluvia” from those stricken by the disease or with fomites such as clothing, sheets, and other articles that patients had used. Fear of contracting the contagion led people to shun their neighbours and friends and even to abandon loved ones. “It just tore society apart” [17]. Known today to be spread by infected mosquitoes, yellow fever was long believed to be a miasmatic disease originating from rotten vegetable matter and other putrefying filth, and most believed the fever to be contagious. There were many debates regarding the agent that caused YF and Carlos Findlay was the first to suggest that mosquitoes transmitted the disease [8,9]. Text box 1 indicates some of the key milestones in the history of YF [18].

The earliest description of yellow fever is found in a Mayan manuscript in 1648, but by genome sequence analysis it appears that yellow fever virus evolved from other mosquito-borne viruses about 3000 years ago [19]. Yellow fever originated in Africa and in the 1500s yellow fever virus was probably introduced into the New World via ships carrying slaves from West Africa. Epidemics soon became common in the coastal communities of South and Central America and along the southern and eastern seaboard of North America as far north as Boston. Between 1668 and 1893, there were more than 135 epidemics in the USA [17]. Large epidemics occurred throughout the 18th and 19th centuries in the Caribbean islands, the United States, Africa, Europe, West Indies, and South America.

4. Geographical distribution

YF is present in both the rural and urban tropical areas of 45 endemic countries in Africa and Latin America, with a potential combined population of over 900 million individuals

[20]. The vast majority of cases and deaths take place in sub-Saharan Africa, where yellow fever is a major public health problem occurring in epidemic patterns. Africa also experiences periodic yet unpredictable outbreaks of urban yellow fever. Thirty-two African countries are now considered at risk of yellow fever, with a total population of 610 million people, among which more than 219 million live in urban settings [21]. The countries in Africa and the Americas to be at the risk of yellow fever is given in text box 2 [22].

Year	Description of events
1648	An epidemic of probable yellow fever erupts in the Yucatan Peninsula (Mexico)
1750	Griffin Hughes was the first to use the term "yellow fever" to describe the disease in his book
1793	An epidemic in Philadelphia kills about 10% of the population and sparks debate between "contagionists" and "anti-contagionists."
1802	StubbinsFfirth, a Philadelphia medical student, begins self-experiments to disprove the theory of contagion.
1854	Luis Daniel Beaupterhuy of Venezuela suggests that a mosquito might transmit yellow fever.
1881	Carlos J. Finlay of Havana publishes his hypothesis that a specific mosquito (<i>Cubex cubensis</i> now <i>Aedes aegypti</i>) might transmit yellow fever.
1880s	Yellow fever in Panama kills tens of thousands of French workers, causing Ferdinand DeLesseps to abandon his attempt to build a canal across the isthmus.
1901	The Reed Commission publishes its definitive proof of the mosquito hypothesis based on the data obtained at Camp Lazear.
1902	William Crawford Gorgas supervises on the eradication of yellow fever from Havana by controlling <i>Ae. aegypti</i> .
1916	The Rockefeller Foundation begins its commitment to eradicate yellow fever.
1925	The Rockefeller Foundation opens a laboratory in Yaba, Nigeria, to investigate the etiology of yellow fever.
1927	The causative agent of YF disease, YFV, was first isolated from a Ghanaian patient named Asibi
1930	Max Theiler demonstrates that white mice are susceptible to yellow fever by intracerebral inoculation, which leads to a "mouse protection test" for seroepidemiologic studies and to an effective vaccine.
1933	Fred L. Soper and colleagues report an outbreak of yellow fever in a rural area of Brazil in which <i>Ae. aegypti</i> was not present, suggesting other vectors.
1937	Large-scale immunizations with the 17-D yellow fever vaccine are begun.
1940s	Due to mass vaccination campaigns and efforts to remove <i>Ae. aegypti</i> breeding sites, urban YF was dramatically controlled in Africa, particularly in French speaking West African countries
1951	Theiler receives the Nobel Prize for his work that led to the discovery of the 17D vaccine.
2002	The World Health Organization estimates that yellow fever affects each year up to 200,000 persons with up to 30,000 deaths.

Text Box 1. Key Milestones in the History of Yellow Fever (Bryan et al., 2004) [18]

Africa	
West Africa	Benin, Burkina Faso, Cape Verde, Co [^] te d'Ivoire, Equatorial Guinea, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, Togo
Central Africa	Angola, Burundi, Cameroon, Central African Republic, Chad, Democratic Republic of the Congo, Gabon, Rwanda
East Africa	Ethiopia, Kenya, Somalia, Sudan, Tanzania, Uganda
America	
Central America	Panama
South America	Argentina, Bolivia, Brazil, Colombia, Ecuador, Guyana, French Guyana, Paraguay, Peru, Suriname, Trinidad and Tobago, Venezuela

Text Box 2. Countries in Africa and the Americas at the risk of yellow fever

The yellow fever endemic countries in the tropical region of Africa and America are shown in the map (Figure 1) [23]. YF is endemic in ten South and Central American countries and in several Caribbean islands. Bolivia, Brazil, Colombia, Ecuador, and Peru and Venezuela are considered to be at greatest risk. Although the disease usually causes only sporadic cases and small outbreaks, nearly all the major urban centers in the American tropics have been reinfested with *Ae. aegypti* and most urban dwellers are vulnerable because of the low immunization coverage. Latin America is now at greater risk of urban epidemics than at any time in the past 50 years [21].

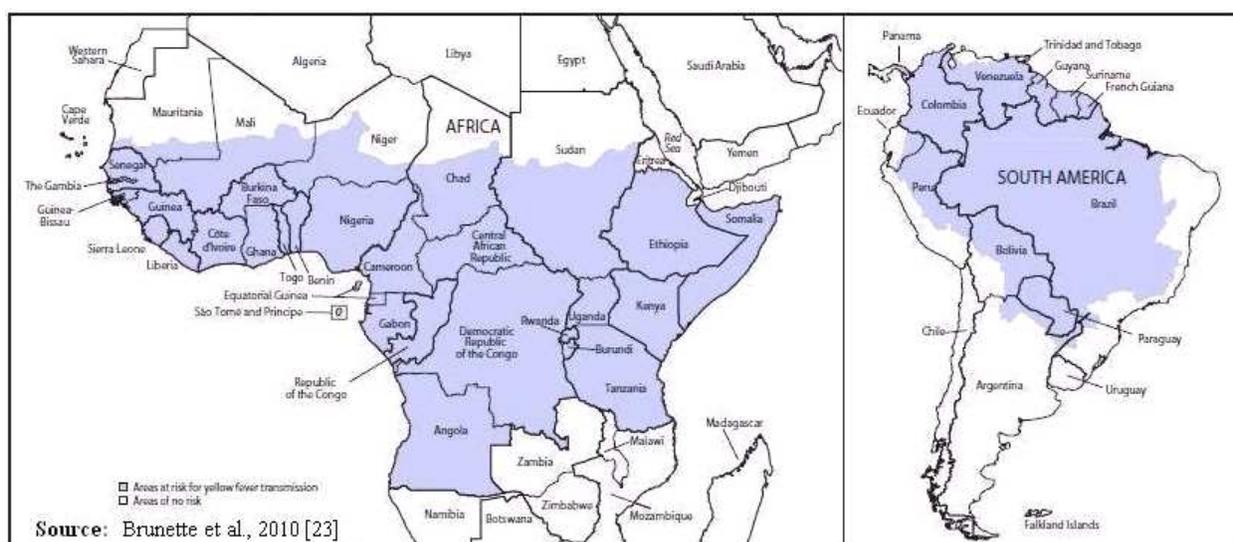


Figure 1. Yellow fever endemic countries in the tropical regions of Africa and America

5. The paradoxical absence of yellow fever from Asian countries

YF has never been reported from Asia, but, should it be accidentally imported, the potential for outbreaks, as the appropriate mosquito vector is present over there [21]. The lack of YFV in Asia is not clearly understood, although a number of hypotheses have been put forward [24]. The mosquito vector *Ae. aegypti* is prevalent in Asia and Pacific countries and has been important in the rapid emergence of dengue as a major public health problem in the twentieth century [25]. Laboratory studies indicate that Asian strains of *Ae. aegypti* can transmit YFV but are less competent than strains from the Americas. Demographic factors, including the remote location of sylvatic YF transmission and the cross-protective immunity provided by prior exposure to dengue and other flaviviruses, likely play a role in the lack of YF in Asia [26].

6. History of human YF outbreaks

At the beginning of the 20th century, a large number of yellow fever epidemics were recorded in both African and American cities, and these occurred against a background of annual cases. Table 1 and 2 lists an overview on the historical outbreaks in both tropical Africa and America by year and countries. Yellow fever epidemics are re-emerging in Africa and America, and the occurrence of repeated rural outbreaks increases the risk for major urban epidemics. The first disease outbreak that can reliably be regarded as YF was documented in 1648 and occurred in the Yucatan, Mexico and Guadeloupe [27].

Year	Countries	Name of City	Cases	Deaths
1668	United States America	New York and Philadelphia	NA	NA
1793	United States America	NA	NA	NA
Between 1668 and 1870 nearly 15 epidemics	United States America	New York	NA	In 1798, 1 500 people died
between 1668 and 1867 30 epidemic in 1793	United States America	Philadelphia	NA	3500
1793 outbreak	United States America	Philadelphia	NA	4000
1853	United States America	New Orleans	NA	7849
1854	United States America	Charleston	NA	682 persons
1878	United States America	Mississippi Valley	NA	13,000 people
1795 outbreak	West Indies	European troops stationed there	NA	3 1,000 people died
1905	United States America	New Orleans	4000	423
1647		Barbados	NA	6000
1802	Haiti	NA	NA	29000

Year	Countries	Name of City	Cases	Deaths
1878	United States America	Over 100 American towns	NA	20000
1942	Brazil	NA	NA	NA
1981-1982	Bolivia	NA	NA	NA
2003	Colombia	States of Cesar, Magdalena and La Guajira	28	11

Table 1. The history of Yellow fever outbreaks in subtropical regions of America

7. Recent emergence and resurgence of YF

In the 18th and 19th centuries, YF was a huge public health problem until mosquito control measures and production of an effective vaccine brought the epidemics under control in the 20th century. Yet as we enter the 21st century this virus is once again a significant public health problem [15,26,28] and is classified as a reemerging disease. Urban YF has not been reported from the Americas since 1954, but jungle yellow fever transmitted by *Haemagogus* vectors increasingly affects forest dwellers in Bolivia, Brazil, Columbia, Ecuador, and Peru, and periodically causes small outbreaks [15, 29,30]. The reinvasion of South America by *Ae. aegypti* after relaxation of the eradication programme in the 1970s, and presence of *Ae. aegypti* in cities near areas in which sylvatic yellow fever is endemic, poses a threat of urbanisation of yellow-fever transmission [25,29]. Following several decades of relative calmness, YF reappeared in Africa in the 1980s, endangering populations not only in the so-called endemic countries but in the rest of the world too [31]. The resurgence of YF is also closely connected with changes in the modern world and with the interaction of various economic, climatic, social and political factors [32].

8. Compounding factors for emergence and resurgence of YF

YF has been subjected to partial control for decades, but there are signs that case numbers are now increasing globally, with the risk of local epidemic outbreaks [33]. The agent of YF, yellow fever virus, can cause devastating epidemics of potentially fatal, hemorrhagic disease. We rely on mass vaccination campaigns to prevent and control these outbreaks. However, the risk of major YF epidemics, especially in densely populated, poor urban settings, both in Africa and South America, has greatly increased due to: (1) reinvasion of urban settings by the mosquito vector of YF, *Ae. aegypti*; (2) rapid urbanization, particularly in parts of Africa, with populations shifting from rural to predominantly urban; and (3) waning immunization coverage. Consequently, YF is considered an emerging, or reemerging disease of considerable importance [22].

Year	Countries	Number of cases	Year	Countries	Number of cases
1912	Zaire	NA	1994	Gabon	28
1917	Zaire	NA	1994	Ghana	79
1927-1928	Zaire	NA	1994	Kenya	7
1936	Sudan, Uganda, Kenya	NA	1994	Nigeria	1227
1940	Sudan, Uganda, Kenya	NA	1995	Gabon	16
1958	Zaire	NA	1995	Liberia	360
1959	Sudan	NA	1995	Senegal	79
1960-1962	Ethiopia	100,000	1995	Kenya	3
1965	Senegal	20,000	1995	Sierra Leone	1
1966	Ethiopia, Sudan	10,000	1996	Benin	120
1969	Nigeria	NA	1996	Ghana	27
1971	Angola	NA	1996	Senegal	128
1972	Zaire	NA	1997	Benin	18
1978	Gambia	8400	1997	Ivory Coast	11
1983	Upper Volta	NA	1997	Ghana	6
1988	Angola	NA	1997	Nigeria	7
1992-1993	Kenya	NA	1997	Liberia	1
Epidemics between 1986 and 1994	Nigeria	Approximately 120,000	1998	Burkina Faso	2
1990	Cameroon	20,000	2000	Nigeria	2
1992	Kenya	NA	2000	Liberia	102
1993	Ghana	39	2000	Guinea	512
1993	Kenya	27	2001	Ivory Coast	203
1993	Nigeria	152	2001	Guinea	18
1994	Cameroon	10	2005	Sudan	491

Table 2. The history of Yellow fever outbreaks in the subtropical regions of Africa

8.1. Unchecked and unplanned urbanization

It is one of the key determinant in terms emergence and resurgence of many vector-borne diseases particularly YF. With an annual growth rate of nearly 4%, Africa's cities are the fastest expanding in the world. Not only are more and more people living in the cities but the number of cities is also increasing. Whereas today 62.1% of Africa's population lives in rural areas, it is predicted that by 2020 this proportion will be reversed, i.e. that 63% of the continent's population will be urban dwellers. Between now and 2015, it is estimated that the number of cities with more than 1 million inhabitants will increase from 43 to 70 in Africa [34]. On the edge of modern cities, shanty towns with no access to basic sanitation (running water and waste disposal) are also developing rapidly. Domestic water containers and all manner of refuse littering the streets (aluminium and tin cans, old tyres, etc.) favor the multiplication of breeding sites for mosquito larvae [35].

8.2. Climate change

Climate change affects the spread of vector borne diseases both directly and indirectly. Global warming and increased rainfall contribute to the abundance and distribution of vectors like mosquitoes. Current evidence suggests that inter-annual and inter-decadal climate variability have a direct influence on the epidemiology of vector-borne diseases [36]. It is estimated that average global temperatures will have risen by 1.0-3.5°C by 2100 [37], increasing the likelihood of many vector-borne diseases [36]. If the water temperature rises, the larvae take a shorter time to mature [38] and consequently there is a greater capacity to produce more offspring during the transmission period.

The extrinsic incubation period of dengue and yellow fever viruses is also dependent on temperature. Within a wide range of temperature, the warmer the ambient temperature, the shorter the incubation period from the time the mosquito imbibes the infective blood until the mosquito is able to transmit by bite. The implication is that with warmer temperatures not only would there be a wider distribution of *Ae. aegypti* and faster mosquito metamorphosis, but also the viruses of dengue and yellow fever would have a shorter extrinsic incubation period and thus would cycle more rapidly within the mosquito. A more rapid cycle would increase the speed of epidemic spread [39].

8.3. Globalization

Kelley Lee (2000) [40] has defined globalization as 'the process of closer interaction of human activity across a range of spheres, including the economic, social, political and cultural, experienced along three dimensions: spatial, temporal and cognitive'. The recent emergence and resurgence of vector-borne diseases are the result of human activities-transportation of goods and people-and will continue with increasing globalization of trade [41]. The increasing phenomenon of globalization has been observed to alter the YF disease pattern.

8.4. International travel and trade

Every year, about 9 million people from Asia, Europe, and North America travel to countries where yellow fever is endemic; the number of travellers who actually visit areas within these countries where transmission of the virus occurs might exceed 3 million in the coming years [42]. In Africa yellow fever was mainly a problem of the sub-Saharan countries of West Africa, but reached as far east as central Sudan and Kenya [43-46]. A large number of outbreaks were reported in eastern Mexico and other Central American countries. At this time, YF was an epidemic disease mainly of port cities [35].

8.5. Rural-urban migration

West Africa is witnessing significant migratory flows owing to rural exodus, movements of religious groups such as the Mourides in Senegal, cross-border movements of seasonal workers and nomadic pastoral communities, trade routes stretching from the Sahel to the coast of the Gulf of Guinea, the phenomenon of new urban dwellers returning regularly to their rural communities of origin, and migration by populations fleeing armed conflicts.

These human movements increase the risk of contamination of non-immune persons traveling in areas where contaminated vectors persist and, conversely, favour the introduction of the disease into previously YF free zones [47].

8.6. Genetic and behavioral variation

YF outbreaks are common in Africa despite the current knowledge of the disease transmission and the availability of a vaccine. In Africa, YF cases are not uniformly distributed throughout the endemic area; rather, more cases are reported in West Africa compared to East and Central Africa. Genetic differences between genotypes of YF in Africa probably contribute to the observed distribution of YF outbreaks. Genetic and behavioral variation in mosquito vectors may also play a major role in the distribution of YF outbreaks. The other factors also contribute to the epidemiology of YF, including host genetic background, climate, vaccination coverage, vertebrate hosts and movement of vertebrate hosts [48].

9. Yellow fever vectors

Yellow fever virus is transmitted principally by insects (mosquitoes), but ticks (*Amblyomma variegatum*) may play a secondary and minor role in Africa. It was not until 1901 that yellow fever transmission to humans was associated with the blood-feeding by the *Ae. aegypti* mosquito (Figure 2), which was a major breakthrough in understanding this dreadful disease. Dispatched to Cuba by the United States government to investigate the cause of YF, Walter Reed and colleagues confirmed that the primary mode of YF transmission to humans was the *Ae. aegypti* mosquito (Figure 2) and the in ground-breaking virologic studies demonstrated that the disease was caused by an agent that could be filtered from the blood of infected individuals [49]. The reservoir of yellow fever virus is the susceptible vector mosquito species that remains infected throughout its life and can transmit the virus transovarially. Yellow fever can persist as a zoonosis in the tropical areas of Africa and America, with nonhuman primates responsible for maintaining the infection. Man and monkey play the role of amplifiers of the amount of virus available for the infection of mosquitoes [50].

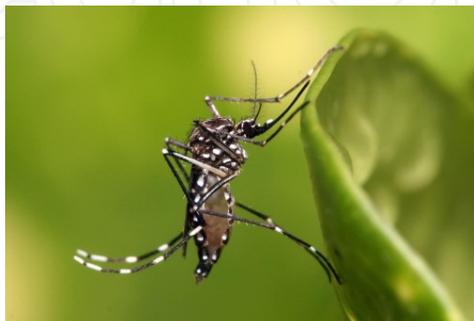


Figure 2. *Aedes aegypti*, the primary disease vector for yellow fever (Photo by Muhammad Mahdi Kharim, published under the GNU free documentation licences)

10. Yellow fever virus

Ever since the causative agent of YF disease YFV, was first isolated in 1927 from a Ghanaian patient named Asibi [50], the Asibi YFV strain is still widely used by the scientists of today. YFV is the prototype member of the family Flaviviridae (from the Latin flavus, meaning yellow), and genus Flavivirus, which get their name from the Latin word for yellow (flavus). The genome is a single-stranded, positive-sense RNA, 10,500 - 11,000 nucleotides in length. The genus Flavivirus contains approximately 70 viruses, and the major flavivirus diseases are yellow fever (YF), dengue, West Nile, Japanese encephalitis, and tick-borne encephalitis [51]. Unlike other mosquito-borne flaviviruses, YFV has a tropism for the liver and causes a viscerotropic disease whereas many other mosquito-borne flaviviruses have a tropism for the brain, or in the case of the DEN viruses they target cells of reticuloendothelial origin [52].

It was one of the earliest viruses to be identified and linked to human disease. Although substantial variation exists among strains, they can be grouped into monophyletic geographical variants, called topotypes. African isolates are usually grouped into two topotypes, associated with East and West Africa [53,54], although some studies have argued for up to five [55]. Two more have been identified from South America, although one has not been recovered since 1974, suggesting that it may be extinct in the wild. There is no evidence for a difference in virulence between the topotypes [56]. YF activity often occurs in areas after increases in temperature and rainfall that will favor increased biodiversity, including increased numbers of animals and arthropods while reduced rainfall limits mosquito vector density [49]. It has been known for over 50 years that increased temperatures are associated with enhanced transmission of YF virus [56] due to shortened extrinsic incubation period and increased biting by mosquitoes of vertebrate hosts [49].

11. Epidemiology

The virus is maintained in endemic areas of Africa and South America by enzootic transmission between mosquitoes and monkeys, and obviously the epidemiology of the disease reflects the geographical distribution of the mosquito vectors [57].

11.1. Transmission

The enzootic transmission cycle involves tree-hole-breeding mosquitoes such as *Aemagogus janthinomys* (South America) and *Ae. africanus* (Africa), and nonhuman primates. Infection of mosquitoes begins after ingestion of blood containing a threshold concentration of virus ($\sim 3.5 \log_{10} \text{ ml}^{-1}$), resulting in infection of the midgut epithelium. The virus is released from the midgut into the hemolymph and spreads to other tissues, notably the reproductive tract and salivary glands. A period of 7-10 days is required between ingestion of virus and virus secretion in saliva (the extrinsic incubation period), after which the female mosquito is capable of transmitting virus to a susceptible host.

Vertical transmission of virus occurs from the female mosquito to her progeny and from congenitally infected males to females during copulation. Virus in the egg stage provides a mechanism for virus survival over the dry season when adult mosquito activity and horizontal transmission abate. The virus is maintained over the dry season by vertical transmission in mosquitoes. Ova containing virus survive in dry tree-holes and hatch infectious progeny mosquitoes when the rains resume [58].

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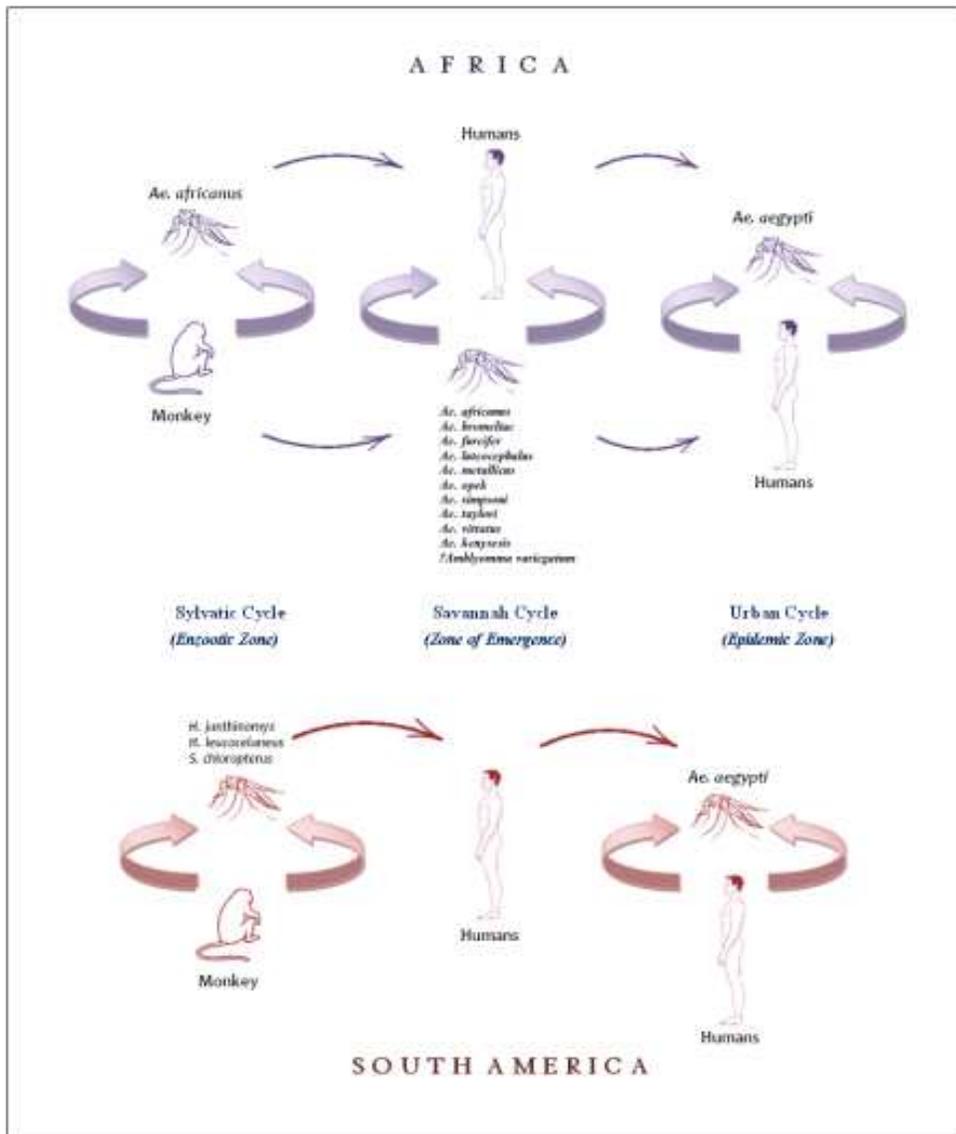


Figure 3. Yellow Fever Transmission cycles in Africa and South America

11.2. Transmission cycle patterns and ecology

In Africa, three transmission cycles can be distinguished: the sylvatic, urban, and savannah cycles. In South America, only sylvatic and urban cycles have been identified (Figure 3). In all the three cycles, yellow fever virus is transmitted between primates by diurnally active tree hole-breeding mosquitoes. Neither the virus nor the clinical disease differs in these three cycles, but identifying the type of transmission cycle is important for disease control. In all of these cycles, endemic and epidemic disease patterns can occur [59]. Sylvatic yellow fever (YF) in South America is maintained in an epizootic cycle between non-human primates and *Haemagogus* and *Sabethes* mosquitoes, tree-hole breeding species that reside in the forest canopy. Humans are infected incidentally in the sylvatic cycle when they inhabit or work in the forest where infected mosquitoes are present [60].

In the “Jungle” or “Sylvatic” cycle, the virus is transmitted among monkeys by tree-hole breeding mosquitoes. Humans are infected incidentally when entering the area (e.g., to work as foresters) and have what is termed “jungle yellow fever”. The main vector in Africa is *Aedes africanus*, while in South America it is *Haemagogus* species. Other mosquito species involved in transmission include *Ae. africanus*, *Ae. furcifer*, *Ae. vittatus*, *Ae. luteocephalus*, *Ae. opok*, *Ae. metallicus*, and *Ae. simpsoni* in Africa, and *Sabetheschloropterus* in South America. The primate species acting as vertebrate hosts of the virus also differ by geographic area.

The “Urban” cycle involves transmission of YF virus between humans by *Ae. aegypti*, a domestic vector that breeds close to human habitation in water, and scrap containers including used tires in urban areas or dry savannah areas. In this situation, the disease is known as “urban yellow fever” [49]. YF is transmitted in urban cycles between humans and the container-breeding, anthropophilic mosquito *Aedes aegypti* [15]. In Africa, a third cycle is recognized, the intermediate or savannah cycle, where humans in the moist savannah regions come into contact with the jungle cycle. This has been referred to as the “Zone of Emergence.” Although YF is considered to be a mosquito-borne disease, *Amblyomma variegatum* ticks have been shown to be naturally infected with the virus in central Africa [61]. The significance of this observation in the ecology of YF virus has yet to be determined.

Urban cycle epidemics develop from anthroponotic, also known as human-to-human, transmission in which humans serve as the sole host reservoir of the peridomestic *Ae. aegypti* mosquito vector. Urban epidemics occur when anicteric but viremic persons who are not yet severely ill, travel from jungles and savannas to cities where they infect local *Ae. aegypti* mosquitoes, a species that is abundant in urban areas and in areas where humans store water. When YF is identified in any setting, the likelihood that it resulted from human-to-human transmission or its possible introduction into an urban setting must be rapidly assessed to determine the need for emergency vaccination [62]. The intrinsic incubation period in human beings is between two and six days. The extrinsic incubation period in a mosquito varies from four to 18 days (average 12 days), with the temperature and humidity. Once the mosquito becomes infective, it remains so for the rest of its life [63].

12. Clinical signs and symptoms

YF is the original viral haemorrhagic fever (VHF), a pansystemic viral sepsis with viraemia, fever, prostration, hepatic, renal, and myocardial injury, haemorrhage, shock, and high lethality. Patients with yellow fever suffer with a terrifying and untreatable clinical disease as yellow fever is responsible for 1000-fold more illness and death than Ebola. Yellow fever stands apart from Ebola and other VHFs in its severity of hepatic injury and the universal appearance of jaundice [10]. It is difficult to distinguish YF clinically from many other tropical diseases and often impossible when the condition is mild or atypical. The clinical symptoms associated with the early stages of YF infection are indistinguishable from those of malaria, and where the two diseases coexist, YF should not be ruled out even in the absence of jaundice or the finding of malaria parasites in a blood smear [64,65]. The clinical disease varies from non-specific abortive illness to fatal haemorrhagic fever [66]. Disease onset is typically abrupt, with fever, chills, malaise, headache, lower back pain, generalised myalgia, nausea, and dizziness. On physical examination the patient is febrile and appears acutely ill, with congestion of the conjunctivae and face and a relative bradycardia with respect to the height of fever (Faget's sign). The average fever is 39° C and lasts for 3.3 days.

13. Diagnosis of YF

Clinical diagnosis of yellow fever is possible when the pathognomonic features of biphasic/triphasic acute illness and typical clinical features occur in unvaccinated individuals with a compatible exposure history. Unfortunately, these features are present only in a minority of patients [67]. Laboratory confirmation of YF is pivotal to diagnosis, but unfortunately requires highly trained laboratory staff with access to specialized equipment and materials.

Laboratory diagnosis of YF is made by detection of either virus or virus antigen or genome (by enzymelinkedimmunosorbent assay (ELISA), polymerase chain reaction (PCR), or inoculation virus into suckling mice, mosquitoes, or cell cultures), or by serology (immunoglobulin M capture ELISA), though cross-reactions with other flaviviruses complicate serologic methods of diagnosis. Postmortem examination of the liver reveals pathognomonic features of YF, including mid-zonal necrosis, and definitive diagnosis can be made by immunohistochemical staining of tissues (liver, heart, kidneys) for yellow fever antigen. It is important to note that liver biopsy should never be used for diagnosis during YF illness because of the risk for fatal hemorrhage at the biopsy site [67].

14. Treatment

In the absence of specific therapy, treatment of YF is chiefly supportive. Because most YF cases occur in areas lacking basic hospital facilities and where patients do not have access to modern intensive care. In the early stages of the disease, therapy should focus on controlling

the fever and vomiting, relieving the headache and abdominal pains, and correcting the dehydration. During the hepatorenal phase, suitable therapy based on careful patient monitoring should be administered to control the bleeding and manifestations associated with hepatorenal damage. Appropriate treatment to control malaria and secondary bacterial infections should be administered when necessary [64,65].

15. Prevention and control

Because no antiviral treatment exists for the disease, prevention through use of personal protection measures and vaccination is crucial to lower disease risk and mortality [14]. A number of approaches have been taken to control YF. Historically, the development of live vaccines was used to control the disease in Africa, whereas mosquito vector control was used in the Americas. Following the demonstration that YFV is transmitted by *Ae. aegypti* came the realization that it should be possible to control the disease by controlling mosquito populations [26]. The re-emergence of yellow fever in Africa and South America during the past decade tempers previous optimism that this disease as a public health problem could be eliminated during the twentieth century [15]. Vaccination and eradication of *Ae. aegypti* are the only effective strategies to reduce YF morbidity and mortality in the affected areas.

15.1. Yellow fever vaccine

Yellow fever vaccine is given for two reasons: to protect travellers visiting areas with the risk of yellow fever virus transmission and to prevent the international spread by minimizing the risk of importation and translocation of the virus by viraemic travellers [14]. Following the successful isolation of YFV in 1927 by American (strain Asibi) and French (strain French viscerotropic virus) workers, researchers placed great effort on the development of vaccines. The development of two live vaccines in the 1930s represents a milestone in the control of the disease. Strain Asibi was passaged through chicken tissue to develop the 17D vaccine strain, whereas strain French viscerotropic virus was passaged through mouse brain to develop the French neurotropic vaccine (FNV). Both vaccines are highly efficacious and they dramatically reduced the number of YF cases in Africa. Unfortunately, the FNV caused cases of postvaccinal neurotropic disease in vaccinees and was discontinued in 1971, whereas 17D is still used today throughout the world [26].

Although immunity from vaccination probably lasts for a lifetime [68,69], a 10 year interval between vaccinations is stipulated in the International Health Regulations (2005) for individuals travelling to countries with a yellow fever vaccination entry requirement. The International Certificate of Vaccination or Prophylaxis is a traveler's official documentation and it becomes valid 10 days after vaccination and remains so for 10 years [36]. Re-immunization is required every 10 years to maintain a valid international vaccination certificate. The World Health Organization recommends vaccination of children at 9 months old, concomitant with measles vaccination, because of better cost/benefit analysis than campaign vaccinations to control outbreaks [70]. It is recommended that the yellow fever vaccine be

administered at 12 months of age. In the case of outbreaks, it can be administered as early as 6 months of age [71]. Yellow fever vaccine is a live vaccine, so theoretically it should not be given to pregnant women or to immunosuppressed individuals. A single fatal adverse reaction (encephalitis) has been reported in an immunosuppressed individual with HIV/AIDS.

15.2. Vector control

Vector control is defined as measures of any kind directed against a vector of disease and intended to limit its ability to transmit the disease [72]. In yellow fever control specifically in certain circumstances, mosquito control is vital until vaccination takes effect.

15.2.1. Source reduction

The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites and applying insecticides to water where they develop in their immature stages [13]. Indeed, source reduction is one of the key components in the vector control programme since the target is exceptionally specific unlike adult control [73]. Vector-control strategies that were once successful for elimination of yellow fever from many regions have faltered, leading to reemergence of the disease [3]. Application of spray insecticides to kill adult mosquitoes during urban epidemics, combined with emergency vaccination campaigns, can reduce or halt yellow fever transmission and the "buying time" for vaccinated populations to build immunity [13].

Historically, mosquito control campaigns successfully eliminated *Ae. aegypti*, the urban yellow fever vector, from most mainland countries of central and South America. However, this mosquito species has re-colonized urban areas in the region and poses a renewed risk of urban yellow fever. Mosquito control programmes targeting wild mosquitoes in forested areas are not practical for preventing jungle (or sylvatic) yellow fever transmission [13]. The period between about 1950 and the 1970s was one of the complacency about the control of YF, probably arising from the feeling that YF vaccination had solved the problem. *Ae. aegypti* control was reduced and overall disease record keeping appears to have diminished. For the period 1960–2005, only 110 yellow fever points were recorded in Africa and 171 in South America. In both regions, these records more or less fall within the same areas of risk shown for the first half of the last century, although there is a noticeable lack of new records in Central America and proportionately more cases within the Amazon basin [33].

15.2.2. Insect repellents

Ae. aegypti, has adapted their peak biting activities in the early evening and early morning, when their potential hosts are less protected. Mosquito repellents have a unique role under these conditions. Easily accessible, safe and effective mosquito repellents provide a valuable supplement to IRS and ITN use, and in areas with day-biting, exophagic vectors, this may be the only option for reducing the level of disease transmission [74]. The core principle of repellents usage is that they are extremely useful and helpful whenever and wherever other personal protection measures are impossible or impracticable [75]. Insect repellents are ex-

ceptionally helpful to the travelers, who visit for a short-span of time in the disease endemic areas. The main advantage is that the repellents are relatively cheap, highly effective and can be applied as a short-term measure [76].

A laboratory study was carried out to evaluate the relative efficacy of N,N-diethylm-toluamide (DEET) and N,N-diethyl-phenylacetamide (DEPA)-treated wristbands against three major vector mosquitoes. Overall, both DEET and DEPA have shown various degrees of repellency impact against all three vector mosquitoes. DEPA treated wristbands did not show any significant differences in terms of reduction in human landing rate and the mean complete protection time against *An. stephensi* and *Ae. aegypti* were between 1.5 and 2.0 mg/cm² [77]. A study revealed the repellent efficacy of dimethyl-phthalate (DMP) treated wristband against *Ae. aegypti* under the laboratory conditions. It is estimated that 74.4 and 86.5% of reduction of man landing rates were obtained against *Ae. aegypti* at concentrations of 1.5 and 2.0 mg/cm² respectively [1]. These studies results suggest that repellent-treated fabric strips could serve as a means of potential personal protection expedient to avoid insect's annoyance and to reduce vector-borne disease transmission.

However, generally synthetic repellents have several limitations, including reduced efficacy owing to sweating, unpleasant odor, relatively expensive and can cause allergic reactions [72]. Plants have been used since ancient times to repel/kill blood-sucking insects in the human history and even now, in many parts of the world, people use plant substances to drive-away the mosquitoes and other blood-sucking insects [78]. Currently repellents of plant origin have been receiving massive attention due to their environmental and user friendly nature [79].

It is unlikely that vector control strategies alone will result in the elimination of yellow fever; such strategies must be combined with effective vaccination programs. Besides, in YF endemic countries, people particularly travelers should take precautions to avoid mosquito bites to reduce the risk of yellow fever. Besides, using insect repellents, people must use permethrin-impregnated clothing, and bed nets and staying in the screened room could be advisable.

16. Conclusion

YF has played a central role in the history of infectious diseases. It was the first disease to be demonstrated to be transmitted by an arthropod, one of the first diseases to be shown to be caused by a virus, and one of the first infectious agents to be controlled by the development of a live vaccine [80]. Indeed, the challenges and dangers posed by yellow fever remain formidable. It is mainly contributed by the global warming, land use changes, uncontrolled population growth, unchecked urbanization, rural - urban migration, international trade, conflict and civil disruption. Although the tools for diagnosis, vector control, vaccine and surveillance are available, their implementation is extremely poor or inadequate in many of the resource-constrained YF endemic countries. In addition, the global-warming concomi-

tant effect immensely contributed to the high reproduction rate and the capacity of insect vectors to establish and to adapt to new environmental conditions.

Certainly, the present scrutiny clearly suggests that the yellow fever encephalitis is emerging and resurging as a global public health threat in a changing environment. It contributes to remain as a disease of increasing epidemic risk. Therefore, the following issues such as high population density, development of peri-urban areas with rural interfaces, urban construction in forest areas, inconsistent vector control programme, spread of new pathogens, inadequate coverage and short-supply of yellow fever vaccine, must be addressed effectively for the betterment of humankind, eventually to build a yellow fever free world in the near future.

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