The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle?

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Abstract

Yellow fever and dengue are old diseases, having caused major epidemics in centuries past. Both were effectively controlled in the mid 1900s, yellow fever in Francophone Africa by vaccination and yellow fever and dengue in the Americas by effective control of the principal urban vector of both viruses, *Aedes aegypti*. In the last 25 years of the 20th century, however, there was a resurgence of yellow fever in Africa, and of dengue worldwide. The factors responsible for this resurgence are discussed, as are current options for prevention and control.

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Keywords: Dengue; Yellow fever; Aedes aegypti; Hemorrhagic fever; Mosquitoes

Résumé

Les fluctuations des situations épidémiologiques de la fièvre jaune et de la dengue de 1900 à 2003s: une évolution cyclique?

La fièvre jaune et la dengue sont des maladies anciennes qui ont entraîné, dans les siècles passés de terribles épidémies. Toutes deux ont été maîtrisées vers le milieu du 20e siècle, grâce à la vaccination pour ce qui est de la fièvre jaune en Afrique francophone et, sur le continent américain, par le contrôle efficace d’*Aedes aegypti*, le principal vecteur de ces deux virus en milieu urbain. Durant les 25 dernières années, cependant, on a assisté à une très forte résurgence de la fièvre jaune en Afrique et de la dengue dans l’ensemble du monde tropical. Les facteurs responsables de cette évolution sont discutés ici, tout comme les orientations actuellement préconisées pour la prévention et la maîtrise de ces affections.

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Mots-clé: Dengue; Fièvre jaune; Aedes aegypti; Fièvre hémorragique; Moustiques

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0147-9571/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cimid.2004.03.013
1. Introduction

Yellow fever (YF) and dengue fever/dengue hemorrhagic fever (DF/DHF) are diseases caused by mosquito-borne viruses belonging to the family Flaviviridae, genus Flavivirus [1]. YF is the prototype virus of this family, first isolated from a human case in West Africa in 1927 [2]. DF/DHF are caused by four closely related viruses called dengue 1, dengue 2, dengue 3 and dengue 4 (DENV-1, -2, -3 and -4). Both YF and DF/DHF viruses are maintained in primitive rainforest cycles involving lower primates and canopy dwelling mosquitoes (Fig. 1). YF virus is enzootic in the rainforests of Africa and the Amazon Basin in the Americas (Fig. 2) [2,3] whereas DEN viruses occur in similar cycles in rainforests of Asia and West Africa [4,5]. Both YF and DEN viruses can be transmitted in an urban cycle between humans by the highly domesticated Aedes aegypti mosquito [3,6,7]. This species is a very efficient epidemic vector of both viruses because of its close association with humans in urban settings, and its blood-feeding behavior of taking blood from multiple human hosts during a single gonotrophic cycle [7,8]. The DEN viruses are unique in that they are the only known arboviruses that have fully adapted to humans and are maintained in large urban centers of the tropics (Fig. 3) in an Ae. aegypti-human-Ae. aegypti cycle without apparent input from the enzootic cycles [8]. Thus, in contrast to YF, while the forest enzootic cycle of DEN-viruses exists, it is not important in the recent resurgence of DF/DHF as a global public health problem.

Both DEN and YF virus infection in humans cause a spectrum of illness ranging from inapparent infection to severe hemorrhagic disease that is sometimes fatal [6,8,9]. The majority of infections present as mild to severe febrile illness, while only a small percentage of patients progress to develop hemorrhagic disease. The case fatality rate for DHF is about 5% on average, while that for YF is about 20% [6,8,9].

2. Historical

Both YF and DF are old diseases and historically were major public health problems, causing widespread epidemics during the 17th, 18th, 19th and early 20th centuries [6,10,11]. The initial geographic expansion of both YF and DF was closely tied to the global spread of Ae. aegypti mosquitoes from Africa to other parts of the tropics as the shipping industry and commerce expanded in the 17th and 18th centuries [11]. Both YF

Fig. 1. Transmission cycles of YF and dengue viruses.
virus and *Ae. aegypti* almost certainly had an African origin [6,10], while it is uncertain where the DEN viruses evolved. However, old reports and the maintenance of all four virus serotypes in enzootic forest cycles suggests that these viruses may have evolved in Asia from a progenitor virus that was most likely from Africa [11]. Regardless of their origin, the viruses were introduced to villages by humans or monkeys who had been exposed in the forest; in the villages, the viruses were propagated by peridomestic mosquitoes such as *Ae. aegypti* (YF/Africa) and *Ae. albopictus* (DF/Asia). From the villages the viruses were introduced into port cities where *Ae. aegypti* had become
established and from there both the mosquitoes and the viruses were transported to inland cities and to port cities all over the tropical world by barges and sailing vessels.

3. Changing epidemiology, 1900–1970

3.1. Yellow fever—Americas

The first recorded epidemic of what is thought to have been YF was in the Yucatan Peninsula in 1648, and was likely part of a larger epidemic that involved a number of Caribbean Islands from 1647–1649 [6,10]. From that time to the early 20th century, YF was the most important epidemic disease in the New World, with summer epidemics reaching the northeastern part of the United States as far north as Boston. As Soper [10] put it, ‘no country in the Americas failed to pay tribute to this tropical scourge.’

A major breakthrough in understanding the epidemiology of YF occurred in 1900 when Reed and the Yellow Fever Commission working in Cuba, documented that YF was caused by a filterable agent transmitted by \textit{Ae. aegypti} mosquitoes [12]. Once this transmission cycle was documented, prevention and control programs, focusing on \textit{Ae. aegypti} control were implemented widely, resulting in a dramatic decrease in the number of epidemics and the incidence of YF [6,10]. In those areas where the mosquito control programs were relaxed, the disease re-emerged. By 1915, however, the only recognized endemic areas of YF remaining in the Americas were Guayaquil, Ecuador and Bahia and Pernambuco on the east coast of Brazil [10], and the Rockefeller Foundation, encouraged by the successful control programs, embarked on a campaign to eradicate YF from the Western Hemisphere. By 1925, the only known remaining endemic area was a small coastal area in northeast Brazil. After an absence of 20 years, however, YF re-emerged in Rio de Janeiro in 1928, and subsequent investigation led to the discovery of a forest cycle of YF involving lower primates and \textit{Haemagogus} species of mosquitoes [3,6,10].

The advent of DDT and its efficient use for mosquito control in the post-WWII years, renewed the thinking that YF could be prevented in urban areas by eradication of \textit{Ae. aegypti}. A successful hemispheric program was initiated by the Pan American Health Organization in 1946 [13] (Fig. 4). The last urban epidemic of YF in South America occurred in Sera Madureira, Acre State, Brazil in 1942 [6]. Although small outbreaks have occurred in Trinidad in 1954 and in 1979, the evidence that \textit{Ae. aegypti} was the vector was not compelling [14]. In the past 50 years, YF has been maintained in the Amazon Basin, with periodic outbreaks or sporadic cases associated with the enzootic forest cycle [15]. For example, in the early 1950s, enzootic YF spread northward through Central America to Mexico [6]. In recent years, there have been several significant outbreaks in Bolivia, Peru, Ecuador and Brazil [15–18].

3.2. YF—Africa

The first recorded epidemic of YF in Africa occurred among British troops in St. Louis de Senegal in 1778 [2]. Although major outbreaks of YF were subsequently documented in West Africa, they were not as explosive or severe as the epidemics that occurred in
the New World; case fatality rates have always been lower in Africa than the Americas [19]. Little was known of the disease in Africa until the Rockefeller Foundation established the African YF Commission in 1925 [2]. This group made many important discoveries, including the first isolation of the YF virus from a human by inoculating the blood of a patient, Asibi, who had a mild form of YF, into several monkeys in July 1927. They subsequently showed that monkeys are very important hosts, that there were monkey-Ae. africanus-monkey cycles in the forests, and a monkey and human cycle involving another mosquito species, Ae. simpsoni, in villages [2]. They also developed the first YF vaccine in 1931 [20]. Both the French and the Rockefeller YF Commission subsequently developed other vaccines that were widely used to control YF [21,22].

The period from 1940 to 1970 in Africa saw effective control of epidemic YF in Francophone West Africa through the use of YF vaccination [6]. Multiple outbreaks continued to occur in the British West African colonies, however, because widespread immunization campaigns were not conducted. In East Africa, YF epidemics have been historically rare, but in 1959, small outbreaks occurred on the Sudan–Ethiopian border, which subsequently spread along the Omo River valley causing a major epidemic between 1960 and 1962 [2,6]. Smaller outbreaks continued to occur in West and central Africa from the 1960s to the present [19].

Major advances in our knowledge of sylvatic yellow fever were made by French scientists working in West and Central Africa during the 1960s to the 1980s [23]. They documented a number of the sylvatic mosquito vectors of YF, including Ae. africanus, Ae. luteocephalus, Ae. opok, Ae. furcifer-taylori and the Ae. simpsoni group, documented vertical transmission in some mosquito species, and isolated YF virus from both larvae and adults of the hard tick, Amblyomma varigatus [23]. Finally, they defined the spatial distribution of the disease and identified zones where humans are at greatest risk of sylvatic infection. The principal enzootic focus of YF in Africa is the great equatorial rainforest that extends all the way across Africa to Uganda and south to Angola.
The savannah-forest mosaic and the moist savannah, which extend out from the rainforest, have repeated YF activity during the rainy season. The riverine gallery forests that extend through these areas serve as conduits for the epizootic activity. Further out from the rainforest is the dry savannah where the rainy season is short and sylvatic mosquito vectors are not abundant. *Ae. aegypti* may breed in stored water containers in this area and can transmit YF when the virus is introduced, initiating a human-mosquito-human transmission cycle [6,23].

### 3.3. Dengue-Americas

Dengue, like YF was a major epidemic disease at the dawn of the 20th century, with major epidemics occurring periodically throughout the region, often beginning in one country and spreading throughout the region over several years [11,24]. Like YF, few countries were spared epidemic activity. Epidemics that were clinically compatible with DF occurred as early as 1635 and 1699 in the West Indies and Central America, respectively [11]. In 1780, a major epidemic occurred in Philadelphia in the US [25]. Major epidemics were common in the US into the 1930s, the last outbreak until recently, occurring in New Orleans in 1945 [11,24,26].

The demonstration that YF was transmitted by mosquitoes in 1900 was followed a few years later by a similar demonstration for dengue viruses [27]. The *Ae. aegypti* control programs targeting urban YF prevention were, therefore, very effective against DF as well. As *Ae. aegypti* was controlled in urban areas of tropical America, epidemic DF declined or disappeared in much of the region that had successfully eliminated the mosquito vector (Fig. 4). A characteristic of DF in the Americas during the first 70 years of the 20th century was that the disease was classical DF, and that the epidemics were caused by a single virus serotype [11]. While large epidemics with thousands of cases were common, transmission was usually self-limited and the virus disappeared after several months; severe hemorrhagic disease and fatalities were rare.

### 3.4. Dengue-Asia/Pacific

Epidemic DF was a common occurrence in Asia in the first 50 years of the 20th century [11]. Epidemic waves would move through the region every 10 to 40 years, depending on when a new virus was introduced. DEN viruses were endemic in many cities of Asia during this time as documented by the numerous accounts of expatriates arriving in a tropical Asian city only to become ill with a severe dengue-like illness within weeks to months of arrival [11]. In the pre-virology era, the geographic distribution of the DEN virus serotypes was not known, but isolations of all four virus serotypes from the region in the 1940s and 1950s suggest that they were probably present earlier as well [11,28–30]. This conclusion is supported by colonial observations that native adults in tropical Asian countries rarely became ill with DF [11]. Also, a forest enzootic transmission cycle of DEN viruses involving monkeys and canopy dwelling *Ochlerotatus* (formerly *Aedes*) (*Finlaya*) mosquitoes was documented in the Malay Peninsula [4]. Evidence was obtained that all four DEN virus serotypes were maintained in this monkey-mosquito-monkey cycle.
The epidemiology of DF changed dramatically in Asia and the Pacific during and after World War II [11,31]. The insertion of hundreds of thousands of susceptible Allied and Japanese soldiers into endemic areas of Asia, combined with the increased population densities and expanding geographic distribution of *Ae. aegypti* mosquitoes because of the increased occurrence and movement of war materials, caused major epidemics among the troops of both armies. In addition, DEN virus movement to new geographic areas was enhanced by the numerous large troop movements. Although not known for sure, it is thought that it was these epidemiologic changes that caused Asian cities to become hyperendemic, with the co-circulation of multiple DEN virus serotypes (Fig. 5) [11]. And it was the increased transmission of multiple serotypes that most likely resulted in the emergence of epidemic DHF in the 1950s. The first epidemic occurred in Manila, Philippines in 1953–54, followed by Bangkok in 1958, and Singapore, Malaysia, and Vietnam in the early 1960s [11,32].

3.5. Dengue-Africa

The occurrence of DEN viruses in Africa has not been well documented. Prior to the 1960s, DEN viruses had not been isolated on the continent. Epidemics of DF were reported in the early 1900s, primarily in South Africa and Senegal [5,11]. An epidemic was reported in Yemen in the 1920s, and the last reported epidemics prior to the 1980s, were in Durban, South Africa and St. Louis, Senegal in 1927–28. The first DEN-viruses isolated in Africa were from humans in Nigeria [33]. Subsequently, all four serotypes have been isolated from both West and East Africa [5,11]. An enzootic forest cycle involving monkeys and several species of mosquito has been documented in West Africa, but only for DEN-2 virus, which has also been isolated from male mosquitoes, thus documenting vertical transmission as was shown with YF virus [5,34].

Fig. 5. Global geographic distribution of DEN viruses in 1970 and 2004.
4. The resurgence of epidemic disease, 1970–present

The past 30 years has seen a dramatic geographic spread of DEN viruses within countries and between regions and continents [8,11]. This has resulted in increased frequency of epidemic disease in all tropical parts of the world and the emergence of epidemic DHF in the Pacific Islands and tropical America, in addition to Asia. During this time, the whole of the tropical world has become hyperendemic (multiple DEN viruses co-circulating) (Fig. 5). In 2004, DF/DHF is one of the most important epidemic diseases affecting tropical developing countries worldwide; it has a major public health, social and economic impact on communities where epidemics occur [35]. It is estimated that between 50 and 100 million new dengue infections occur each year, depending on epidemic activity, accompanied by an estimated 500,000 cases of DHF [8,9]. The average case fatality rate for DHF is 5%, but in countries where physicians are well educated on the pathophysiology of DHF and have good facilities, the rate is usually less than 1%. In other countries, the case fatality rate has been reported as high as 40% [36]. This global resurgence of epidemic DF/DHF has been reviewed recently [8,35].

The resurgence of epidemic YF in the past 30 years has not been as dramatic as DF/DHF. While there has been increased epidemic activity in both Africa and the Americas, the outbreaks for the most part have been limited, and associated with the sylvatic cycles. Thus an outbreak in Kenya, the first ever reported, was relatively small and associated with a wandering epizootic along the riverine gallery forests, most likely originating in Ethiopia [37,38]. Recent small outbreaks have occurred in Nigeria, Liberia, Cameroon, Côte d’Ivoire, and Senegal [39]. Larger urban outbreaks have occurred in Nigeria and Côte d’Ivoire [39,40]. In the Americas, outbreaks have occurred in Peru, Ecuador, Venezuela, Bolivia and Brazil [15,16–18]. Of concern is that several of these outbreaks have occurred in, or in close proximity to urban areas where Ae. aegypti occurs, thus greatly increasing the risk of urban YF transmission [39]. In at least one outbreak in Santa Cruz, Bolivia, limited urban transmission was documented [16]. Another cause for concern is the increase in eco-tourism in recent years. Since 1990, six cases of fatal YF have occurred in tourists who visited YF endemic countries in Africa or the Americas without having a prior YF immunization [40–41]. In 2004, the american tropics are at the highest risk for urban epidemics of YF since the 1940s.

5. Prospects for the future

The reasons why there has been such a dramatic global resurgence of epidemic DF and the emergence of DHF are not fully understood, but clearly are related to the demographic and societal changes that have occurred in the past 50 years [8]. Unprecedented population growth, primarily in the urban centers of developing countries has been a major driving force, increasing the movement of people, and thus pathogens such as DEN and YF viruses. Modern transportation insure a rapid transit of both viruses and mosquitoes, and uncontrolled urbanization and a breakdown in the public health infrastructure increase the probability that secondary transmission will occur after a virus is introduced.
There is nothing on the horizon that suggests that these ecologic factors, which greatly facilitate transmission, will change in the near future.

YF and DF have a very similar disease ecology. Both viruses cause high viremia in humans that may persist for several days, and both are transmitted in the urban setting by the highly domesticated *Ae. aegypti* mosquito, thus increasing the probability of transport to new geographic locations. This has already occurred with the DEN viruses and to a certain extent with YF virus [39,41]. Because of its urban ecology, it is anticipated that epidemic DF/DHF will continue unabated for the unforeseeable future. The biggest threat to the future is that YF virus will become urbanized and begin to spread like DF has over the past 25 years. If that happens, the global health community will have an unprecedented public health emergency to deal with. There are over 2 billion people living in *Ae. aegypti* infested areas in Asia and the Pacific. Capabilities for mosquito control in the countries of these regions are nearly non-existent. The majority of people live in large urban centers under crowded conditions in intimate association with large populations of *Ae. aegypti* mosquitoes, thus creating ideal conditions for increased transmission of *Ae. aegypti*-borne diseases. While there is an effective, safe economical vaccine for YF, its supply is very limited and it would take months to increase production to the point where adequate doses could be produced. If YF was introduced to an Asian-Pacific country, it would most likely be misdiagnosed as DHF, leptospirosis, rickettsiosis, hantavirus disease or malaria, thus potentially allowing it to spread to become established in numerous countries before it was recognized and an effective control program could be mounted. Thus, YF virus could be introduced and become established in Asian-Pacific countries weeks to months before it was recognized. Once it was recognized, it would likely create overreaction and panic on the part of the press, the public and health officials. Regardless of whether the YF virus caused a major epidemic in this region, there would be a major crisis, creating social disruption and great economic loss to all countries of the region, similar to the Indian plague epidemic of 1994 [42,43].

It is not known whether YF virus would become established in Asia [39,44,45]. YF virus was most likely introduced sporadically to Asia in times past, but secondary transmission was never been documented [46]. There are several possible explanations why there have not been YF epidemics in the Asia-Pacific region. First, logistics; during the time when major YF epidemics were occurring in the Americas, the virus and the mosquitoes depended on sailing vessels to be transported to new geographic locations. The probabilities of the virus being introduced to Asia were low because there was not as much commerce between Caribbean, Central and South American counties and Asia, as with the US and Europe. Second, the high heterotypic flavivirus antibody (DEN-1, DEN-2, DEN-3, DEN-4, Japanese encephalitis, and others) rates in Asian populations, while not protecting against YF infection, could possibly modulate the infection and down-regulate viremia and clinical expression, as has been shown in monkeys [47]. Milder illness is likely associated with lower viremia levels, the thus decreasing the likelihood of secondary transmission by mosquitoes. Third, there has been some suggestion that Asian strains of *Ae. aegypti* mosquitoes are less susceptible to YF virus than are American strains. Finally, it is possible that evolutionary exclusion may prevent YF virus from becoming established in areas where closely related flaviviruses are endemic. Most likely, a combination of these factors have contributed to preventing YF from becoming established in Asia in the past.
The logistic and demographic factors that influence DF and YF virus spread at the beginning of the 21st century, however, are very different from past centuries. First, tens of millions of people travel by jet airplane among cities of the regions, and between regions; this provides the ideal mechanism in people incubating the viruses, to transport them to exotic locations. It is estimated that in 1998, nearly 16 million tourists traveled to YF endemic countries, 75% of them to countries in the Americas (Fig. 6). There has been an increase in eco-tourism in recent years, and since 1996, six tourists have died in the United States and Europe as a result of infection with YF virus acquired during travel to YF endemic countries without vaccination [39,41]. Thus, if urban epidemic transmission of YF begins in the Americas, there could be thousands of YF infected people traveling to Asian-Pacific countries where *Ae. aegypti* exposure is high, thus dramatically increasing the probability that YF transmission will occur in Asia.

There is a vaccine for YF; it is a live attenuated virus vaccine that is probably the most effective, safe and economical vaccine available [48]. However, it is not efficiently used in YF endemic countries for primary prevention, instead being used as an emergency response tool to control epidemics after they have been reported. This is a flawed public health policy because passive YF surveillance, like DF surveillance, is poor and insensitive; by the time an immunization program is mounted, the epidemic has usually peaked and is beginning to wane. A classic example of this scenario was the YF outbreak in Abidjan, Côte d’Ivoire in 2001; the last confirmed case of YF occurred a month prior to the emergency vaccination program being implemented [49]. Also, YF vaccine stocks are limited; if urban transmission were to begin, there would not be enough vaccine for American cities, let alone Asia and Pacific cities. Moreover, few countries in either region have the mosquito control infrastructure to mount an effective prevention program based on *Ae. aegypti* control. Thus, whether or not there is documented YF transmission in the Asian-Pacific region, there will be an ‘epidemic of panic’ that will make the 1994 Indian plague incident pale by comparison [42,50].
References


