

REVIEW ARTICLE

The Global Emergence/Resurgence of Arboviral Diseases As Public Health Problems

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During the past 20 years there has been a dramatic resurgence or emergence of epidemic arboviral diseases affecting both humans and domestic animals. These epidemics have been caused primarily by viruses thought to be under control such as dengue, Japanese encephalitis, yellow fever, and Venezuelan equine encephalitis, or viruses that have expanded their geographic distribution such as West Nile and Rift Valley fever. Several of these viruses are presented as case studies to illustrate the changing epidemiology. The factors responsible for the dramatic resurgence of arboviral diseases in the waning years of the 20th century are discussed, as is the need for rebuilding the public health infrastructure to deal with epidemic vector-borne diseases in the 21st century. © 2002 IMSS. Published by Elsevier Science Inc.

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Introduction

The last 30 years of the 20th century have witnessed a dramatic emergence of newly recognized viral diseases, with over 100 new viruses recognized. Some were important causes of major epidemics of human disease (B. Mahy, 2001, personal communication) (1–3). The majority of the newly recognized viral diseases of humans are zoonoses that have other animal reservoirs and which, due to focal and/or global environmental, societal, and demographic changes were able to jump species to infect humans. Only a few of these newly recognized viruses are arboviruses, which have been relatively unimportant in terms of human disease. Much more important during the same period has been the dramatic epidemic resurgence of a number of well-known arbovirus diseases thought to be effectively controlled or unimportant, e.g., dengue, West Nile, Japanese encephalitis, yellow fever, Rift Valley fever, Venezuelan equine encephalitis, and Ross

River, to name just a few (4,5). This paper will briefly review the global resurgence of arboviral diseases in the past 20 years, present several case studies of some of the more important arboviruses to illustrate the changes in epidemiology that occurred during this time, and discuss the factors responsible for the recent emergence.

Natural History

The word arbovirus is an ecological term used to describe viruses that require a blood-sucking arthropod to complete their life cycle (6). By definition, arboviruses require a minimum of two hosts, a vertebrate and an arthropod. Generally, the virus must produce a level of viremia in the vertebrate host for the arthropod to become infected while taking a blood meal.

There are 534 viruses registered in the International Catalogue of Arboviruses, 214 of which are known or probable arboviruses (7). Another 287 viruses are considered possible arboviruses and 33 are listed as probably or definitely not arboviruses. Of these 534 viruses, 134 have been documented to cause illness in humans (7). Arboviruses are taxonomically diverse, belonging to eight viral families and 14 genera. Most arboviruses of public health importance belong to three families: *Flaviviridae*; *Togaviridae*, and *Bunyaviridae* (8) (Table 1).

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Table 1. The more important arboviruses causing human disease

Family/Virus	Vector	Vertebrate host	Ecology ^b	Disease in humans ^a	Geographic distribution	Epidemics
<u>Togaviridae</u>						
<i>Chikungunya</i> ^a	Mosquitoes	Humans, primates	<u>U</u> ,S,R	SFI	Africa, Asia	Yes
<i>Ross River</i> ^a	Mosquitoes	Humans, marsupials	<u>R</u> ,S,U	SFI	Australia, South Pacific	Yes
<i>Mayaro</i> ^a	Mosquitoes	Birds	<u>R</u> ,S,U	SFI	South America	Yes
<i>O'nyong-nyong</i> ^a	Mosquitoes	?	R	SFI	Africa	Yes
<i>Sinbis</i>	Mosquitoes	Birds	R	SFI	Asia, Africa, Australia, Europe, Americas	Yes
<i>Barmah Forest</i> ^a	Mosquitoes	?	R	SFI	Australia	Yes
<i>Eastern equine encephalitis</i>	Mosquitoes	Birds	R	SFI, ME	Americas	Yes
<i>Western equine encephalitis</i>	Mosquitoes	Birds, rabbits	R	SFI, ME	Americas	Yes
<i>Venezuelan equine encephalitis</i> ^a	Mosquitoes	Rodents	R	SFI, ME	Americas	Yes
<u>Flaviviridae</u>						
<i>Dengue 1–4</i> ^a	Mosquitoes	Humans, primates	<u>U</u> ,S,R	SFI, HF	Worldwide in tropics	Yes
<i>Yellow fever</i> ^a	Mosquitoes	Humans, primates	<u>R</u> ,S,U	SFI, HF	Africa, South America	Yes
<i>Japanese encephalitis</i> ^a ?	Mosquitoes	Birds, pigs	<u>R</u> ,S,U	SFI, ME	Asia, Pacific	Yes
<i>Murray Valley encephalitis</i>	Mosquitoes	Birds	R	SFI, ME	Australia	Yes
<i>Rocio</i>	Mosquitoes	Birds	R	SFI, ME	South America	Yes
<i>St. Louis encephalitis</i>	Mosquitoes	Birds	<u>R</u> ,S,U	SFI, ME	Americas	Yes
<i>West Nile</i> ^a ?	Mosquitoes	Birds	<u>R</u> ,S,U	SFI, ME	Africa, Asia, Europe, U.S.	Yes
<i>Kyasanar Forest disease</i> ^a	Ticks	Primates, rodents, camels	R	SFI, HF, ME	India, Saudi Arabia	Yes
<i>Omsk hemorrhagic fever</i>	Ticks	Rodents	R	SFI, HF	Asia	No
<i>Tick-borne encephalitis</i>	Ticks	Birds, rodents	<u>R</u> ,S	SFI, ME	Europe, Asia, North America	No
<u>Bunyaviridae</u>						
<i>Sandfly fever</i> ^a	Sandflies	?	R	SFI	Europe, Africa, Asia	Yes
<i>Rift Valley fever</i> ^a	Mosquitoes	?	R	SFI, HF, ME	Africa, Middle East	Yes
<i>La Crosse encephalitis</i>	Mosquitoes	Rodents	R,S	SFI, ME	North America	No
<i>California encephalitis</i>	Mosquitoes	Rodents	R	SFI, ME	North America, Europe, Asia	Yes
<i>Congo-Crimean hemorrhagic fever</i> ^a	Ticks	Rodents	R	SFI, HF	Europe, Asia, Africa	Yes
<i>Oropouche</i> ^a	Midges	?	<u>R</u> ,S,U	SFI	Central and South America	Yes

^aArboviruses that produce significant human viremia levels; ^bU = urban; S = suburban; R = rural; underline designates the most important ecology; ^cSFI = systemic febrile illness; ME = meningoencephalitis; HF = hemorrhagic fever.

The arboviruses are, with few exceptions, zoonoses that depend on animal species other than humans for maintenance in nature (7). Humans generally are dead-end or incidental hosts who usually do not contribute to the transmission cycle by developing viremia and infecting arthropods. In terms of public health, the most important arboviruses are those that cause major mosquito-borne epidemics because they produce viremia in humans (9) (Table 1). The most important reservoir hosts for arboviruses of public health importance are birds or rodents, and the most important arthropod vectors are mosquitoes and ticks (Table 1). At least one arbovirus (dengue), however, has adapted completely to humans and is maintained in large urban centers of the tropics in a mosquito-human-mosquito transmission cycle that no longer depends on other animal reservoirs, although these viruses are also still maintained in zoonotic cycles in the rain forests of Asia and Africa in a mosquito-monkey-mosquito cycle (10).

Arboviruses as a group have a global distribution, but the majority are found in tropical areas where climate conditions permit year-round transmission by cold-blooded arthropods (5,7,9). Individual arboviruses may have a focal geographic distribution that is limited by the ecologic parameters governing their transmission cycle. In general,

the important limiting factors include temperature, rainfall patterns, and humidity, which in turn influence vegetation patterns and other ecologic parameters that determine the geographic distribution of arthropod vectors and vertebrate hosts.

Emergence/Resurgence of Arboviral Diseases

In the past 20 years, global epidemic arboviral activity has dramatically increased (5). Figure 1 highlights the most important epidemics occurring since 1990. Few regions of the world escaped epidemic arboviral disease during this time, most caused by viruses once thought to be controlled or by viruses that were known but that had never been considered public health problems. The geographic distribution of some mosquito vectors and some viruses has expanded globally, accompanied by more frequent and larger epidemics, e.g., dengue fever. In other cases, the viruses have been introduced into new geographic regions and have taken advantage of susceptible vertebrate and arthropod hosts to become established and cause major epidemics/epizootics, e.g., West Nile virus in the U.S. In still other cases, viruses have expanded their geographic distribution regionally,

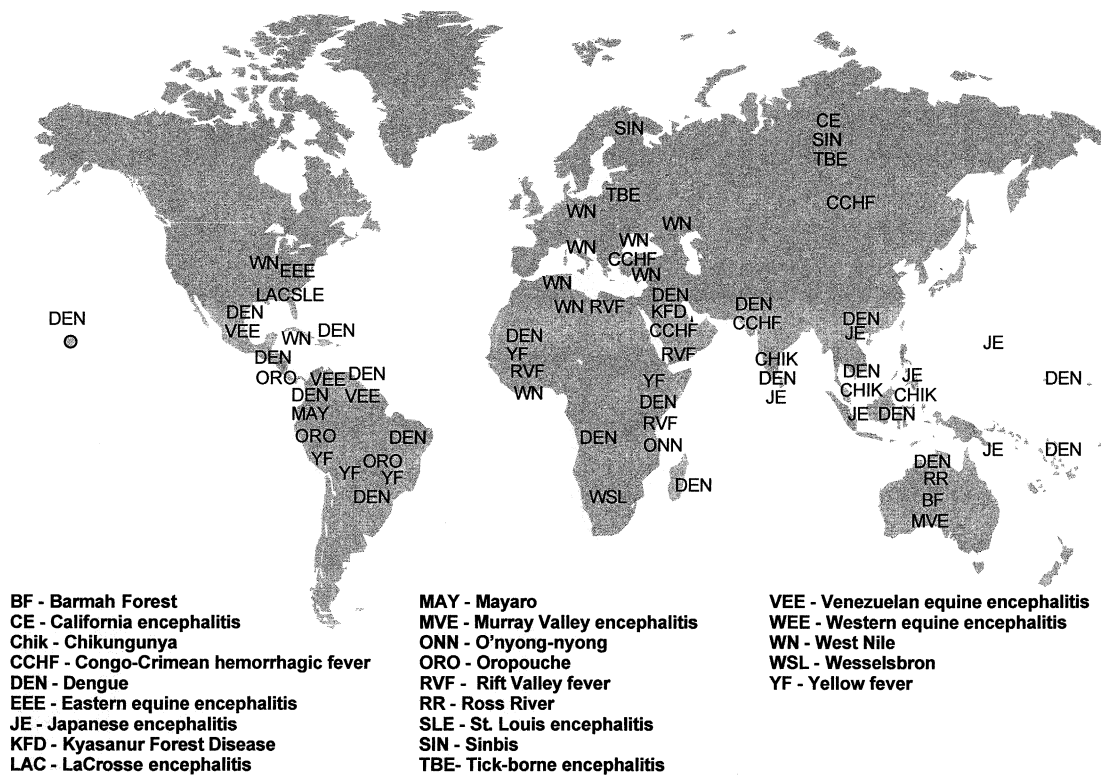


Figure 1. Epidemic arboviral diseases, 1990–2000.

causing major epidemics, e.g., Rift Valley fever, Ross River, and Japanese and Venezuelan equine encephalitis. Finally, at least one virus, e.g., yellow fever, has the potential to cause a global public health emergency because most urban centers of the tropics are permissive for transmission.

The changing epidemiology of arboviral diseases is complex and unique to each virus. Several diseases will be discussed as case studies to illustrate the changes that have occurred and that have allowed these agents to become major public health problems at the beginning of the 21st century.

Dengue/Dengue Hemorrhagic Fever

The dengue viruses (family Flaviviridae: genus *Flavivirus*) are unique among the arboviruses as the only members of this group that have evolved and fully adapted to the human host and his/her environment, essentially eliminating the need for maintenance in the primitive enzootic forest cycle. Dengue fever is an old disease that was spread around the world as commercial shipping expanded in the eighteenth and nineteenth centuries (10). By the beginning of the 20th century, it was a major public health problem in most tropical countries. With the exception of Southeast Asia, epidemic dengue was effectively controlled in most of these countries in the 1950s and 1960s as a side benefit of malaria and yellow fever control programs.

There are four dengue viruses (DEN-1, DEN-2, DEN-3,

and DEN-4) that are antigenically distinct but have the same epidemiology and cause similar illness in humans. All four viruses are now maintained in an endemic cycle involving humans and *Aedes aegypti* mosquitoes in most urban centers of the tropics. One to four DEN viruses may be endemic in the same human population; generally, they are associated with only mild illness (silent transmission) during inter-epidemic periods but cause epidemics associated with more severe disease every 3–5 years. Co-circulation of various virus serotypes in a community (hyperendemicity) is the single most common risk factor associated with the emergence of the severe form of disease—dengue hemorrhagic fever (DHF)—in an area (10,11). The factors responsible for emergence of hyperendemicity associated with periodic epidemics in an area are not well understood. They are likely a combination of the increased movement of viruses in people among countries and regions, the level of herd immunity to specific virus serotypes in human population, and genetic changes in circulating or introduced viruses that give them greater epidemic potential, thus rendering them more likely to be transmitted from host to host.

The dengue viruses are the most widespread geographically of the arboviruses and are found in tropical and subtropical areas where 2.5–3 billion people are at risk of infection (10–12) (Figure 2). Each year an estimated 50–100 million dengue infections occur, depending on epidemic activity, with several hundred thousand cases of the severe form of disease, DHF, and thousands of deaths. In many

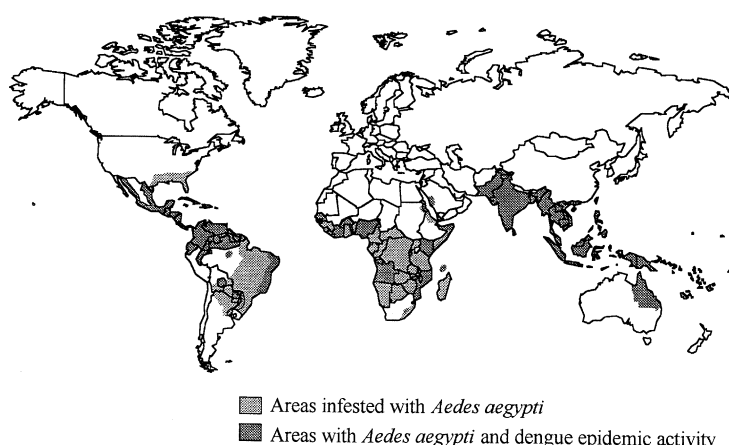
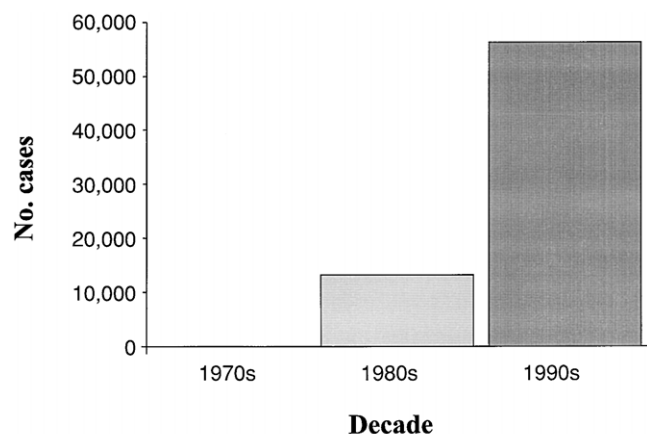


Figure 2. World distribution of dengue, 2001.

Southeast Asian countries, DHF is a leading cause of hospitalization and death among children. In the American tropics there has been a dramatic resurgence of epidemic dengue fever and the emergence for the first time in history of DHF in the past 20 years (Figure 3). In 2002, dengue is the most important arboviral disease of humans; increased disease incidence and epidemic activity are closely correlated with trends of increased population growth in urban areas of the tropical developing world (Figure 4), increased movement of people among population centers via modern transportation, and lack of effective mosquito control (11,13).

Although considerable progress has been made in recent years to develop a vaccine for DEN/DHF, none is expected in the near future. Prevention and control of epidemic disease, therefore, must rely on mosquito control for the indefinite future. There have been several recent reviews of this disease; thus, here it will not be discussed further (10–15).



Data: Pan American Health Organization (PAHO)

Figure 3. Emergence of dengue hemorrhagic fever in the Americas.

West Nile Virus

West Nile (WN) virus (family Flaviviridae: genus Flavivirus) was first isolated from a person with a nonspecific febrile illness in Uganda in 1937 (16). It was not observed again until the 1950s, when WN virus was shown to be widespread in the Middle East and India and caused outbreaks of human disease in Israel. Other than sporadic epidemics in France (1962) and South Africa (1974 and 1983–1984) and occasional isolations from vertebrate hosts or mosquitoes, WN virus was rarely seen and was considered of only minor importance to public health.

In the mid-1990s, the epidemiology of WN virus apparently changed. Epizootics and epidemics of severe neurologic disease in horses, birds, and humans began to occur with increasing frequency (17–25). Epizootics occurred in horses (Morocco, 1996; Italy, 1998; Israel, 1998; U.S., 1999, 2000, 2001; France, 2000) and in birds (Israel, 1997, 1998, 1999, 2000; U.S., 1999, 2000, 2001), and epidemics occurred in humans (Algeria, 1994; Tunisia, 1997; Romania, 1996, 1997; the Czech Republic, 1997; Congo, 1998; Russia, 1998, 1999, 2000; U.S., 1999, 2000, 2001; Israel, 1999, 2000). The reasons for this dramatic emergence of epizootic/epidemic disease caused by a virus that rarely gave rise to severe disease are not well understood, but a new more virulent strain of virus with greater epidemic potential likely emerged and was propagated in the Mediterranean region and subsequently spread to new geographic regions in the late 1990s (19).

Surveillance for arbovirus diseases is generally poor in most countries, and when epidemics do occur they are often not reported to international health agencies. Also, when epidemics primarily affect animals with only peripheral human involvement, such as occurred in North Africa and the Middle East in the 1990s, health authorities are often not notified. Thus, only the epidemic in Bucharest, Romania in 1996 was reported to the international health community (18). The public health community was unaware of the out-

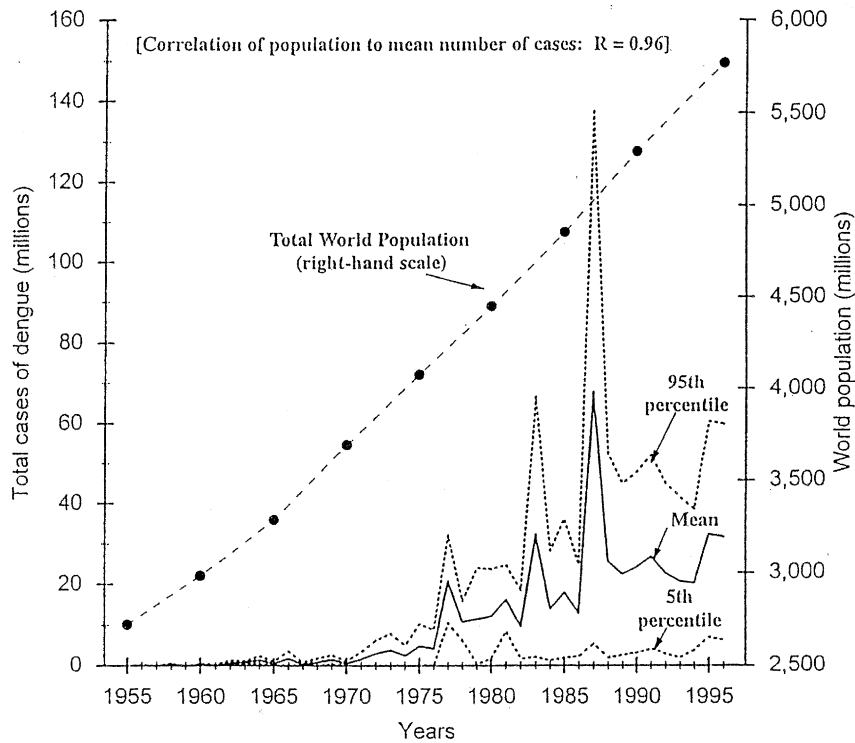


Figure 4. Relationship between global population growth and DF/DHF incidence.

breaks of neurologic disease in domestic geese in Israel that began in 1997 and continued through 2000, and of neurologic disease in horses in a number of countries. Had these epizootics been discussed among public health and veterinary health officials, it is likely that the major epizootic among birds in New York City in summer 1999 would have been recognized and associated with WN virus earlier; thus, human disease might have been diminished, if not prevented.

Geographic expansion of WN virus to the Western Hemisphere was detected in 1999. The epicenter of the outbreak was in the Queens section of New York, but the epizootic spread to at least four states (New York, New Jersey, Connecticut, and Maryland) and involved severe and fatal neurologic disease in humans, birds, horses, and several other mammalian species (19). By the end of the 1999 transmission season, 62 human cases of severe neurologic disease, including seven deaths (11% case-fatality rate [CFR]) were reported (23). Numerous equine cases were documented, including an epizootic on Long Island, New York, with 25 clinical cases and nine deaths (36% CFR) (26). A serologic survey among stable mates and other horses in the area showed that 31% had been infected with WN virus by detection of specific neutralizing antibody (CDC 1999, unpublished data). Thousands of birds belonging to many native species died of WN virus infection in northeastern U.S. (19,27–29).

Evidence suggests WN virus was introduced into the

New York City area in the spring or early summer of 1999 from the Middle East, although there is uncertainty concerning when and from where introduction actually occurred. Genetic sequence studies have shown that the U.S. virus is identical to the WN virus that caused the epizootic in domestic geese in Israel in 1998 (30) (Figure 5). Concurrent with the 1999 U.S. outbreak, a major epidemic in humans associated with severe and fatal neurologic disease occurred in Volgograd, Russia, but no disease in birds was reported (22). In that epidemic, there were an estimated 480 human cases of overt WN disease, 84 of which were diagnosed as encephalitis; 40 persons died. Finally, an outbreak among humans in Tel Aviv, Israel may have occurred in the fall of 1999; although an epidemic was not reported, two patients died of WN virus-associated neurologic disease during that time, suggesting more widespread transmission (30).

How WN virus was introduced into the U.S. is not certain, but there are several possibilities. First, it is known that WN virus moves north in spring and south in fall with migrating birds (25,31,32). A WN virus-infected bird migrating north from Africa may have become disoriented and ended up in New York City. Second, there is a large legal and illegal traffic of exotic birds and other animals in the U.S., and one or more of these animals imported into the U.S. from the Middle East could have been infected with WN virus. A third possibility is that a WN virus-infected mosquito hitched a ride on an airplane from the Middle East. These planes land at JFK International Airport in New

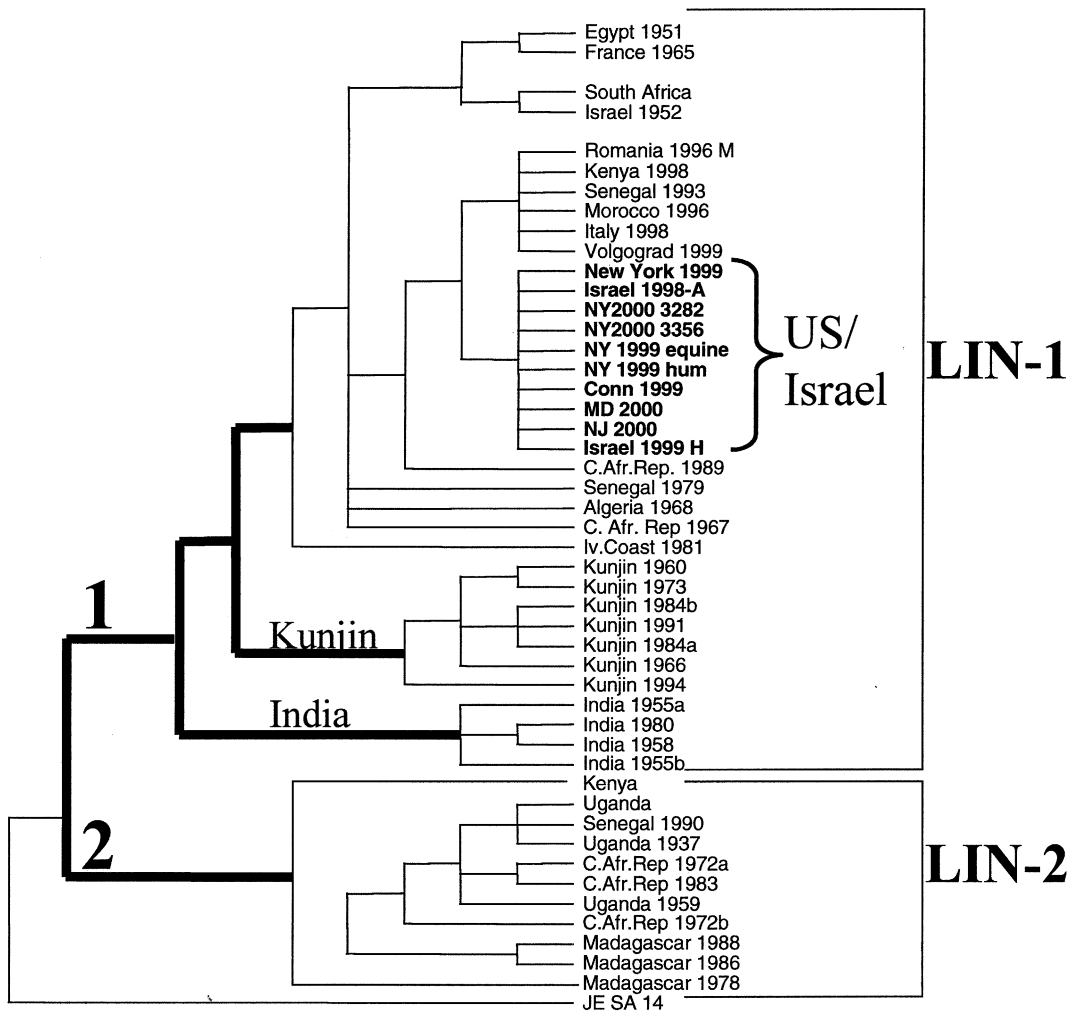


Figure 5. Phylogenetic relationships of West Nile viruses.

York City, however, and there is no evidence to suggest that the epizootic/epidemic began in that area. Fourth, a human traveler infected in the Middle East and incubating the virus could have become ill after arriving in New York City. Finally, WN virus could have been purposely introduced into New York City. There is no evidence to support this latter possibility as all data collected to date are compatible with a natural introduction in the spring of 1999. Serologic surveys of limited archived serum samples from humans, horses, and birds have found no evidence of WN virus in the U.S. prior to 1999 (CDC, unpublished data) (33).

It should be remembered that invasive species rarely become established in a new geographic region as a result of a single introduction. With the exception of those involving humans and birds, the previously mentioned possibilities would likely be rare events, if they occurred at all. On the other hand, a large number of people travel back and forth between New York City and the Middle East on a weekly basis, and hundreds of exotic birds and other animals are imported to the New York area each year. Although we will

probably never know for sure, the most likely scenario is that the virus was introduced by some of the many thousands of visitors who come to New York City each week from the Middle East. Limited data from the Israel epidemics suggest that some humans have a viremia level high enough to infect mosquitoes (34,35).

The appearance of WN virus in the Western Hemisphere in 1999 was yet another instance in which an exotic virus was introduced into a new geographic area and became a public health problem. In this case, however, it was an alert for public health officials in the U.S., where the public health infrastructure for vector-borne diseases had deteriorated badly over the past 30 years and became virtually nonexistent in many state and local health departments (36). With special funding from the U.S. Congress, guidelines for surveillance, prevention, and control were drafted and implemented in all 48 lower continental states (33). Because the most dramatic effect of the introduction of WN virus into the U.S. was the epizootic among birds, especially the American crow (*Corvus brachyrhynchos*)—thousands of crows,

as well as other bird species, have died of WN virus infection over the past 3 years—dead bird surveillance provides a highly sensitive method of monitoring the geographic spread of WN virus in North America and was used to monitor geographic and temporal spread of WN virus in the U.S. during 2000 and 2001 (19,28,33).

In 2000 and 2001, surveillance for WN virus was intensified and expanded to include the first states to which the virus was expected to spread south via migratory birds and, second, all states of the continental U.S. (19,28,33). Emphasis was placed on dead bird surveillance, mosquito surveillance, and on surveillance for neurologic disease in equines and humans. In 2000, WN virus was detected in 12 states and the District of Columbia, the state farthest south being North Carolina. The virus had most likely been introduced into more southern states, however, because in 2001 WN virus was found in Florida in early June, suggesting that WN virus was probably introduced into that area in the fall of 1999 or 2000. In 2001, WN virus was detected in all states (27 states and the District of Columbia) east of the Mississippi River, except for West Virginia and South Carolina (CDC, unpublished data) (37). The virus is no doubt present in the latter two states as well, but has not been detected because of lack of effective surveillance.

In 2000, fewer human cases of WN virus infection occurred than in 1999, most likely because of intensive mosquito control efforts in northeastern states (19); 21 cases and two deaths (CFR = 9.5%) were reported from three states (New York, New Jersey, and Connecticut) (19,23,28). In 2001, however, the virus was much more widespread, with 66 cases and nine deaths (CFR = 14%) reported from 10 states (CDC, unpublished data) (37). A single case of WN virus encephalitis in a person with no travel history was documented in the Cayman Islands, suggesting that the virus has also been introduced into the Caribbean and Central and South America (CDC, unpublished data).

The epizootic in equines intensified dramatically in 2001, with 733 confirmed cases and numerous deaths. Overall, 111 species of North American birds have been affected by WN virus in 27 U.S. states, the District of Columbia, and Ontario, Canada (Figure 6). In addition, the virus has been isolated from a variety of mammals, including two species of bats, skunks, squirrels, rabbits, chipmunks, and cats, and from 29 species of mosquitoes belonging to seven genera. All data suggest that the epizootic in birds is being driven by *Culex pipiens*-complex mosquito species, but the number of opportunistic and mammalophilic species found infected greatly increases the risk to humans and horses (38).

The introduction of WN virus into the Western Hemisphere already has had a great public health and economic impact on the areas affected. It is difficult to estimate the total economic impact of this disease, but New York has estimated that its costs alone have been in excess of \$100 million U.S. dollars (USD). Other states have spent millions to tens of millions of USD rebuilding and improving the pub-

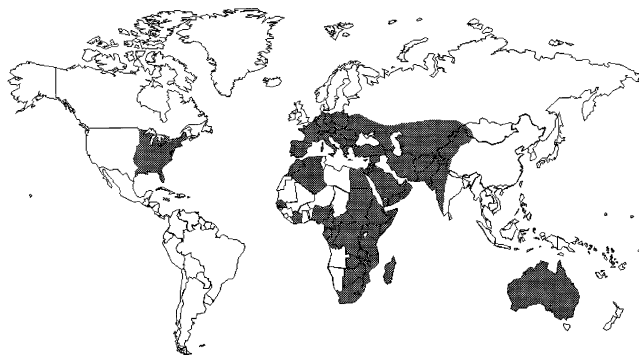


Figure 6. World distribution of West Nile virus.

lic health infrastructure needed to implement surveillance, prevention, and control programs for WN virus and other arboviral diseases. It is likely that WN virus will become established in the western part of the U.S. as well as in the Caribbean and in Central and South America. Countries that have endemic dengue and yellow fever will need to redesign their surveillance systems to distinguish between these flaviviruses.

There is no human vaccine for WN virus, but an experimental killed vaccine for equines has recently been developed. However, the safety and efficacy of this vaccine have not yet been determined. Prevention and control of epidemic/epizootic disease must rely on active surveillance and effective mosquito control.

Japanese Encephalitis

Japanese encephalitis (JE) virus is closely related to WN virus, both belonging to the JE serocomplex (family Flaviviridae: genus *Flavivirus*). JE virus is maintained in an enzootic cycle involving aquatic birds and primarily *Culex* species mosquitoes (39). Pigs act as efficient amplification hosts, and their presence in the peridomestic environment in JE-enzootic areas greatly increases the risk of human and equine infections. Humans and horses are both incidental hosts for JE virus, but infection can lead to illness and death (39).

JE is enzootic in Asia (Figure 7) and is most commonly found in rural rice-growing areas where flooded fields and irrigation systems provide ideal larval habitats for *Culex* vector mosquitoes. JE virus is the leading cause of viral encephalitis in the world with more than 40,000 cases reported annually in Asia (40). It is primarily a disease of children. CFR in humans ranges from 10 to 35%, and as many as 25% of survivors may have serious neurologic sequelae (40).

The epidemiology and transmission patterns of JE virus have changed over the past 20 years (41). Historically, JE has existed in two transmission patterns: 1) an enzootic/endemic pattern in tropical areas with year-round trans-



Figure 7. Geographic distribution of Japanese encephalitis virus.

mission, and 2) an epidemic pattern in subtropical and temperate regions with seasonal epidemics occurring during summer months (42). The epidemiologic pattern of virus activity is most likely a function of the climate, geography, and immune status of host populations. The role that the virus strain plays in determining disease transmission patterns is not yet fully understood.

In subtropical and temperate countries, the epidemic form of disease has been controlled through vaccination and changes in agricultural and animal husbandry practices. At the same time, however, JE has become an emerging disease in the Indian subcontinent, parts of Southeast Asia, and in the Pacific (41). JE virus has caused major epidemics in parts of India where the virus had never been detected previously. In Nepal, epidemic JE was first reported in 1978 but has since spread throughout Nepalese lowland plains and currently occurs in all 25 Terai districts. JE has become one of the most important public health problems in Nepal. In the 1990s, JE virus moved into the Pacific region, causing an epidemic in Saipan in 1990 and in Torres Strait, Australia in 1995 (43,44). JE virus had not been detected in the Western Pacific since 1947 and had never been reported in New Guinea or Australia. Since 1995, continued JE virus activity has been documented; two human cases were detected in 1998 (45). It is possible that JE virus could become established in northern Australia and perhaps in other regions such as the U.S., where at least seven mosquito species and native birds are susceptible to and capable of transmitting JE virus (46).

There are two effective vaccines for JE virus. A killed vaccine prepared in suckling mouse brain (Biken vaccine) has been instrumental in helping prevent epidemic JE in Japan, Korea, Taiwan, and Thailand and a live, attenuated vaccine prepared in primary hamster kidney cells has been effective in China (47). In addition, changes in agricultural and animal husbandry practices have also contributed to decreasing the risk of this infection.

Yellow Fever

Yellow fever (YF), a native virus of Africa, is the type species of the family Flaviviridae: genus *Flavivirus*. It is maintained in an enzootic cycle involving monkeys and canopy-dwelling *Aedes* species mosquitoes in sub-Saharan tropical rain forests; it is periodically introduced into urban areas where it causes epidemics transmitted by the domesticated form of *Ae. aegypti* (48). Both YF virus and *Ae. aegypti* mosquitoes were introduced into the Western Hemisphere during the slave trade in the early 1600s. In the American tropics, a similar rain forest enzootic cycle became established in the Amazon region, involving New World monkeys and mosquitoes of *Haemagogus* species.

YF is an old, well-known disease that caused major epidemics in the Americas and in Africa from the seventeenth to the twentieth centuries. Like DEN/DHF, these were primarily urban epidemics transmitted by *Ae. aegypti*. Elimination of this mosquito from most countries of Central and South America in the 1950s and 1960s effectively controlled urban YF epidemics as well as epidemic DEN in the region (Figure 8). Epidemic YF was controlled in Africa at the same time by immunization with a highly effective, safe, and economical vaccine.

In the past 15 years there has been a resurgence of epidemic YF in Africa (49). Major epidemics have occurred in West Africa, and epizootic YF has occurred in Kenya, East Africa for the first time in history in 1992–1993 (50). Moreover, at least two fatal cases of YF were imported to Europe from West Africa in recent years, suggesting more intense transmission (51,52).

The last urban YF epidemic in Latin America occurred in 1942 (48). In the intervening 60 years, the urban centers of the American tropics have grown dramatically, and in the past 20 years most have been reinfested with the principal urban vector mosquito, *Ae. aegypti*, including large cities located in the Amazon basin where YF virus is maintained in an enzootic cycle (Figure 8). In 2002, an estimated 150–300 million people, most of whom are susceptible to YF virus, are living in crowded urban centers of the American tropics in intimate association with equally large popula-

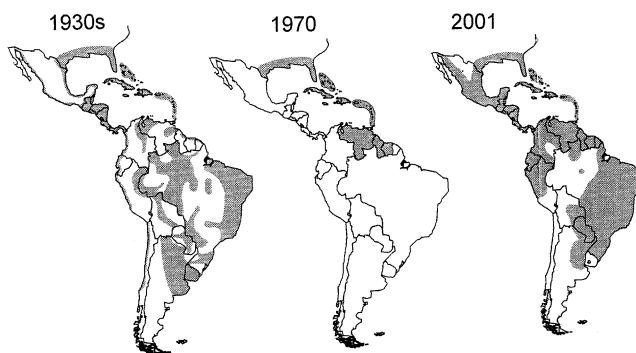


Figure 8. *Aedes aegypti* distribution in the Americas, 1930s, 1970, 2001.

tions of *Ae. aegypti*. The whole region, therefore, is currently at the highest risk for epidemics of urban YF in 50 years (53). A small outbreak of urban YF has already been documented in Santa Cruz, Bolivia in 1998 (54). In 2001, an epidemic occurred in Brazil and although urban transmission was not documented, there was a high risk because of *Ae. aegypti* infestation of the area. A major concern at the beginning of the 21st century is that urban YF epidemics will once again occur in the American tropics. If this occurs in today's world of modern transportation and crowded urban populations, and with increasingly rapid movement of larger numbers of people among population centers, YF, like DEN viruses, will spread rapidly throughout the American region, and from there most likely to Asian and Pacific countries, most of which are heavily infested with *Ae. aegypti* (10,53). This scenario would result in a major global public health emergency.

YF has never been documented in Asia. The reasons for this are not well understood because YF was likely introduced into the area in the past. At least three plausible reasons may explain why epidemic YF never occurred in Asian and Pacific countries (55). First, past urban YF epidemics occurred in the Americas and West Africa before modern transportation, and the simple logistics of introducing YF virus into Asia were much more difficult than at present. While YF virus was probably introduced, it was most likely a rare occurrence, and the probability of a person incubating YF virus and arriving in an area in which there were adequate *Ae. aegypti* mosquitoes to initiate secondary transmission was very low. Secondly, *Ae. aegypti* mosquitoes in Asia may not be as susceptible to YF virus as those in the Americas and Africa. Although some experimental evidence suggests that *Ae. aegypti* from different geographic areas vary in their susceptibility to YF, data to support this hypothesis are not definitive (56,57). Third, a number of other flaviviruses are endemic to Asia, mainly the four dengue serotypes and JE, and most residents of Asian countries have detectable flavivirus antibodies. There is limited experimental evidence that heterotypic flavivirus (DEN) antibody modulates YF infection in monkeys causing milder illness and lower levels of viremia, thus allowing the monkeys to survive YF infection (58; A. Sabin, 1946, unpublished data). It should be noted, however, that heterotypic flavivirus antibody does not convey protection against YF infection.

It is not known which of these factors were the most important in preventing epidemic YF in Asia in the past; possibly all three contributed. In 2002, however, global demographics and population movement are very different in that literally tens of millions of persons travel to and from Asia from the Americas via air each year, greatly increasing the probability that if urban transmission begins in the Americas, the virus will be repeatedly introduced into Asia and Pacific countries on a regular basis, thus increasing the risk of epidemic transmission in a new geographic region in which approximately two billion people are susceptible to YF infection.

There is an effective live-attenuated virus vaccine for YF (48). This disease could be effectively controlled and would no longer be a potential global public health threat if YF vaccine were incorporated into the WHO Expanded Program on Immunization in all African and American countries at risk. It is in the best interest of the global public health community to initiate this program without delay rather than waiting until the crisis occurs and then attempting to respond after it is too late (36).

Rift Valley Fever

Rift Valley fever (RVF) virus (family Bunyaviridae: genus Phlebovirus) was first isolated in 1930 during an outbreak in the Rift Valley in Kenya (59). It has subsequently been shown to have a natural geographic distribution in most countries of sub-Saharan Africa (60). The natural history of RVF virus is not fully understood, but it is clear that the virus is maintained enzootically over much of sub-Saharan Africa. Periodically, explosive epizootics occur when there is heavy rainfall in areas where there are herds of sheep or cattle and other livestock (60,61). Domestic livestock serve as amplifying hosts for the virus, which serve in turn to infect more mosquitoes. The natural vertebrate reservoir host is not known.

Epizootics of RVF are unique because they often do not begin in one place and spread to other areas. Rather, they erupt almost simultaneously over wide geographic areas in association with increased rainfall. Because of this observation as well as some experimental evidence, it is hypothesized that floodwater *Aedes* mosquitoes, belonging to the subgenera *Aedimorphus* and *Neomelanicion*, are the actual reservoirs for RVF virus. It is thought that the virus is maintained via transovarial transmission in these floodwater mosquitoes (61–64); infected mosquito eggs are deposited in the mud of damboes (ground depressions), where the virus is protected until the eggs hatch. When it rains, these damboes are flooded, the eggs hatch, and a proportion of the adult mosquitoes are already infected with RVF virus when they emerge. They thus transmit the virus when they partake of their first blood meal, initiating amplification and possibly epidemic transmission if there are herds of cattle or sheep in the area. A number of *Aedes* as well as *Culex* species of mosquitoes have shown to be efficient vectors of this virus (62–68).

Although epizootics/epidemics of RVF have occurred over the majority of sub-Saharan Africa, the virus has expanded its geographic distribution in the past 25 years. During 1977–1978, a large epidemic occurred in Egypt for the first time (65). The virus disappeared after a few years but returned again in the early 1990s. In 1998, RVF caused a large epidemic in Somalia and Kenya associated with the heavy rains that followed the 1997–1998 El Niño season (69). In 2000, RVF virus again moved into a new geo-

graphic region, causing a large epidemic/epizootic in Saudi Arabia and Yemen (70). It is not known how the virus was introduced into Egypt or the Middle East, but it may have been transported in infected domestic animals. Others think that RVF virus may have been introduced by infected floodwater *Aedes* mosquitoes flying from Africa. Either way, the potential for future movement of this virus is great because the virus infects a wide variety of domestic animals, and causes a high level of viremia in many, has a very broad mosquito host range, and is capable of transovarial transmission. Thus, the chances of RVF virus becoming established in new geographic areas into which it is introduced are great. In the Americas, for example, several species of mosquitoes are highly susceptible to RVF virus (71).

The introduction of RVF virus into new geographic regions is of particular concern because it can cause devastating epizootics among domestic animals, especially sheep and cattle, as well as major epidemics of severe and fatal disease among humans. In cattle and sheep, RVF virus infection causes abortion and a high CFR (72). In humans, RVF virus infection causes several different disease syndromes. The majority of infected humans have a nonspecific viral syndrome, but a small percentage of patients may progress to develop hemorrhagic fever, encephalitis, or ocular disease. Case-fatality rate in humans is <1% (72).

Prevention and control of RVF in humans rely on preventing disease in domestic animals in the peridomestic environment. A veterinary vaccine is available and could be used more effectively to prevent animal, and thus human, disease. It could also be used to prevent the spread of RVF virus to new locations. Another option, but more difficult to implement effectively, is mosquito control. Efforts should be focused on the floodwater *Aedes* species that may be involved in the maintenance cycle. For example, known damboes in areas where humans and domestic animals are at risk could be kept from flooding by plowing ditches to drain the water after it rains. In addition, control strategies must be developed for *Culex* and other species that may be involved in epidemic/epizootic transmission.

Venezuelan Equine Encephalitis

Venezuelan equine encephalitis (VEE) virus (family *Togaviridae*; genus *Alphavirus*) is the prototype for an antigenic complex of very closely related viruses isolated from a variety of animals including horses, rodents, and mosquitoes (73–75). These viruses are classified on the basis of serology into six subtypes, which include VEE (subtype I), Everglades (II), Mucambo (III), Pixuna (IV), Cabasson (V), and an unnamed virus (AG80-663-VI). These viruses have an American geographic distribution ranging from Argentina to the U.S. For this paper, only VEE virus (subtype I) will be discussed.

VEE (subtype I) viruses are further subdivided into five variants or serotypes (AB–F). VEE AB and C viruses are considered epizootic variants and are pathogenic for horses

(73–75). It is not known how they are maintained in nature, but they have been responsible for major epizootics that have caused thousands of equine and human infections. VEE D, E, and F viruses are considered to be enzootic and cycle in tropical and subtropical swamps and forests in a natural rodent reservoir host—*Culex (Melanoconion)* species mosquito vector cycle. These latter viruses are not virulent for equines and are not known to cause epizootics (73–75).

Clinically, patients infected with both epizootic or enzootic variants of VEE virus develop a nonspecific viral syndrome (74,75). Although it is not known for sure, data suggest that the majority of infections with epizootic-variant viruses lead to disease, whereas many infections with enzootic variants may be inapparent. Epizootic virus infection can lead to encephalitis in a small proportion of cases, occurring more frequently in children than in adults. Death is rare but can occur following infection with either enzootic or epizootic variants of VEE virus.

Periodic epizootics/epidemics of VEE occurred in northern South America (Venezuela, Colombia, Ecuador, and Peru) from the 1930s through the 1960s (73,75). In 1969, a major epizootic, caused by IAB VEE, began in Guatemala/El Salvador and spread throughout Central America and Mexico, ultimately reaching Texas, U.S., in 1971–1972 (73,75). Epizootic VEE then disappeared for 19 years until 1992, when a small outbreak of IC virus occurred in Venezuela (75,76). Another large epidemic/epizootic of IC VEE occurred in 1995, beginning in Venezuela and moving around the La Guajira Peninsula into Colombia (75,77). This epidemic/epizootic involved thousands of horses and an estimated 92,000 human infections in Colombia alone. This latter epizootic was caused by an IC VEE virus different from the 1992 outbreak virus but similar to a virus not isolated since 1962–1964 (76,78). Sequences of the 1964 and 1995 viruses were identical, suggesting that the 1995 epizootic may have been caused by a virus that escaped from the laboratory (78). It is not known for sure where the viruses that caused these epidemics/epizootics originated, but modern molecular technology is helping answer some of the questions (75,76,78).

Prevention and control of epizootic/epidemic VEE depends on effective use of veterinary vaccines for these viruses. There are two vaccines available, a killed vaccine (C-84) and a live, attenuated vaccine (TC-83). Unfortunately, equine vaccination in many countries is not widespread. During epizootic/epidemic transmission, mosquito control is an important adjunct to vaccination.

Other Arboviruses

The diseases discussed above are only a few of the more important arbovirus diseases that are a threat to human and domestic animal health at the beginning of the 21st century. Many others have the potential to cause epidemic disease

and spread geographically. Alphaviruses such as Ross River, Chikungunya, Mayaro, O'nyong-nyong, Barmah Forest, Me Tri, and Eastern and Western equine encephalitis, flaviviruses such as St. Louis and Murray Valley encephalitis, and bunyaviruses such as Oropouche, sandfly fever, and others, could all cause major epidemics.

Factors Responsible for the Recent Emergence/Resurgence

The reasons for the dramatic resurgence of epidemic arbovirus disease in the waning years of the 20th century are complex and incompletely understood. It is obvious, however, that the changing epidemiology and emergence of epidemic disease are associated with demographic and societal changes that have occurred during the past 50 years (4,5,11).

Probably the most important is the unprecedented global population growth that has occurred since the end of World War II, most taking place in the developing world. This population growth has driven many of the other demographic and societal changes that have influenced transmission dynamics of arboviral diseases, e.g., urbanization, deforestation, new dams and irrigation systems, poor housing, sewer and waste management systems, and lack of reliable water systems that make it necessary to collect and store water. All of these and other factors have contributed to increased mosquito populations and closer contact between humans and mosquito vectors.

Another factor has been complacency concerning vector-borne diseases; few new and effective mosquito control methods have been developed in the past 30 years (36). In general, research on and implementation of mosquito control have been unfunded because mosquito-borne diseases have been considered by decision-makers to either be under control or not important public health problems. The result has been ineffective mosquito control programs in most countries for 30 years.

Finally, the changing global demographics that have resulted from modern transportation have had a major influence on the distribution and transmission dynamics of arboviral diseases (5). The jet airplane is used to move people, animals, and commodities, thus providing the ideal mechanism to move exotic pathogens and animal species to new geographic regions around the globe. Thus, exotic species of viruses, bacteria, parasites, and their arthropod vectors are constantly introduced into new geographic areas. Most of these introductions are not detected until an epidemic or some other unusual event calls attention to their presence. By that time they are usually well established, and it is too late to eliminate them from the new area.

Summary and Conclusions

It is clear that in today's world of modern transportation, public and animal health officials must improve communication with each other and work together to improve surveillance, prevention, and control programs for arboviral and other zoonotic diseases. The recent introduction of WN

virus into the Western Hemisphere has underscored the high risk for introduction of other viral diseases such as RVF, JE, YF, DEN, and others. The public health infrastructure in most countries is inadequate to deal with epidemic arboviral diseases. Funding agencies must move quickly to develop the infrastructure for surveillance, prevention, and control if we hope to prevent major epidemics of exotic arboviral and other zoonotic diseases in the 21st century.

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