Yellow fever and dengue: a threat to Europe?

P Reiter (paul.reiter@pasteur.fr)[1]

1. Insects and Infectious Disease Unit, Institut Pasteur, Paris, France

This article has been published on 11 March 2010

The introduction and rapidly expanding range of *Aedes albopictus* in Europe is an iconic example of the growing risk of the globalisation of vectors and vector-borne diseases. The history of yellow fever and dengue in temperate regions confirms that transmission of both diseases could recur, particularly if *Ae. aegypti*, a more effective vector, were to be re-introduced. The article is a broad overview of the natural history and epidemiology of both diseases in the context of these risks.

Background

There is logic in dealing with yellow fever and dengue together, for they have much in common:

- Both are caused by viruses of the family *Flaviviridae*, genus *Flavivirus*.
- Both viruses are strictly primatophilic – they only infect primates, including man.
- In their original habitat, both are zoonotic infections transmitted by forest-dwelling mosquitoes.
- Both can cause haemorrhagic illness in humans, often with fatal consequences.
- Both owe their importance as human pathogens to two forest mosquitoes that have become closely associated with the peridomestic environment.
- The viruses and their urban vectors owe their worldwide distribution to transportation of goods and people.
- Both diseases have a history of transmission in temperate regions, including Europe.

According to the World Health Organization, there are currently 200,000 worldwide cases and 30,000 deaths from yellow fever per year, 90% of them in Africa [1], and as many as 50 million cases of dengue [2].

Epidemics of yellow fever, sometimes catastrophic, were once common in North America as far north as New York and Boston (Table), and in European ports as far north as Cardiff and Dublin [3]. Large epidemics of dengue occurred in the same regions from the 18th century onwards. A massive epidemic, estimated at one million cases, with at least 1,000 deaths, occurred in Greece in 1927-28 [4,5]

Aedes aegypti, the primary urban vector for both viruses, was once established as far north in Europe as Brest and Odessa (Figure 1). It disappeared from the entire Mediterranean region in the mid-20th century, for reasons that are not clear. *Ae. albopictus*, generally regarded as a less important vector of dengue [7], is also capable of transmitting yellow fever. It was introduced to Europe in the 1970s, is well established in at least twelve countries (Figure 2) [8], and is likely to spread northwards, perhaps as far as Scandinavia.

The number of persons who visit countries endemic for dengue and yellow fever is continually rising [11,12]. It is therefore cogent to consider whether introduction of these viruses is likely to lead to autochthonous and even endemic transmission in Europe.

Transmission

Five factors are key to the epidemiology of vector-borne diseases: the ecology and behaviour of the host, the ecology and behaviour of the vectors, and the degree of immunity in the population. A holistic view of this complexity is key to assessing the likelihood of transmission in Europe [13].

Origin of the viruses

There is little doubt that the yellow fever virus (YFV) originated in Africa, and that viruses circulating in the New World are of African origin. Curiously, yellow fever has never been recorded in Asia, although *Ae. aegypti* is widespread there.

There are four antigenically distinct DENV serotypes that cause very similar disease in humans. It is widely accepted that all four are of Asian origin [14], although DENV-2 is enzootic in Africa [15].

Zoonotic vectors and hosts

In the Old World, the sylvatic vectors of yellow fever and dengue are canopy-dwelling mosquitoes of the genus *Aedes* and three subgenera, *Stegomyia, Finlaya,* and *Diceromyia*, that feed exclusively on monkeys. In the Americas, the principal zoonotic vectors of yellow fever are *Sabethes* and *Haemogogus* species; both are also strictly primatophilic [3].

Check for updates

Sylvatic transmission to humans

Sylvatic infections are acquired when humans enter woodland where there is zoonotic transmission. In recent years, a number of unvaccinated tourists have died of yellow fever after visiting enzootic areas [16,17].

Vector-host specificity

Host specificity is a characteristic of many vectors; it is conceivable that it improves the chances of locating hosts. This may be particularly useful in the sylvatic environment, where bands of monkeys roam between established sleeping sites.

The specificity of DENV and YFV to primatophilic vectors may have evolved to exploit this relationship, and/or to surmount barriers to infection in the insect.

Whatever the reason, given the absence of wild primates, it is unlikely that any vector species native to Europe is able to transmit these viruses.

Peridomestic transmission

Neither YFV nor DENV would have major importance as human pathogens in the absence of two mosquito species, *Ae. (Stegomyia) aegypti* and *Ae. (S.) albopictus*, both of which have become closely associated with the peridomestic environment. Infected humans returning from an enzootic area may initiate transmission to humans in human settlements if either of these species is present (although to date, no yellow fever infections have been attributed to *Ae. albopictus*).

Table

Major epidemics of yellow fever in North America, north of Mexico

Year		Year	
1668	New York, Philadelphia and other settlements	1803	Boston, Philadelphia
1690	Charleston	1804	Philadelphia
1691	Boston	1805	Philadelphia
1693	Charleston, Philadelphia, Boston	1807	Charleston
1694	Philadelphia, New York, Boston	1811	New Orleans, Florida, New Jersey
1699	Charleston, Philadelphia	1817	New Orleans, Charleston, Baltimore
1702	New York	1819	New Orleans, Charleston, Baltimore, Philadelphia, New York
1703	Charleston	1820	New Orleans, Philadelphia
1728	Charleston	1821	New Orleans, Mississippi Valley, Alabama, Charleston, Baltimore, Philadelphia, New York, Boston
1732	Charleston	1822	New Orleans, New York
1734	Charleston, Philadelphia, New York, Albany, Boston	1823	Key West
1737	Virginia	1824	New Orleans, Charleston
1739	Charleston	1825	Mobile, Natchez, Washington
1741	Virginia, Philadelphia, New York	1827	New Orleans, Mobile
1743	Virginia, New York	1828	New Orleans, Memphis
1745	Charleston, New York	1829	Key West, Mobile, Natchez
1747	New Haven	1837	New Orleans, Mobile, Natchez
1748	Charleston	1839	Galveston, Mobile, Charleston
1751	Philadelphia, New York	1841	Key West, New Orleans
1762	Philadelphia	1843	Galveston, Mobile, Mississippi Valley, Charleston
1778	Philadelphia	1847	New Orleans, Mobile, Natchez
1780	Philadelphia	1852	Charleston
1783	Baltimore	1853	New Orleans
1791	Philadelphia, New York	1854	New Orleans, Mobile, Alabama, Charleston
1792	Charleston	1855	Mississippi Valley, Norfolk
1793	Philadelphia	1856	New Orleans, Charleston
1794	Philadelphia	1858	Charleston
1795	Philadelphia	1867	Key West, Galveston, New Orleans, Mobile, Philadelphia
1796	Philadelphia	1870	New York
1797	Philadelphia	1873	New Orleans, Mississippi Valley, Alabama, Memphis
1798	Philadelphia	1876	Charleston
1799	Philadelphia	1877	Port Royal SC
1800	Philadelphia	1878	New Orleans, Memphis, Mississippi Valley to St Louis, Chattanooga, many other cities
1801	Norfolk, New York, Massachussetts	1879	Memphis
1802	Philadelphia	1905	New Orleans

Reproduced from [6] with permission from *Environmental Health Perspectives*.

FIGURE 1

Historical distribution of *Aedes aegypti*
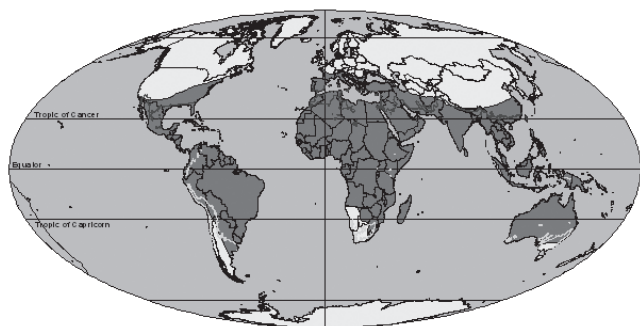
Dark grey areas: maximum range distribution of *Ae. aegypti*, black lines: January 10°C isotherm in the northern hemisphere; mid grey lines: the July 10°C isotherm in the southern hemisphere.
The distribution limit broadly fits the 10°C isotherm in the southern hemisphere, but far less so in the northern hemisphere.
Source: adapted from a map published by Christophers [9].

Dengue is endemic in many urban and rural populations throughout the tropics. 'Virgin soil' epidemics in large cities are often explosive. In 1988, for example, there were an estimated 420,000 cases in four months in the coastal city of Guayaquil, Ecuador [18]

The large urban outbreaks of yellow fever that were common until the early 20th century remain a real and constant danger in enzootic countries that do not enforce routine vaccination. Moreover, it is reasonable to assume that areas that are prone to dengue transmission are equally prone to yellow fever, so areas without history of the latter, including those in southeast Asia, may well be at risk.
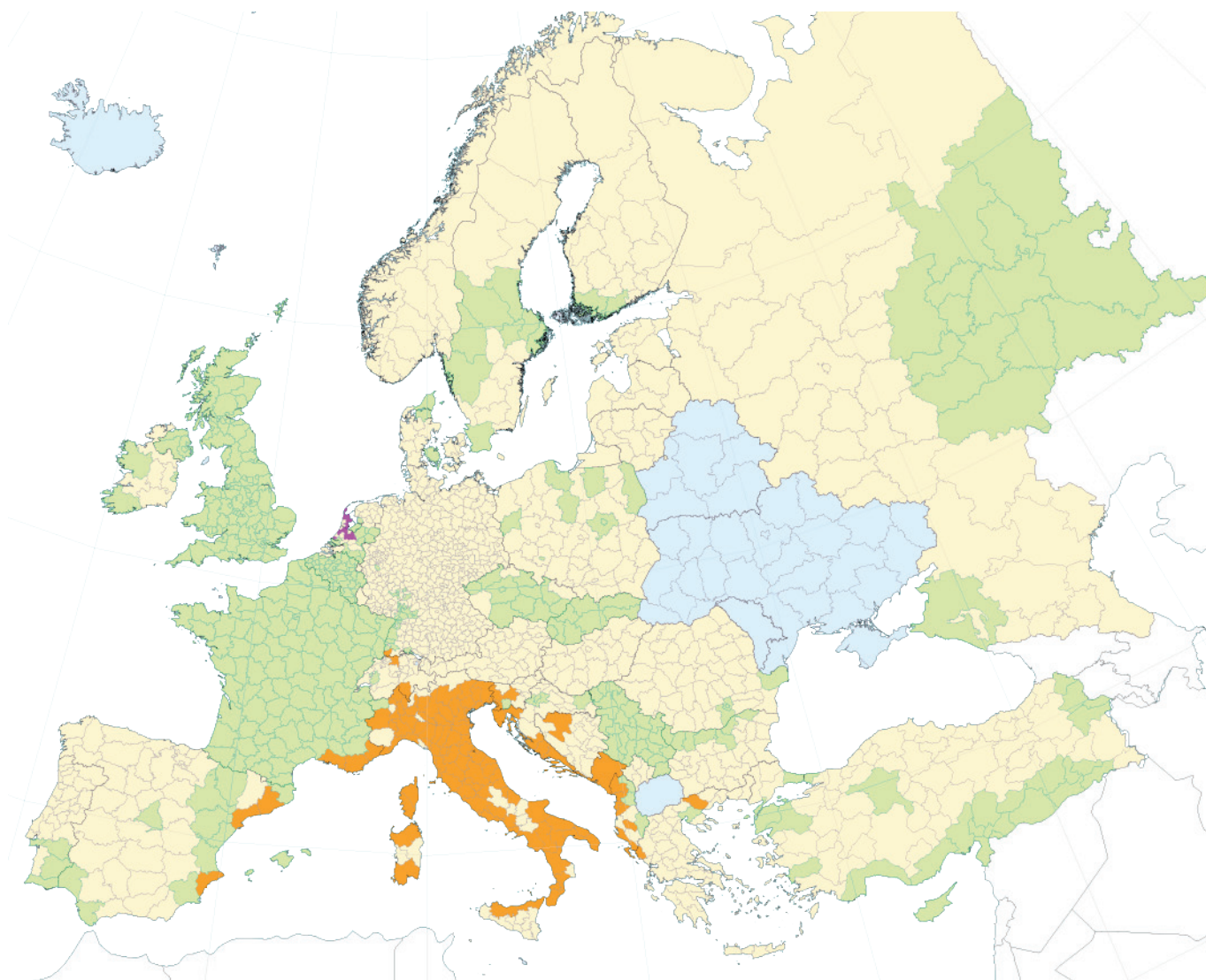
Vectors
The yellow fever mosquito, Aedes aegypti

Ae. aegypti is the quintessential urban vector of yellow fever and dengue. It is a remarkable species because

FIGURE 2

Current (2009) distribution of *Aedes albopictus* in Europe by administrative unit

Orange: overwintering expanding populations; purple: populations only observed indoors (in glass houses); green: not detected in past 5 years; pale yellow: no recent data on mosquito fauna; blue: no information on any mosquito studies; white: not included in this study.
Source: [10].

the 'domesticated' form is rarely found more than 100 m from human habitation and feeds almost exclusively on human blood. Nevertheless, like its forest ancestor, it remains day-active with a preference for heavy shade. It freely enters homes and other buildings and spends much of its time hidden in dark places, often among clothing, a stable microclimate with few predators. Its human host is abundant and lives under the same roof, an arrangement that minimises the hazards of questing for a blood meal. It lays eggs in man-made objects that contain water, from discarded tires and buckets to the saucers under flowerpots and water-storage barrels. In short, humans are the perfect host: they provide safe shelter, plentiful food and abundant sites for procreation. Indeed, in most cities of the tropics, homes are so close together and breeding sites so abundant that they can be regarded as a single factory for mosquitoes in an urban jungle. In the past three decades, attempts to reduce populations of the species have rarely been successful and never sustained [19,20].

The Asian Tiger mosquito, Aedes albopictus

Ae. albopictus is often abundant in the peridomestic environment, particularly in areas with plentiful vegetation. However, in addition to humans, it feeds freely on animals and birds, and so can exist far from human habitation. Since non-primates are not susceptible to the viruses, such blood meals do not contribute to the transmission cycle, and for this reason, *Ae. albopictus* has generally been regarded as a secondary vector [7]. Nevertheless, dengue epidemics have been recorded in places where *Ae. albopictus* is the only vector [21], and in recent years, the species has proved highly effective in urban transmission of another African sylvatic virus, chikungunya virus [22,23].

Globalisation of vectors and viruses

Aedes aegypti

Ae. aegypti and yellow fever arrived in the New World together, as passengers in the slave trade. Slave ships generally made the passage from Africa to the Americas in four to six weeks. The virus was enzootic in regions where the slave caravans captured local inhabitants, and urban transmission was rife in the ports of dispatch. The casks used for shipboard storage of water must have been prolific breeding sites for the mosquito, and the slaves were an abundant source of blood. With the slaves and the mosquito came the virus, and it was not uncommon for ships to arrive in port with large numbers of dying persons aboard, hence the yellow flag of quarantine.

In the United States, the species has been recorded from 21 states (Alabama, Arkansas, Florida, District of Colombia, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maryland, Missouri, Mississippi, New York, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee, Texas, and Virginia) [24]. In many of these, winter temperatures below -20°C are not unusual. Presumably the mosquitoes survive in sheltered sites,

for they are not resistant to freezing. Thus there is no obvious climatic reason why the species, were it to be re-introduced, could not survive in most areas in Europe.

Aedes albopictus

In its original range, *Ae. albopictus* was present from Beijing and northern Japan to tropical Asia [25]. In 1983, however, the mosquito was found in Memphis, Tennessee [26], and, two years later, a survey revealed that it was widely distributed, often common, in the southern United States. Investigation revealed a global trade in used tyres that were frequently infested with eggs and larvae of the species [27]. Japan was the principal exporter, and a study of winter diapause at various latitudes in Asia confirmed that the day-length that triggered diapause was identical in the southern United States and in southern Japan [28]. The mosquito is now widespread in the United States, and is a major nuisance species as far north as Nebraska and Illinois, where winter snowfall can be well above 200 cm, average January night-time temperatures are -10°C, and temperatures as low as -33°C have been recorded. It is also established in Mexico and all the countries of Central and South America except Chile. In Africa it is well established in Nigeria, Gabon, Equatorial Guinea and Cameroon [29,30], and in Europe it has been reported from 16 countries [8]. Recent infestations in the Netherlands have been traced to imports of 'lucky bamboo' from sub-tropical China [31], but these mosquitoes do not appear to have survived the winter, perhaps because they have no winter diapause.

Clinical features

Yellow fever

As with most viral diseases, yellow fever can present with a wide spectrum of symptoms, from mild to fatal. In clinical cases, there is generally a sudden onset of fever with severe headache, arthralgias, and myalgia. The striking yellowing of the eyes and skin, caused by hepatic dysfunction, may appear on the third day and indicates a poor prognosis. The fever often follows a 'saddleback' curve, with a brief drop in temperature and symptoms after the third day, followed by a return with increased severity that can lead to spontaneous haemorrhage ('coffee ground' vomit), delirium, renal failure, coma and death. Fatality rates of clinical cases can be as high as 80% [3], on a par with Ebola, Marburg and other haemorrhagic viral infections.

Dengue

As many as 80% of all dengue infections are asymptomatic. Among clinical cases, early stages are similar to those of yellow fever, although with excruciating arthralgia and myalgia, hence the term 'break-bone fever'. Fever and other symptoms rarely last more than seven days, but convalescence can be prolonged and debilitating. The later stages of the illness often include a widespread rash [32].

A portion of dengue cases, usually less than 5%, can be severe and a fraction of these may be fatal [33]. Severe dengue, commonly referred to as dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) to distinguish it from 'classic' dengue, is associated with spontaneous haemorrhage and an increase of vascular permeability that can lead to life-threatening hypovolemic shock. The causes of this condition have been debated for decades, but remain unresolved [34-36]. A widely held but hotly contested hypothesis is that after infection with one serotype, secondary infections by one or more of the others can precipitate the syndrome by a process referred to as antibody-dependent enhancement, but the occurrence of severe dengue in epidemics of primary infection, such as the Greek epidemic and a recent epidemic in Cape Verde [37], contradicts this hypothesis. An associated controversy is the validity of graded sets of criteria to categorise severity that are recommended by the World Health Organization, and these have been revised several times in recent years [38]. Both issues are of prime importance for the management and treatment of patients.

It is a common misconception that DHF/DSS first appeared in the 1950s in south-east Asia. It is certainly true that the syndrome became a serious public health problem in that period, but it was not a new phenomenon: significant mortality associated with haemorrhagic symptoms had been described in the earliest epidemic of dengue-like disease on record, in Philadelphia in 1789, as well as in later epidemics in East Africa and in Australia [14,39]. Moreover, as already mentioned, at least 1,000 people died in the Greek epidemic in 1927-28. In the years after the Second World War, however, rapid expansion of densely populated urban areas, coupled with enormous infestations of *Ae. aegypti*, led to a massive increase in the prevalence and incidence of the disease in south-east Asia, so a plausible explanation for the emergence of this 'new' syndrome is that escalating numbers of classic infections simply led to an increased awareness of the relatively rare manifestations – the 'iceberg effect'.

Treatment

There is no specific treatment for yellow fever or dengue virus infections; supportive therapy is the only option, although there is active research into antiviral drugs against these diseases [40]. For dengue fevers, intravenous fluids are used to counter haemoconcentration, and platelet transfusions in the event of severe thrombocytopaenia [41]. Strict avoidance of anticoagulants, including aspirin, is important.

Prevention
Vaccination
Yellow fever

A safe, effective yellow fever vaccine, based on a live attenuated strain, has been available for more than half a century, and mass vaccination is a highly effective approach to prevent urban transmission, but the incidence of the disease, particularly in Africa, confirms that coverage is inadequate, and there is a real and present danger of a major urban epidemic. Moreover, there is good reason to believe that the 2.5 billion people who live in regions at risk of dengue infection are also at risk of yellow fever; if so, then, given the lax attitude towards vaccination of travellers in most countries, the danger of a catastrophic epidemic beyond regions generally associated with transmission is also real, and this could include parts of Europe infested with *Ae. albopictus*. If such an event were to occur, current stocks of vaccine would probably be inadequate to respond to worldwide demand.

Dengue

No vaccine against dengue is available, but attenuated virus vaccines and second-generation recombinant vaccines are in active development [42]. A large-scale trial (phase IIb) of a chimeric tetravalent vaccine [43] has been under way since February 2009 [44]. If successful, then a vaccine might be licenced within five years.

Vector control

At the beginning of the 20th century, urban yellow fever was eliminated from many countries by energetic campaigns to eliminate *Ae. aegypti* breeding sites. After the Second World War, focal application of the synthetic pesticide dichlorodiphenyltrichloroethane (DDT) to infested containers and their surroundings was an outstanding success; according to the Pan American Health Organization, the species was eradicated from 22 countries in the Americas [45]. The reason for the efficacy of this method has only recently become apparent: 'skip-oviposition' (the deposition of small numbers of eggs in many different sites) made it highly probable that they would encounter treated sites [19]. No substitute for DDT is currently available, so many authorities resort to spraying insecticidal aerosols (ultra-low-volume) of organophosphates or pyrethroids from hand-held machines, road vehicles or aircraft. Unfortunately, the method is expensive and generally ineffective, at least against *Ae. aegypti*, because the species spends much of its time indoors at sites that are inaccessible to the aerosol [20,46]. Moreover, even if a large number of mosquitoes were to be eliminated by this treatment, the impact on adult mosquito populations would probably be too short for an effective impact on transmission [47]. Although the World Health Organization recommends that health authorities evaluate the technique under local circumstances [6], their principal strategy is community-based source reduction, the elimination of breeding sites by the community. Unfortunately, there is no evidence that this approach has been successful in any part of the world.

Control of *Ae. albopictus* is probably even more difficult than for *Ae. aegypti*, given its ability to breed away from human habitation, but insecticidal aerosols may be more effective for *Ae. albopictus* because the mosquito tends to rest outdoors.

The future in Europe

Dengue is essentially an urban disease because of the urban ecology of its vectors and the behaviour of its hosts. Rapid urbanisation has made it an increasingly serious public health problem in the tropics [48]. Millions of people travel from the tropics to Europe and North America each year (for example, 1.2 million people who live in the UK visit the Indian subcontinent, with average stays of 29 days) and, after malaria, dengue infection is the second most frequent reason for hospitalisation after their return [11,12].

The history of dengue and yellow fever in Europe is evidence that conditions are already suitable for transmission. The establishment of *Ae. albopictus* has made this possible, and the possibility will increase as the species expands northwards, or if *Ae. aegypti* is re-established. The epidemic of chikungunya in northern Italy in 2007 [8,49] confirms that *Ae. albopictus* is capable of supporting epidemic transmission, although laboratory studies indicate that the strain of virus involved was particularly adapted to this species [50,51]. Nevertheless, it is not unreasonable to assume that climatic conditions that permit malaria transmission will also support transmission of yellow fever and dengue, in which case transmission could extend into northern Europe [52].

Lastly, it is widely stated that the incidence of vector-borne diseases will increase if global temperatures increase. While there is no doubt that temperature and rainfall play a role in their transmission, it is clear that many other factors are involved [6]. A more urgent emerging problem is the quantum leap in the mobility of vectors and pathogens that has taken place in the past four decades, a direct result of the revolution of transport technologies and global travel [53]. The potential impact of this globalisation of vector-borne diseases is a challenge for the future.

References

1. World Health Organization (WHO). Yellow Fever. Geneva, December 2009. Fact sheet No 100. Available from: http://www.who.int/mediacentre/factsheets/fs100/en/

2. World Health Organization (WHO). Dengue and dengue haemorrhagic fever. Geneva, March 2009. Fact sheet No 117. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/index.html

3. Monath TP. Yellow fever as an endemic/epidemic disease and priorities for vaccination. Bull Soc Pathol Exot. 2006;99(5):341-7.

4. Papaevangelou G, Halstead SB. Infections with two dengue viruses in Greece in the 20th century. Did dengue hemorrhagic fever occur in the 1928 epidemic? J Trop Med Hyg. 1977;80(3):46-51.

5. Rosen L. Dengue in Greece in 1927 and 1928 and the pathogenesis of dengue hemorrhagic fever: new data and a different conclusion. Am J Trop Med Hyg. 1986;35(3):642-53.

6. Reiter P. Climate change and mosquito-borne disease. Environ Health Perspect. 2001;109 Suppl 1:141-61.

7. Reiter P, Fontenille D, Paupy C. Aedes albopictus as an epidemic vector of chikungunya virus: another emerging problem? Lancet Infect Dis. 2006;6(8):463-4.

8. Scholte E-J, Schaffner F. Waiting for the tiger: establishment and spread of the Aedes albopictus mosquito in Europe. Takken WaKB, editor. Wageningen, The Netherlands: Wageningen Academic Publishers; 2007.

9. Christophers SR. Aëdes aegypti (L.) the yellow fever mosquito, its life history, bionomics and structure. 1960. Cambridge University Press Cambridge, MA.

10. Aedes albopictus distribution maps. European Centre for Disease Prevention and Control (ECDC). Stockholm; March 2010 Available from: http://ecdc.europa.eu/en/activities/pages/programme_on_emerging_and_vector-borne_diseases_maps.aspx

11. Wichmann O, Gascon J, Schunk M, Puente S, Siikamaki H, Gjorup I, et al. Severe dengue virus infection in travelers: risk factors and laboratory indicators. J Infect Dis. 2007;195(8):1089-96.

12. Wilder-Smith A, Schwartz E. Dengue in travelers. N Engl J Med. 2005;353(9):924-32.

13. Reiter P. Climate change and mosquito-borne disease: knowing the horse before hitching the cart. Rev Sci Tech. 2008;27(2):383-98.

14. Gubler D. Dengue and dengue hemorrhagic fever: its history and resurgence as a global public health problem. Gubler D, Kuno G, editors. Dengue and dengue hemorrhagic fever. Wallingford, Oxon, UK; New York: CAB International; 1997, p. 478.

15. Diallo M, Ba Y, Sall AA, Diop OM, Ndione JA, Mondo M, et al. Amplification of the sylvatic cycle of dengue virus type 2, Senegal, 1999-2000: entomologic findings and epidemiologic considerations. Emerg Infect Dis. 2003;9(3):362-7.

16. McFarland JM, Baddour LM, Nelson JE, Elkins SK, Craven RB, Cropp BC, et al. Imported yellow fever in a United States citizen. Clin Infect Dis. 1997;25(5):1143-7.

17. World Health Organization (WHO). One imported case of confirmed yellow fever detected in Belgium. Wkly Epidemiol Rec. 2001;76:357.

18. Centers for Disease Control and Prevention (CDC). International Notes Dengue Epidemic -- Ecuador, 1988. MMWR Morb Mortal Wkly Rep. 1989;38(24);419-421. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00001411.htm

19. Reiter P. Oviposition, dispersal and survival in Aedes aegypti; implications for the efficacy of control strategies. Vector Borne Zoonotic Dis. 2007: Summer;7(2):261-73.

20. Reiter P, Gubler DJ. Surveillance and control of urban dengue vectors. Gubler DJ, Kuno G, editors. Dengue and Dengue Hemorrhagic Fever. New York: CAB International; 1997. p. 425-62.

21. Effler PV, Pang L, Kitsutani P, Vorndam V, Nakata M, Ayers T, et al. Dengue fever, Hawaii, 2001-2002. Emerg Infect Dis. 2005;11(5):742-9.

22. Pages F, Peyrefitte CN, Mve MT, Jarjaval F, Brisse S, Iteman I, et al. Aedes albopictus mosquito: the main vector of the 2007 Chikungunya outbreak in Gabon. PLoS ONE. 2009;4(3):e4691.

23. Renault P, Solet JL, Sissoko D, Balleydier E, Larrieu S, Filleul L, et al. A major epidemic of chikungunya virus infection on Reunion Island, France, 2005-2006. Am J Trop Med Hyg. 2007;77(4):727-31.

24. Darsie R, Ward R. Identification and geographical distribution of the mosquitoes of North America, north of Mexico. Salt Lake City, Utah, USA: American Mosquito Control Association; 1981.

25. Hawley WA. The biology of Aedes albopictus. J Am Mosq Control Assoc Suppl. 1988;1:1-39.

26. Reiter P, Darsie R. Aedes albopictus in Memphis, Tennessee (USA): An achievement of modern transportation? Mosquito News. 1984;44:396-9.

27. Reiter P, Sprenger D. The used tire trade: a mechanism for the worldwide dispersal of container breeding mosquitoes. J Am Mosq Control Assoc. 1987;3(3):494-501.

Check for updates

28. Hawley WA, Reiter P, Copeland RS, Pumpuni CB, Craig GB, Jr. Aedes albopictus in North America: probable introduction in used tires from northern Asia. Science. 1987;236(4805):1114-6.

29. Paupy C, Ollomo B, Kamgang B, Moutailler S, Rousset D, Demanou M, et al. Comparative Role of Aedes albopictus and Aedes aegypti in the Emergence of Dengue and Chikungunya in Central Africa. Vector Borne Zoonotic Dis. 2009 Sep 2.

30. Simard F, Nchoutpouen E, Toto JC, Fontenille D. Geographic distribution and breeding site preference of Aedes albopictus and Aedes aegypti (Diptera: culicidae) in Cameroon, Central Africa. J Med Entomol. 2005;42(5):726-31.

31. Scholte E, Jacobs F, Linton Y, Dijkstra E, Fransen J, Takken W. First record of Aedes (Stegomyia) albopictus in the Netherlands. European Mosquito Bulletin. 2007;22:5-9. Available from: http://e-m-b.org/sites/e-m-b.org/files/European_Mosquito_Bulletin_Publications811/EMB22/EMB22_02.pdf

32. Farrar J. Clinical features of dengue. Halstead SB, editor. Dengue. London: Imperial College Press; 2008. p. 171-91.

33. Morens DM. Dengue fever and dengue hemorrhagic fever. Pediatr Infect Dis J. 2009;28(7):635-6.

34. Halstead SB, Lan NT, Myint TT, Shwe TN, Nisalak A, Kalyanarooj S, et al. Dengue hemorrhagic fever in infants: research opportunities ignored. Emerg Infect Dis. 2002;8(12):1474-9.

35. Rosen L. The Emperor's New Clothes revisited, or reflections on the pathogenesis of dengue hemorrhagic fever. Am J Trop Med Hyg. 1977;26(3):337-43.

36. Murgue B. Severe dengue: questioning the paradigm. Microbes Infect. 2010;12(2):113-8.

37. World Health Organization (WHO). Dengue fever in Cape Verde - update 1. Geneva, November 2009. Available from: http://www.who.int/csr/don/2009_11_18/en/index.html

38. Deen JL, Harris E, Wills B, Balmaseda A, Hammond SN, Rocha C, et al. The WHO dengue classification and case definitions: time for a reassessment. Lancet. 2006;368(9530):170-3.

39. Carey DE. Chikungunya and dengue: a case of mistaken identity? J Hist Med Allied Sci. 1971;26(3):243-62.

40. Monath TP. Treatment of yellow fever. Antiviral Res. 2008;78(1):116-24.

41. Wills B. Management of dengue. Halstead SB, editor. Dengue. London: Imperial College Press; 2008. p. 193-217.

42. Webster DP, Farrar J, Rowland-Jones S. Progress towards a dengue vaccine. Lancet Infect Dis. 2009;9(11):678-87.

43. Guy B, Nougarede N, Begue S, Sanchez V, Souag N, Carre M, et al. Cell-mediated immunity induced by chimeric tetravalent dengue vaccine in naive or flavivirus-primed subjects. Vaccine. 2008;26(45):5712-21.

44. Efficacy and Safety of Dengue Vaccine in Healthy Children. Washington: National Institutes of Health; February 2010, available from: http://clinicaltrials.gov/ct2/show/NCT00842530

45. PAHO. Dengue and dengue hemorrhagic fever in the Americas: guidelines for prevention and control. Washington, DC: Pan American Health Organization; 1994.

46. Reiter P, Nathan M. Guidelines for assessing the efficacy of insecticidal space sprays for control of the dengue vector, Aedes aegypti. Geneva 2001. World Health Organization (WHO).

47. Newton EA, Reiter P. A model of the transmission of dengue fever with an evaluation of the impact of ultra-low volume (ULV) insecticide applications on dengue epidemics. Am J Trop Med Hyg. 1992;47(6):709-20.

48. Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends Microbiol. 2002;10(2):100-3.

49. European Centre for Disease prevention and Control (ECDC). Mission Report: Chikungunya in Italy. Joint ECDC/WHO visit for a European risk assessment 17-21 September 2007; Available from: http://ecdc.europa.eu/en/publications/Publications/0709_MIR_Chikungunya_in_Italy.pdf.

50. Tsetsarkin KA, McGee CE, Volk SM, Vanlandingham DL, Weaver SC, Higgs S. Epistatic roles of E2 glycoprotein mutations in adaption of chikungunya virus to Aedes albopictus and Ae. aegypti mosquitoes. PLoS One. 2009;4(8):e6835.

51. Vazeille M, Moutailler S, Coudrier D, Rousseaux C, Khun H, Huerre M, et al. Two Chikungunya isolates from the outbreak of La Reunion (Indian Ocean) exhibit different patterns of infection in the mosquito, Aedes albopictus. PLoS One. 2007;2(11):e1168.

52. Reiter P. From Shakespeare to Defoe: malaria in England in the Little Ice Age. Emerg Infect Dis. 2000;6(1):1-11.

53. Reiter P. A mollusc on the leg of a beetle: human activities and the global dispersal of vectors and vectorborne pathogens. Infectious disease movement in a borderless world. Washington, DC: The National Academies Press; 2010. p. 150.