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Review

The epidemiology of yellow fever in Africa

John-Paul Mutebi, Alan D.T. Barrett *

Center for Tropical Diseases and Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555-0609, USA

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Abstract

Yellow fever (YF) is still a major public heath problem, particularly in Africa, despite the availability of a very efficacious vaccine. The World Health Organization estimates that there are 200,000 cases of YF annually, including 30,000 deaths, of which over 90% occur in Africa. In the past 15 years, the number of YF cases has increased tremendously, with most of the YF activity in West Africa. This increase in YF activity is in part due to a breakdown in YF vaccination and mosquito control programs. Five genotypes of YF virus have been found in Africa, and each genotype circulates in a distinct geographical region. West Africa genotype I, found in Nigeria and surrounding areas, is associated with frequent epidemics, whereas the three genotypes in East and Central Africa are in regions where YF outbreaks are rare. Other factors, including genetic and behavioral variation among vector species, are also thought to play a role in the epidemiology of YF in Africa.

Keywords: Yellow fever; Africa; Epidemiology; Vectors; Genotype

1. Introduction

Yellow fever (YF) outbreaks are common in many regions of tropical Africa, especially in western Africa, and are responsible for thousands of cases annually. At least one YF outbreak is reported to the World Health Organization (WHO) every year, and in the past 15 years, the incidence of YF has steadily increased [1,2]. This is alarming, considering that a safe and efficacious YF vaccine, 17D, has been available for over 60 years. In addition, the maintenance cycle of YF virus in the jungle and the epidemic transmission cycle in urban areas are fairly well understood, and urban YF transmission is relatively easy to interrupt by mosquito control measures. Despite advances in preventive measures, YF is still a major public health problem in many regions of tropical Africa and South America. In the past 2 years alone, YF outbreaks have been reported in five African countries (Nigeria, Ivory Coast, Liberia, Senegal and Guinea), and a total of 840 cases, including 216 deaths, were reported to the WHO (Table 1). The recent epidemics in Africa indicate a breakdown of YF control measures, since most cases are in children under the age of 15, who were born after routine YF vaccinations were abandoned [2].

2. Clinical disease

Yellow fever is a viral hemorrhagic fever. It is transmitted to humans and other vertebrate hosts by the bite of infected mosquitoes. The etiological agent is YF virus. In humans, infections with the YF virus cause a broad spectrum of disease, from mild symptoms to severe illness to a fatal disease. Clinical symptoms of YF typically appear 3–6 d after the mosquito bite, but only about 15% of those infected develop clinical YF, and the majority only have a mild disease and quickly recover. The clinical symptoms of YF have been described in detail by Monath [3]. Briefly, there are two main phases of the disease. Clinical symptoms in the first phase (also known as the period of infection) include sudden onset of fever, headache, muscle pain, backache, general weakness, failure of pulse to rise with temperature (Faget's sign), red eyes (injected conjunctiva), nausea and vomiting. During this phase, patients have viraemia, and they are infectious to mosquitoes. Subsequently, there is a short period, the period of remission, when clinical symptoms disappear for up to 24 h, and following the remission period, the second phase (also known as the toxic phase) begins. Symptoms in the toxic phase include high fever, vomiting, epigastric pains, jaundice, hemorrhagic diathesis (hematemesis), coma and death. YF virus is usually absent from the blood of patients during the toxic phase, and anti-YF virus antibodies appear during this stage. The case mortality rate for patients who

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* Corresponding author. Tel.: +1-409-772-6662; fax: +1-409-772-2500.
E-mail address: abarrett@utmb.edu (A.D.T. Barrett)

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Table 1
Outbreaks and number of yellow fever cases reported to the WHO between 1996 and 2001

Year	Country	Location	Cases	Deaths
1995–1996	Liberia	Buchanan	359	9
1996	Benin	Atakora and Borgou	86	65
1996	Ghana	Upper East Ghana	27	5
1997	Liberia	Lofa County	1	1
1998	Burkina Faso	Gaoua region	2	1
2000	Nigeria	Kano State	2	
2000	Liberia	Grand Cape Mount County	102	
2000	Guinea	Northwest Guinea	512	190
2001	Ivory Coast		203	21
2001	Guinea		18	2
2001	Liberia		3	3
Total			1315	297

reach the toxic phase is 20–50%, and may be higher [3,4]. Death usually occurs within 10 d of the onset of symptoms; survivors are immune for life.

3. Yellow fever virus

Ecologically, YF virus is termed an “arbovirus”, as it is transmitted between vertebrate hosts by arthropods. In the case of YF virus, the vertebrate hosts are primates (monkeys and humans), and the arthropod hosts are normally mosquito species. The virus is a member of the family *Flaviviridae*, genus *Flavivirus*. The genus *Flavivirus* is composed of approximately 70 viruses, of which almost half are pathogens of humans and/or animals, and can be considered zoonotic viruses. Flaviviruses have a small positive-sense, single-stranded RNA genome of approximately 11 kilobases. YF virus was the first arthropod-borne human virus to be isolated, and is the prototype member of the genus *Flavivirus*. The prototype strain of YF virus is Asibi, which was isolated in Ghana in 1927. The entire genome of the Asibi strain of YF virus was sequenced by Hahn et al. [5], and consists of 10,862 nucleotides. The genome is arranged into a short 5' non-coding region (NCR), a single open reading frame consisting of 10,233 nucleotides that encodes the structural genes’ capsid (C), premembrane/membrane (prM/M) and envelope (E), and non-structural genes NS1, NS2A, NS2B, NS3, NS4A, 2K, NS4B and NS5, respectively, and a 3' NCR of 511 nucleotides (Fig. 1).

4. Genetic variation among YF strains

Genetic studies of strains of YF virus using molecular techniques have revealed genetic variation among YF strains, associated with different geographic regions. Initial studies by Deubel et al. [6], using oligonucleotide fingerprinting of the genomic RNA, described three variants of YF virus, of which two were found in Africa [6]. Strains from Ivory Coast and Burkina Faso were very similar, but a different variant was described in the Central African Republic [6], thereby showing genetic variation between West African and East and Central African strains of YF virus. Another variant of YF virus was described in South America, indicating that South American YF strains were genetically differentiated from the African strains. The different variants were designated “topotypes”, due to the geographic differences in origins of the strains, and similarity among the different topotypes was 70–75%. Strains isolated in the same geographical region (Senegal and Gambia) between 1976 and 1983 were very similar (92–100% similarity), and had 82–88% similarity to those isolated earlier in 1965 [7]. These studies showed that geographically separate and epidemiologically unrelated YF virus strains were genetically distinct, and that YF strains evolved slowly. The observation that distinct YF topotypes corresponded to geographic regions indicated that oligonucleotide fingerprinting was a useful tool for classifying viruses and could be used in epidemiologic investigations. Furthermore, YF strains of the same topotype were identified in large areas, despite climatic variation within the areas, indicating genetic stability of the YF topotypes over time and space [7].

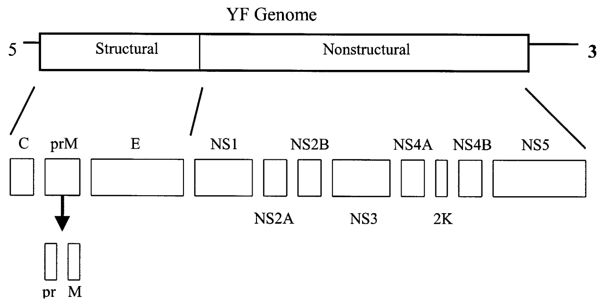

Fig. 1. Genome organization of the YF virus (modified from T.P. Monath, Yellow fever, in S.A. Plotkin, W.A. Orenstein (Eds.), Vaccines, 3rd Edition, W.B. Saunders Company, Inc., Philadelphia, 1999, pp. 815–879).

Subsequent studies by Lepineic et al. [8], based on RT-PCR and nucleotide sequencing of the E protein gene, described four genetic variants (genotypes) of YF virus, of which three were found in Africa. Similar to the previous work by Deubel et al. [6], the genotypes were found in distinct geographic regions; two of the genotypes were found in West Africa and one in East/Central Africa. The YF genotypes were identified on the basis of phylogenetic analyses, and variation within partial fragments of the E gene nucleotide sequence [8]. Similar to the fingerprinting studies above [6], these studies indicated very little sequence variation between YF strains isolated many years apart, indicating genetic stability of the genotypes over time. For example, strains French viscerotropic virus (FVV) (Senegal27) and ArD 76320 (Senegal90) were isolated 63 years apart in 1927 and 1990, respectively, but were over 97% similar at the nucleotide sequence level for the region examined [8]. Apart from demonstrating genetic variation between genotypes, and genetic stability of YF strains within the genotypes, the distribution pattern of the genotypes began to emerge. One genotype in West Africa (West Africa genotype I) was found from eastern Ivory Coast and Burkina Faso to Cameroon including Nigeria, while the second genotype (West Africa genotype II) was found in western Ivory Coast and Mali to Senegal [8]. The third genotype in Africa was found in Eastern and Central Africa, including Central African Republic, Ethiopia and the Democratic Republic of Congo (formerly Zaire).

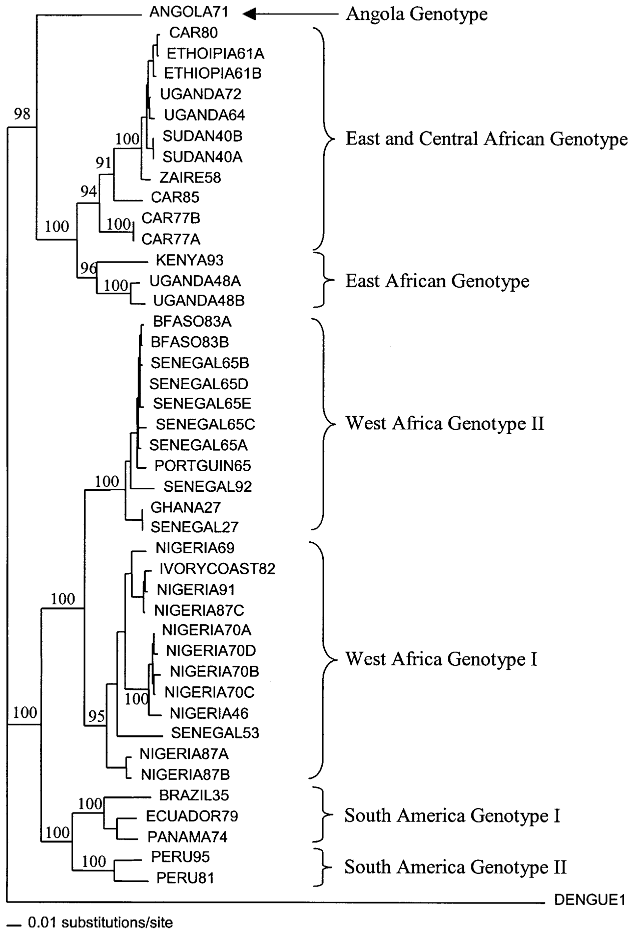

Fig. 2. Neighbor-joining tree derived from nucleotide sequence of the prM/M and E region showing phylogenetic relationships among genotypes of YF virus from Africa and South America. Maximum parsimony and maximum likelihood trees have the same topology.

Studies using different regions of the YF genome [9–11] confirmed the genotype classification proposed by Deubel et al. [6] and Lepineic et al. [8]. In addition, these studies showed that phylogenetic analyses based on different portions of the YF genome gave consistent results, suggesting that different regions of the genome can be used to represent the entire genome of YF virus. For example, studies by Wang et al. [10] used the 5' 1320 nucleotides of the genome, a region from the NS4A and NS4B genes and the 3' NCR, and observed very similar phylogenetic relationships among YF strains. Mutebi et al. [11] analyzed a 670-nucleotide fragment from the prM/M and E region that included part of the prM/M gene and part of the E gene. A large number (38) of YF strains from Africa were included in these studies, and two additional genotypes were described, one in East Africa (East African genotype) and the other in Angola (Angola genotype), indicating that YF virus in Africa was genetically more heterogeneous than originally reported [11]. This was the first time more than one genotype of YF was described in East and Central Africa. The Angola genotype of YF virus was extremely divergent (17–23% nucleotide sequence variation) from all other African genotypes, suggesting that it diverged from other East and Central African genotypes of YF virus a long time ago and has evolved independently. Currently, five genotypes of YF virus are recognized in Africa, each genotype circulating in a different geographic region (Figs. 2 and 3). West Africa genotype I circulates from eastern Ivory coast and eastern Burkina Faso, through Nigeria to Cameroon. Strains in genotype I were genetically more heterogeneous than those in West Africa genotype II, possibly due to frequent adaptation to different transmission cycles during frequent outbreaks and epidemics associated with this genotype. The East and Central African genotype has a much broader distribution, including many counties, but YF outbreaks are rare in this region, and the cycle is generally silent.

Studies by Rice et al. [12] showed that there are three repeat sequences (termed RYFs) in the 3' NCR downstream from the non-structural protein 5 (NS5) stop codon between nucleotides 10,374 and 10,520. Each RYF is approximately 40 nucleotides long, and the RYFs are separated by four to six nucleotides. Wang et al. [10] showed deletions in the 3' NCR of East and Central African and South American genotypes of YF virus that include loss of RYFs. East and Central African genotypes have only two RYFs (RYF1 and RYF3), and South American genotypes have only RYF3 [10]. At present, the significance of the RYFs in the phenotype of YF virus is not well understood. However, the 3' NCR represents a valuable tool in distinguishing East and Central, South American and West African strains of YF virus.

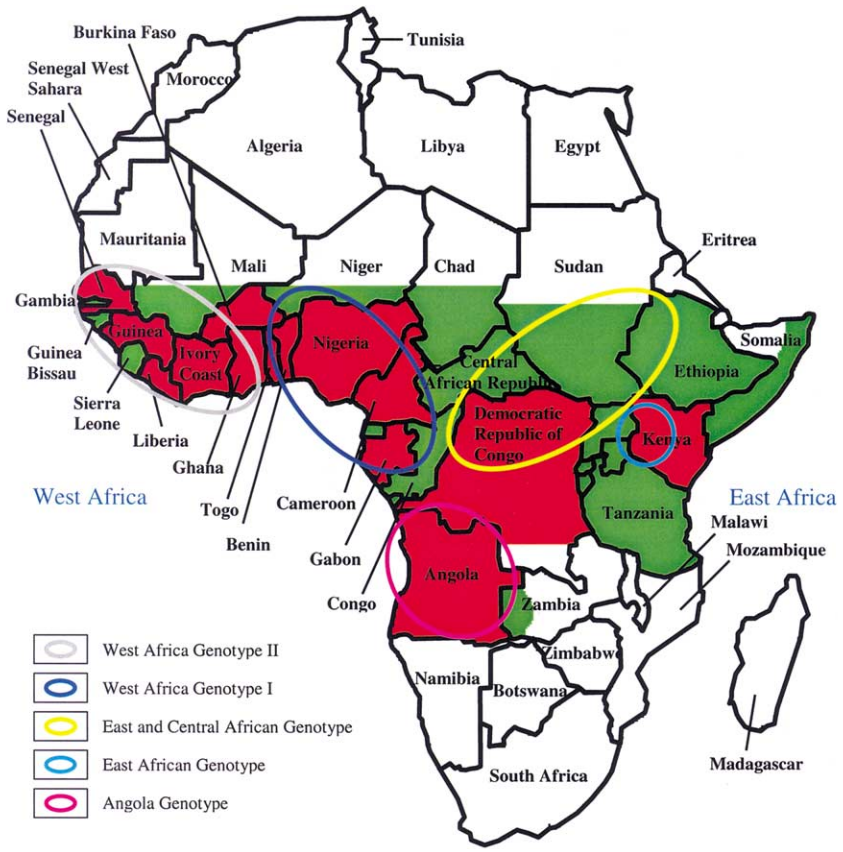

Fig. 3. A map of Africa showing the YF endemic region (shaded in green and red) and the recognized distribution of YF genotypes (colored ellipses). Highlighted in red are countries that have reported YF outbreaks from 1984 to 2001 (data from the WHO).

5. Evolution of YF virus

It is generally assumed that YF virus evolved in Africa prior to being introduced into South America. Several studies based on analyses of nucleotide sequences have provided evidence that supports this hypothesis. YF virus is genetically more heterogeneous in Africa than in South America [8,10,12], suggesting that YF probably originated in Africa. West African strains are phylogenetically closer to South American strains than to East or Central African strains [8–10] (Fig. 2), suggesting that South American strains evolved from West African strains. YF virus is genetically more diverse in East and Central Africa than in West Africa, indicating that the virus may have originated in jungle areas of East and Central Africa. This is supported by analysis of the 3' NCR in viruses from East and Central Africa, which show that the 3' NCR consists of only two RYF repeats (RYF1 and RYF3), and there is no evidence that RYF2 ever existed in the 3' NCR of East and Central African strains. Nucleotide sequence data and phylogenetic analyses suggest that YF virus may have originated in East and Central Africa, extended its range to West Africa, and was then transported from West Africa to South America.

6. Early history

The origin of YF is uncertain and has been a subject of great controversy. The first reliable record of a YF outbreak was in Yucatan, Mexico, in 1648 [13]. However, there are accounts from the Aztecs and other native tribes that seem to suggest that YF outbreaks may have swept through the Gulf of Mexico long before the discovery of America by Columbus [14]. Because of limited early outbreak records and the lack of fossils, we may never know with certainty the exact origin of YF. The early history of YF in tropical Africa is not very clear because of lack of records and reliable descriptions prior to the late 18th century. Laymen wrote most early accounts of YF outbreaks, and there is the possibility that symptoms that were thought to be of YF may have been confused with symptoms of other tropical infectious diseases. The first well-described YF outbreak on mainland Africa was among British troops in St. Louis de Senegal in 1778, reported by Schotte (cited by Carter [13]). However, the history of YF in Africa may go as far back as 1494. According to Finlay (cited by Augustin [14]), a disease that was thought to be YF devastated the Canary Islands in 1494, 2 years after the discovery of America. The Canary Islands are only 60 miles off the coast of Africa, directly on the shipping routes between western Africa and Europe, and YF could have been introduced to the islands by merchant ships.

7. Geographic distribution of YF in Africa

YF endemic areas were primarily mapped in the early 1930s and 1940s by screening large numbers of human serum samples from natives residing in Africa before the widespread use of YF vaccination. The serosurveys carried out by Beeuwkes et al. [15–17], Sawyer and Whitman [18], Findlay et al. [19], Hughes et al. [20] and many others identified regions in Africa where YF virus had been circulating. Currently, the YF endemic region in Africa recognized by the WHO is approximately from 15° north to 15° south of the equator (Fig. 3). This region includes 34 African countries, and it stretches from the southern edge of the Sahara Desert in the north to Angola in the south. Approximately 500 million people reside in this region and are at risk of acquiring YF infection. The YF endemic region in Africa includes primarily three climatic regions. Region 1 is the equatorial rain forest, which extends from Guinea in West Africa to western Uganda in eastern Africa and south to northern Angola. Region 2 is the moist savanna, and this is the zone that extends away from the equatorial rain forest and is characterized by decreasing rainfall. The moist savanna is often referred to as “the zone of emergence”, and this is where most agricultural activity takes place and many YF outbreaks are initiated. Region 3 is the dry savanna, and this region extends further away from the moist savanna.

7.1. YF transmission

YF virus was demonstrated to be transmitted by the mosquito *Aedes aegypti* during urban outbreaks and epidemics in the classical studies of the Walter Reed Commission at the turn of the 20th century [21]. However, in the late 1930s, an alternative YF transmission cycle, the jungle cycle, was described in South America [22]. Later, a jungle transmission cycle for YF virus was described in Africa as well [23]. Currently, three different transmission cycles for YF virus are recognized in Africa, and each cycle occurs in a different ecological setting and involves different species of mosquito vectors.

1. *The jungle cycle: In African forests, the virus is principally maintained by transmission among monkeys and small mammals by the mosquito Aedes africanus[24]* (Fig. 4). *Ae. africanus is a forest mosquito that breeds primarily in treeholes and is only found in the jungles of tropical Africa. The jungle cycle is very similar to that in South America, but in South America the principal mosquito vectors are primarily in two mosquito genera, Hemagogus and Sabethes[22]*. Sporadic human cases in the form of focal outbreaks are typical, and large epidemics involving thousands of people are rare.
2. *The intermediate cycle: The intermediate cycle involves several mosquito species, including Aedes luteocephalus, Aedes furcifer, Aedes metallicus, Aedes opok, Aedes taylori, Aedes vittatus and members of the Aedes simpsoni complex [25]* (Fig. 4). The intermediate transmission cycle is usually in areas with some human activity, such as small village settlements, communal herding areas and farmland. The intermediate transmission cycle has only been described in the moist savanna of Africa, and to date, no such cycle has been described in the Americas. Due to the increased potential for transmission to humans, the potential for large YF epidemics is very high.
3. *The urban cycle: In the urban cycle, the virus is transmitted from human to human by the mosquito Ae. aegypti. This is the most deadly form of disease transmission, potentially involving thousands of human cases.*

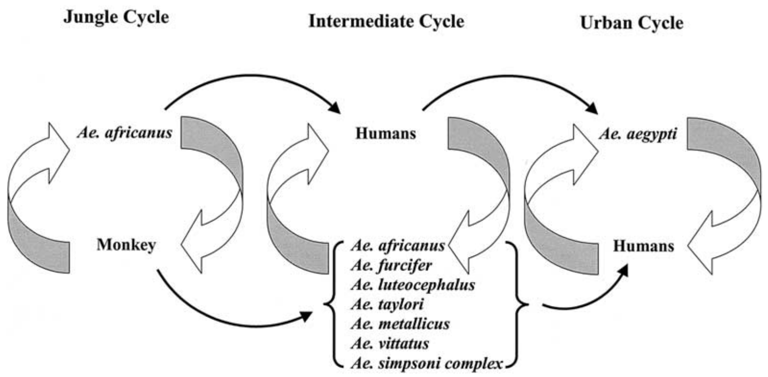

Fig. 4. YF transmission cycles in Africa.

8. Incidence of YF in Africa

More YF cases and epidemics are reported in Africa than South America, indicating that the disease burden is much more severe in Africa (Fig. 5). From 1948 to 2001, 39,024 cases of YF were reported to the WHO, of which 30,390 (78%) were in Africa. An average of 562 YF cases are reported annually in Africa compared to 161 in South America. Fig. 5 shows numbers of YF cases worldwide and in Africa only, and highlights that most cases occur on the African continent. The figures show that the number of YF cases reported in the past 15 years has increased considerably, indicating that the public health burden from YF infections is getting worse. Furthermore, Nasidi et al. [26] and Monath [27] argued that the reporting of YF cases to the WHO is not consistent with the actual number of cases. They estimated that the actual number of cases may be 10 to 500 times higher. Based on these estimates, and those in the WHO *Weekly Epidemiological Record* (1995), the WHO estimated that there are 200,000 cases, including 30,000 deaths, annually, and that over 90% of the cases are in Africa.

The number of cases reported to the WHO every year shows extreme variation in YF activity over the past 60 years (Fig. 5). From 1950 to 1959, YF activity in Africa was low. The total number of cases in Africa reported to the WHO within that decade was 362, which is on average 36 cases every year. In contrast, the total number of cases reported in the Americas during the same decade (1950–1959) was 2918, or on average 292 cases per year. All cases reported in South America were jungle YF cases; the last urban outbreak in South America was in Brazil in 1942. However, the potential for urban YF outbreaks in South America is high due to re-infestation by *Ae. aegypti*, and there is serologic evidence of a small outbreak of urban YF in Santa Cruz, Bolivia, in 1999 [58]. Between 1960 and 1962, there was a major YF outbreak in Ethiopia, which was estimated to have involved approximately 100,000 cases and at least 30,000 deaths [28]. Between 1965 and 1980, YF activity in Africa and in South America was comparable. During that 16-year period, 3901 YF cases were reported to the WHO, 2075 (53%) in Africa and 1826 (47%) in South America [1]. However, there were relatively large YF outbreaks in Senegal in 1965, Burkina Faso and Nigeria in 1969, Sierra Leone in 1975, Gambia in 1978 and Ghana in 1978–1979. Since 1984, the number of YF cases in Africa has been very high (Fig. 5). Between 1984 and 1995, 22,647 YF cases were reported in Africa, 21,299 (94%) of which were in Nigeria. During that period, at least 10 YF outbreaks and 5143 deaths occurred in Nigeria alone. As Robertson et al. [1] indicated, the 18,738 YF cases and 4522 deaths reported to the WHO between 1987 and 1991 were the highest YF activity for any 5-year period since reporting began in 1948. Overall, there have been two major peaks of YF activity in Africa since 1948: one peak between 1960 and 1962, and the other peak between 1985 and 1995 (Fig. 5). The peak in the early 1960s was primarily due to the outbreak in Ethiopia, and the peak in 1985–1995 was predominantly due to YF outbreaks in Nigeria. The tremendous increase in YF cases in Africa since the early 1980s reflects a major breakdown in YF control measures.

Although the YF endemic zone in Africa is broad (Fig. 3), the distribution of YF cases and epidemics is not uniform across all regions. Fig. 3 shows countries with YF epidemics from 1985 to 2001. During this period, a total of 25 outbreaks were recorded: 22 were in West Africa, while only three were in East and Central Africa [2]. The Democratic Republic of Congo and Angola are considered to be in Central Africa despite sharing the Atlantic Ocean coastline on the western side of Africa (Fig. 3). Recently, the WHO has published an African map showing areas considered to be hotspots for YF infections, to protect travelers and tourists who visit these regions. All of the hotspot regions are in West Africa, emphasizing the unequal distribution of YF activity in Africa. Large YF epidemics in East and Central Africa often occur during periods of civil unrest. The outbreak in the Nuba mountains, Sudan, in 1940 occurred during war conditions [29], when large numbers of non-immune humans migrated into a YF endemic region. Earlier serosurveys had indicated 23% seroconversion among inhabitants of the Nuba mountains [18]. Similarly, the epidemic in Ethiopia from 1960 to 1962 was during a period of civil unrest [30]. The epidemic in Kenya in 1992–1993 was mostly in woodland away from human settlement [31], due to large movement of non-immune hu-

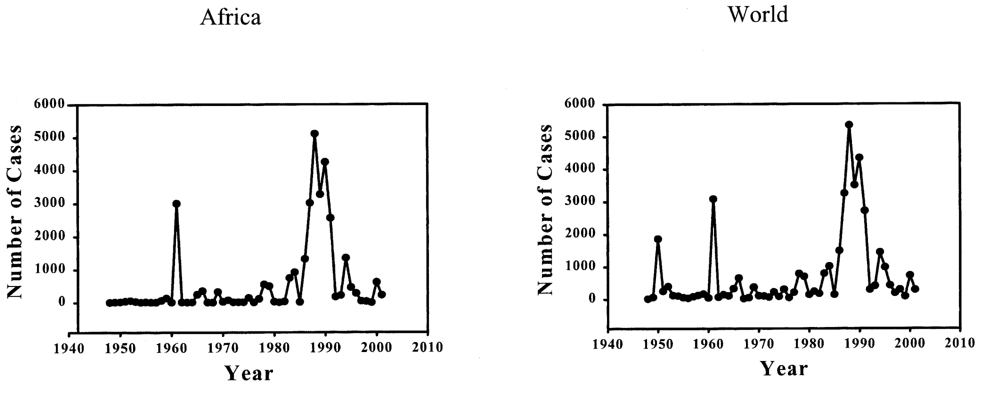

Fig. 5. Number of YF cases reported to the WHO annually in Africa and in the whole world from 1948 to 2001.

mans into a YF endemic area in search of water in a period of drought, and young males were the most affected [32]. In contrast, epidemics in West Africa occur without mass movement of people into highly endemic areas. Furthermore, reliable seroconversion rates obtained in surveys conducted before widespread use of YF vaccines in Africa show comparable rates of seroconversion due to natural infections throughout the YF endemic region in Africa [15–20]. Therefore, the general lack of YF outbreaks in East and Central Africa is not due to lack of infections; rather, other factors must contribute to outbreaks.

The lack of frequent YF outbreaks in East and Central Africa is intriguing. Although climatic conditions vary across the YF endemic zone in Africa, the fact that YF virus is continuously present in the jungles of East and Central Africa suggests that climate may not be the major factor regulating YF outbreaks. Genetic differences between YF genotypes may play an important role in the distribution pattern of YF outbreaks and cases in Africa. There is the possibility that different genotypes of YF virus vary in virulence for humans. Unfortunately, the virulence phenotypes of YF virus are not yet well understood. Associations have been made between viruses of West Africa genotype I and frequent outbreaks, suggesting that they may be more virulent or infectious to humans. In addition, West Africa genotype I is genetically heterogeneous [11], suggesting that it is more adaptable to different transmission conditions, such as those prevalent during YF outbreaks. In addition, genetic and behavioral variation has been noticed among YF vectors in Africa that may affect vector competence. However, the role mosquito vectors play in the distribution of YF is not completely understood, due to limited comparative studies between vector populations within the YF endemic zone in Africa. Variations among mosquito vectors are discussed in greater detail below.

YF cases up to 1995 have been extensively discussed by Monath [3,27], Robertson et al. [1], Tomori [4] and Vainio and Cutts [2] and in many WHO publications. Table 1 summarizes the number of YF cases in Africa reported to the WHO from 1996 to 2001. During this period, a total of 1315 cases were reported, including 297 deaths (Table 1). All cases were in West Africa, and the outbreaks were reported in seven different countries: Liberia, Benin, Ghana, Burkina Faso, Nigeria, Guinea and Ivory Coast.

9. Mosquito vectors in Africa

Since 1965, *Ae. aegypti* has been implicated as the vector in at least eight YF outbreaks in West Africa [3]. Five of the eight epidemics were in the region where West Africa genotype I circulates. With the exception of the YF outbreak in the Nuba mountains in Sudan in 1940, *Ae. aegypti* has not been implicated in outbreaks in East and Central Africa. Outbreaks in East and Central Africa are usually associated with sylvatic mosquito vectors, such as members of the *Ae. simpsoni* species complex. It appears the East and Central African genotypes of YF virus are enzootic, since they are rarely involved in outbreaks. In contrast, West African genotypes of YF virus are epizootic, since they are frequently involved in outbreaks and epidemics, especially West Africa genotype I.

Although several mosquito species are involved in the transmission cycles of YF in tropical Africa, the most important species are *Ae. africanus*, *Ae. aegypti*, *Ae. simpsoni* complex, *Ae. furcifer*, *Ae. taylori* and *Ae. luteocephalus*. The ecological and behavioral diversity of these mosquito species has some influence on the distribution of YF in Africa. As mentioned above, in West Africa, *Ae. aegypti* is responsible for urban YF outbreaks, whereas in East Africa, *Ae. aegypti* has never been incriminated in the transmission of YF virus. In East Africa, *Ae. aegypti* exists in human-biting (anthropophilic) and non-human-biting (non-anthropophilic) populations [33–35], but YF outbreaks have not been reported even in areas where *Ae. aegypti* readily bite humans. In many regions in East Africa, domesticated forms of *Ae. aegypti* are virtually absent [36,37]. Thus, it is not surprising that in the YF outbreak in Kenya in 1992–1993, *Ae. aegypti* was not incriminated as the vector; rather, *Ae. africanus* and *Ae. keniensis* were identified as vectors [31]. The distribution of non-anthropophilic forms of *Ae. aegypti* is not completely understood; however, lack of *Ae. aegypti*-transmitted YF in East Africa where non-anthropophilic populations of *Ae. aegypti* exist suggests that behavioral differences of *Ae. aegypti* probably play a role in the distribution of YF virus in Africa. Interestingly, only anthropophilic populations of *Ae. aegypti* have been reported in investigations in West Africa [38,25], and it is in West Africa that outbreaks of urban YF are frequently reported.

Ae. simpsoni is a species complex of at least three sibling species, *Ae. simpsoni* sensu strictu, *Ae. bromeliae* and *Ae. lilii*. [39]. *Ae. simpsoni* s.s. is restricted to South Africa and plays no part in the epidemiology of YF. *Ae. bromeliae* and *Ae. lilii* are morphologically indistinguishable [40], and one or both species are involved in YF transmission; in this discussion, they are collectively referred to as *Ae. simpsoni.* In West Africa, *Ae. simpsoni* breeds exclusively in treeholes in forested areas [41–43], whereas in East and Central Africa, it breeds primarily in plant axils in plantations close to human settlements [44,45]. *Ae. simpsoni* complex mosquitoes were incriminated as the vectors in the greatest YF epidemic in Africa, which took place in Ethiopia in 1960–1961 [28]. However, *Ae. simpsoni* also occurs in anthropophilic and non-anthropophilic populations [44,46,47], and the two behavioral forms appear to be sibling species [34,48]. Populations of *Ae. simpsoni* in West Africa are predominantly non-anthropophilic [49,50]. However, anthropophilic and non-anthropophilic populations of *Ae. simpsoni* exist randomly in East and Central Africa. In areas where *Ae. simpsoni* is non-anthropophilic, it prefers to blood feed on rodents and plays no role in the epidemiology of YF [34].

The principal jungle vector throughout tropical Africa is *Ae. africanus*[24]. *Ae. africanus* is well adapted to the role of transmitting YF virus between susceptible monkeys; numerous strains of YF virus have been isolated from this species. The biting activity of *Ae. africanus* is characterized by two peaks, one early in the morning just before sunrise and the other in the evening just after sunset [51,52]. The peak biting activity occurs in the forest canopy approximately 60 ft above the ground. During the day, there is limited biting activity by *Ae. africanus* at the ground level in the forests, and this behavior pattern follows the activity pattern of the monkeys [51,52].

Behavior diversity among populations of *Ae. africanus* is not well understood. However, there is reason to believe that *Ae. africanus* also exists in anthropophilic and non-anthropophilic forms [53]. In some areas, *Ae. africanus* has been implicated in peridomestic transmission of YF to humans [54]; therefore, behavioral variations in this species may play a role in the epidemiology of YF. Moreover, anthropophilic mosquitoes are generally also primatophilic; therefore, non-anthropophilic behavior of *Ae. africanus* may influence the distribution of YF virus in the African forests.

Ae. furcifer, *Ae. taylori* and *Ae. luteocephalus* are the main vectors in the moist and the dry savannahs (the emergence zone) of West Africa. *Ae. furcifer* and *Ae. taylori* are morphologically indistinguishable and usually referred to as the *Ae. furcifer–taylori* group. The *Ae. furcifer–taylori* group seems to be highly anthropophilic throughout its distribution range and has been implicated in several outbreaks, including in Gambia in 1978–1979 [55]. *Ae. furcifer* and *Ae. taylori* are abundant in West Africa, but virtually absent in Central and East Africa, and do not playa significant role in YF transmission in East and Central Africa. *Ae. luteocephalus* is widely distributed, but it is only important as a YF vector in regions where *Ae. africanus* is absent. However, it was implicated as the principal vector in the outbreak in Nigeria in 1969 [56].

Apart from the potential for YF transmission interruptions by different behavioral forms of the mosquito vectors, the behavioral differences suggest underlying genetic differences among these vector populations. Since YF virus replicates in the vector, it probably adapts to the various variants of the vector species, which may affect its infectivity or virulence to the vertebrate hosts. Deubel et al. [6], Lepineic et al. [8] and Mutebi et al. [11] described genetic variation in YF virus in Africa, and showed that different genotypes of YF virus exist in different regions. It is also known that behavioral forms of mosquito vectors show regional distribution as well [34]. It is possible that different genotypes of YF virus in Africa have evolved due to adaptation to mosquito vectors, as mosquitoes are the reservoir for the virus and primates act as amplifying hosts for the virus. It is also possible that in this process of adaptation, some YF virus genotypes became attenuated for viscerotropic disease and are rarely involved in YF outbreaks. Nonetheless, the epidemiology of YF in Africa is divided into two forms according to region. YF outbreaks are few and far between in East and Central Africa, whereas YF outbreaks are very common in Western Africa, especially in the region where West Africa genotype I circulates. The fact that YF genotypes in West Africa have three RYF repeats in their 3' NCR and YF genotypes from East and Central Africa have only two RYF repeats suggests genetic differentiation among the organisms involved in YF transmission cycles between West and East/Central Africa. The 3' NCR is speculated to play important roles in translation regulation, replication and encapsidation of flaviviruses [57], and possibly, genetic variation in this region arose as a result of adaptation to different vertebrate host and/or mosquito vector systems. This adaptation to various host/vector systems probably contributed to the evolution of different genotypes of YF virus in Africa. It would not be surprising if the different genotypes of YF virus differ in virulence to humans and monkeys, and that these differences play a role in determining the epidemiology of YF in Africa.

10. Summary

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. West Africa genotype I circulating in Nigeria and surrounding areas is associated with frequent outbreaks and is genetically more heterogeneous than the other genotypes. Genetic and behavioral variation in mosquito vectors may also play a role in the distribution of YF outbreaks. Finally, epidemiology is a complex, multidisciplinary subject. This review has focused on two major factors in the epidemiology of YF, namely the virus and the mosquito host. The authors recognize that other factors contribute to the epidemiology of YF, including host genetic background, climate, vaccination coverage, vertebrate hosts and movement of vertebrate hosts. However, the size of this review precludes a detailed discussion of all the factors contributing to the epidemiology of YF in Africa.

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