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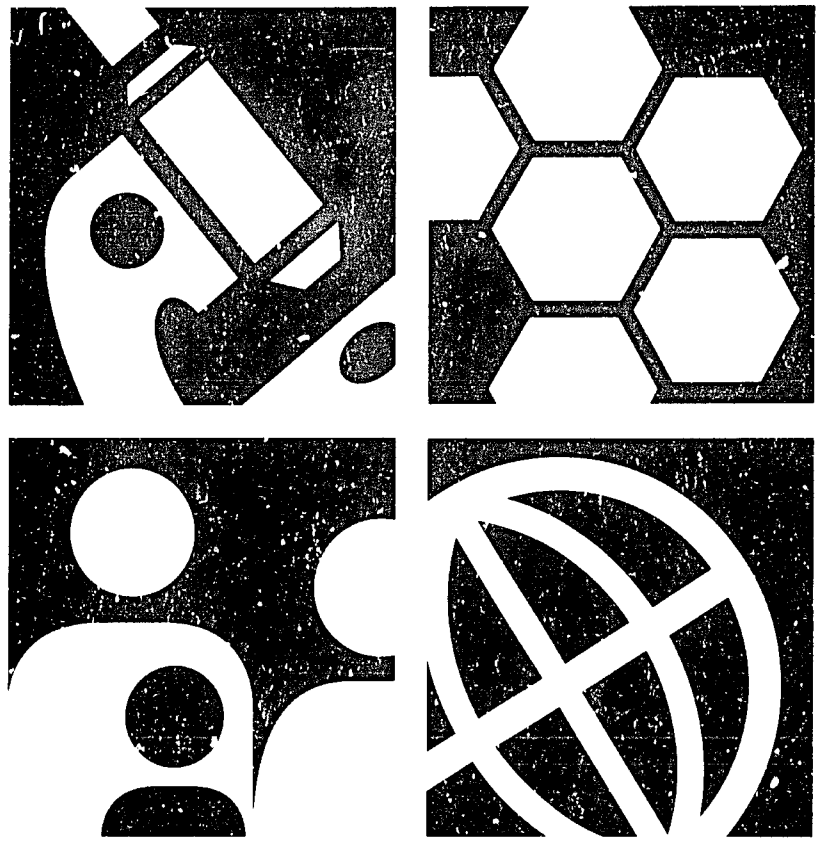

VBC TROPICAL DISEASE PAPER NO. 5

Managed by Medical Service Corporation International
Sponsored by the Agency for International Development

THE ARBOVIRUSES

Dengue, Yellow Fever and Japanese Encephalitis

by

Norman G. Gratz, Sc.D.

December 1990

VBC Tropical Disease Paper No. 5

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Cover design: Anne Masters Design, Inc.

The blue square shows a virus cluster. The other symbols depict essential components of vector-borne disease control: the environment, communities and research.

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Acknowledgement

Preparation of this document was sponsored by the Vector Biology and Control Project under Contract No. DPE-5948-C-00-5044-00 to Medical Service Corporation International, Arlington, Virginia, U.S.A., for the Agency for International Development, Office of Health, Bureau of Science and Technology.

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Executive Summary

There are about 500 arthropod-borne viruses, or arboviruses. Almost one hundred of them are known to cause human disease.

Humans are usually an unimportant host in the transmission cycle of arboviruses. When vector densities and virus loads in reservoir hosts are high, however, yellow fever, Japanese encephalitis, Rift Valley fever and a number of other arboviral infections may become epidemic in human populations.

There are four main groups of clinical symptoms of arboviral infection: acute central nervous system disease, acute non-fatal fevers, hemorrhagic fevers, and joint inflammation and rash. Clinical diagnosis of most of the arboviruses is difficult and usually certain only during an epidemic outbreak. Serological confirmation or identification through virus isolation requires well-developed laboratory facilities that are not available in many poor countries.

Culicine and anopheline mosquitoes are the vectors of most arboviruses. Approximately one-fifth of the 500 arboviruses are transmitted by ticks, phlebotomine sand flies and biting midges.

The most common reservoirs of arboviruses are mammals and birds. Mammalian reservoirs include common domestic livestock, nonhuman primates and wild rodents. Many kinds of migratory birds can transport certain viruses over long distances.

The most important arboviral diseases are yellow fever, dengue, along with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), and Japanese encephalitis (JE). Epidemics of arboviral disease in humans put an enormous strain on health services and supportive hospital treatment costs millions of dollars. Several arboviruses, including Rift Valley fever (RVF), Venezuelan equine encephalitis (VEE) and Eastern equine encephalitis (EEE) are primarily diseases of livestock and are responsible for great economic losses as well as human illness and mortality.

Dengue is primarily an urban disease. Once restricted to Southeast Asia, it has become increasingly common in South America and the whole Caribbean basin. Rapid urbanization increases the risk of dengue in tropical cities.

Unlike dengue, dengue hemorrhagic fever (DHF) is often fatal, particularly in children. Approximately five percent of cases end in death. There is no treatment for DHF and other arboviral diseases except supportive treatment to reduce mortality.

Dengue transmission is more easily prevented than interrupted. The most appropriate form of prevention is through community participation to reduce *Aedes* mosquito breeding sites -- drinking water storage containers and refuse that collects water, including tires and tin cans.

Outbreaks of Japanese encephalitis (JE) are particularly severe among children. Fatality rates range from 20 percent or below in children to nearly 50 percent in patients older than 50. Some degree of irreversible mental impairment can be demonstrated in 30 to 40 percent of convalescent patients between the ages of 5 and 40. Among children younger than four, the percentage is much higher.

JE occurs as epidemics in many areas of eastern Asia. The incidence of the disease is increasing in Southeast Asia, where mosquito vectors develop in irrigated rice-growing areas. Vector breeding is exacerbated by the rearing of pigs, which serve as amplifying hosts for the virus.

Expensive vaccines for JE are produced in Asia and vaccination programs have been conducted for children in Japan and Korea. Reduction of JE incidence in Japan has been the result of extensive vaccination of people living in high risk areas, use of pesticides and fungicides in farms, and changes in irrigation patterns.

Yellow fever cases and deaths in West Africa and the Americas are increasing even though a safe, effective vaccine has been available for more than 50 years. Between 1986 and 1988, a total of 5,395 cases and 3,172 deaths were reported -- the highest totals for any three-year period since countries began reporting the disease to the World Health Organization (WHO) in 1948. Most of these cases were reported from Africa, where studies have shown that yellow fever cases and deaths are underreported by 10 to 500 percent.

All endemic countries are at risk of yellow fever outbreaks because the disease remains endemic in its jungle cycle. Many countries have abandoned expensive routine immunization programs for the far less effective strategy of emergency control during outbreaks.

1. Introduction

The term "arboviruses" is a contraction of the words arthropod-borne viruses. It defines a group of almost 500 different viruses, of which almost 100 are agents of human disease.

Most of the arboviruses are accidentally acquired by man through the bite of an arthropod vector. Humans are usually unimportant hosts in the maintenance of the cycle. In the presence of dense populations of a suitable vector species and high concentrations of virus in reservoir hosts, however, a number of these infections may become epidemic in human populations.

Because there are many arboviral diseases, only a few of major importance are discussed in detail in this paper: dengue and dengue hemorrhagic fever (DHF), Japanese encephalitis (JE), and yellow fever. Ten regionally important arbovirus diseases are included in the annexes.

a. Symptoms

The range of symptoms for the arboviruses of man is great, but there are four main groups of clinical symptoms:

1. acute central nervous system disease, usually with encephalitis ranging in severity from mild meningitis to coma, paralysis and death;

2. acute non-fatal fevers of short duration, which often resemble dengue, but on occasion some may give rise to a more serious illness with central nervous system involvement or hemorrhages;

3. hemorrhagic fevers, which include acute fevers with extensive bleeding, either external or internal, frequently serious and associated with shock and significantly high fatality rates;

4. joint inflammation and rash, usually without fever. These infections cause little permanent disability, but joint pain may persist for several weeks to months.

b. Biogeography

A list of the arboviruses known to cause disease in man is presented in Table 1, Annex 1. This table illustrates the great diversity of vectors and clinical symptoms and the wide distribution of the arboviruses.

The fact that a virus or infection has not been reported from a given country may have only limited significance. Clinical diagnosis of most of the arboviruses is difficult and usually certain only during an epidemic outbreak. Serological confirmation or identification through virus isolation requires well-developed laboratory facilities that are not available in many poor countries.

Arbovirus disease outbreaks may occur suddenly in areas far from the regions where the infectious agent had previously been reported. In some cases, the virus may have been introduced by a human traveller arriving during the incubation period of the infection, a reservoir animal, or (less likely) an infected vector transported by aircraft or wind. In other cases, the virus may have gone unrecognized until an outbreak occurred or until a serological survey revealed its presence.

c. Agents

Arboviruses are defined as animal viruses transmitted biologically by blood-feeding arthropods to vertebrate hosts. Yellow fever virus was the first arbovirus to be cultivated successfully in a laboratory. Field studies on yellow fever resulted in the isolation of many other viruses, which have been classified into related groups according to antigen type. For example, the dengue, yellow fever and Japanese encephalitis viruses belong to the family of Flaviviruses. Recent advances in sequencing RNA have opened the possibility of more precise classifications based on direct comparisons of the genomes of closely related viruses.

d. Vectors

Mosquitoes are the vectors of the majority of the arboviruses, including dengue, yellow fever and Japanese encephalitis. Culicine (*Culex*, *Aedes* and others) and anopheline (*Anopheles*) mosquitoes may serve as vectors of this highly diverse group of viruses. One hundred arboviruses are transmitted by ticks, phlebotomine sand flies and biting midges.

Virtually all of the arboviruses are characterized by a complex cycle of transmission involving vertebrate hosts and arthropod vectors. The arthropod vector ingests the virus when it feeds on an infectious vertebrate. The virus replicates in the vector and, after an appropriate incubation period, can be transmitted to another susceptible vertebrate when the vector takes a blood meal.

d. Reservoirs

The most common reservoirs of arboviruses are mammals and birds, but a number of reptiles also have been incriminated. Mammalian reservoirs include common domestic livestock (cattle, horses, goats, sheep, pigs and camels), nonhuman primates and wild rodents. Numerous types of migratory birds are important in transporting certain viruses over long distances.

Some arboviruses, including dengue, have no recognized animal hosts. For others, the identity or importance of the possible hosts remains uncertain.

e. Child survival

One of the most prevalent arboviral diseases, dengue hemorrhagic fever (DHF), is an increasingly severe threat to child survival in Asia, Latin America and the Caribbean. Without intensive supportive care, five to 10 percent of DHF cases may result in death. DHF and dengue shock syndrome (DSS) are among the 10 leading causes of hospitalization and death in at least eight tropical Asian countries.

Outbreaks of Japanese encephalitis are particularly severe among children. Fatality rates can be as high as 20 percent. Thirty to 40 percent of convalescent patients between the ages of five and 40 show some degree of mental impairment. The percentage of patients with permanent brain damage is much higher among children younger than four.

Other arboviral diseases (see Annexes 2-11) also tend to be more severe in children. Fatality rates among Eastern equine encephalitis patients approach 80 percent, particularly in children. There is a strong correlation between the age of a patient with Western equine encephalitis and the incidence and severity of

the brain damage caused by the infection, with newborns experiencing the highest rates of severe mental impairment.

f. Economic Impact

Epidemics of arboviral disease in humans put a enormous strain on health services. During a 1988 outbreak, half of all pediatric beds in Thailand were occupied by DHF cases, diverting scarce resources that could have been used to address other health problems. The 1977 dengue epidemic in Puerto Rico was estimated to cost $6.4 million to $16.7 million. The cost of the 1980 DHF epidemic in Thailand was about $7-10 million.

Neither of these estimates include indirect costs resulting from reduced productivity, premature death, school absenteeism and losses in tourism. These costs are unquestionably high during epidemics of DHF and other arboviruses, but they have not been calculated.

Although estimating economic losses from arboviral outbreaks that kill hundreds of thousands of livestock is less complicated, few estimates are available. The direct cost of the 1971 outbreak of Venezuelan equine encephalitis in Texas, which killed thousands of horses, was estimated at $20 to $30 million. African swine fever eradication programs in Europe and the Americas between 1957 and 1985 resulted in the slaughter of more than 2 million swine at a cost of more than $50 million.

2. Dengue and Dengue Hemorrhagic Fever (DHF)

There are four antigenically distinct types of dengue virus (dengue 1,2,3 and 4), which are transmitted by mosquitoes. Infections in man vary considerably in their severity and outcome depending on the host's immunological state due to prior exposure to dengue virus. The severe forms are called dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Dengue was first recognized as an arthropod-borne virus early in this century. Several early epidemics of dengue in Asia, the Americas and Europe are thought to have had associated severe hemorrhagic manifestations, but the relationship between DHF and dengue was not identified until 1956, after an outbreak in Manila. Since then, the hemorrhagic or shock syndrome has spread to many areas of Southeast Asia, the Pacific and, more recently, to the Americas.

a. Symptoms of dengue

Classic, uncomplicated dengue begins with a high fever two to seven days after a person is bitten by an infected mosquito. The fever may reach 106 °F during the next five days and is accompanied by bone and joint pain and an intense headache. Within four days after the onset of fever, skin rashes usually appear and sometimes small points of hemorrhage (petechiae) can be seen just under the skin. Nausea, vomiting and glandular swelling, followed by fatigue and depression, are common.

There is considerable variation in the experiences of dengue patients. Older persons may suffer more symptoms. In infants or small children, dengue may mimic a cold with a one-to-five-day fever, runny nose, sore throat and mild cough.

b. Symptoms of DHF

Dengue hemorrhagic fever begins much like dengue, with rapid onset of fever, headache, vomiting and cough, but is followed by deterioration and physical collapse within two to five days. Unlike dengue, it often fatal, particularly in children. The cause of death is leakage of blood serum from capillaries, which results in a sudden drop in blood pressure that is called dengue shock syndrome (DSS). This capillary leakage is thought to be associated with an immunological reaction.

The second or shock phase of DHF begins with cold, clammy arms and legs, a flushed face and kidney failure. Patients are restless, irritable and complain of stomach pain. They bruise easily and frequently have black and blue hemorrhages on the skin. The pulse rate is rapid and weak, and breathing is labored. In about 10 percent of the patients, there is gross bleeding from the mouth, nose, eyes and into the intestinal tract. The infection concludes with a 24- to 36-hour crisis period, when good medical support and intravenous fluids are essential. Recovery is rapid in non-fatal cases. Mortality rates as high as 40 percent were reported during the 1960s, but today, with improved supportive care, usually less than six percent of cases end in death.

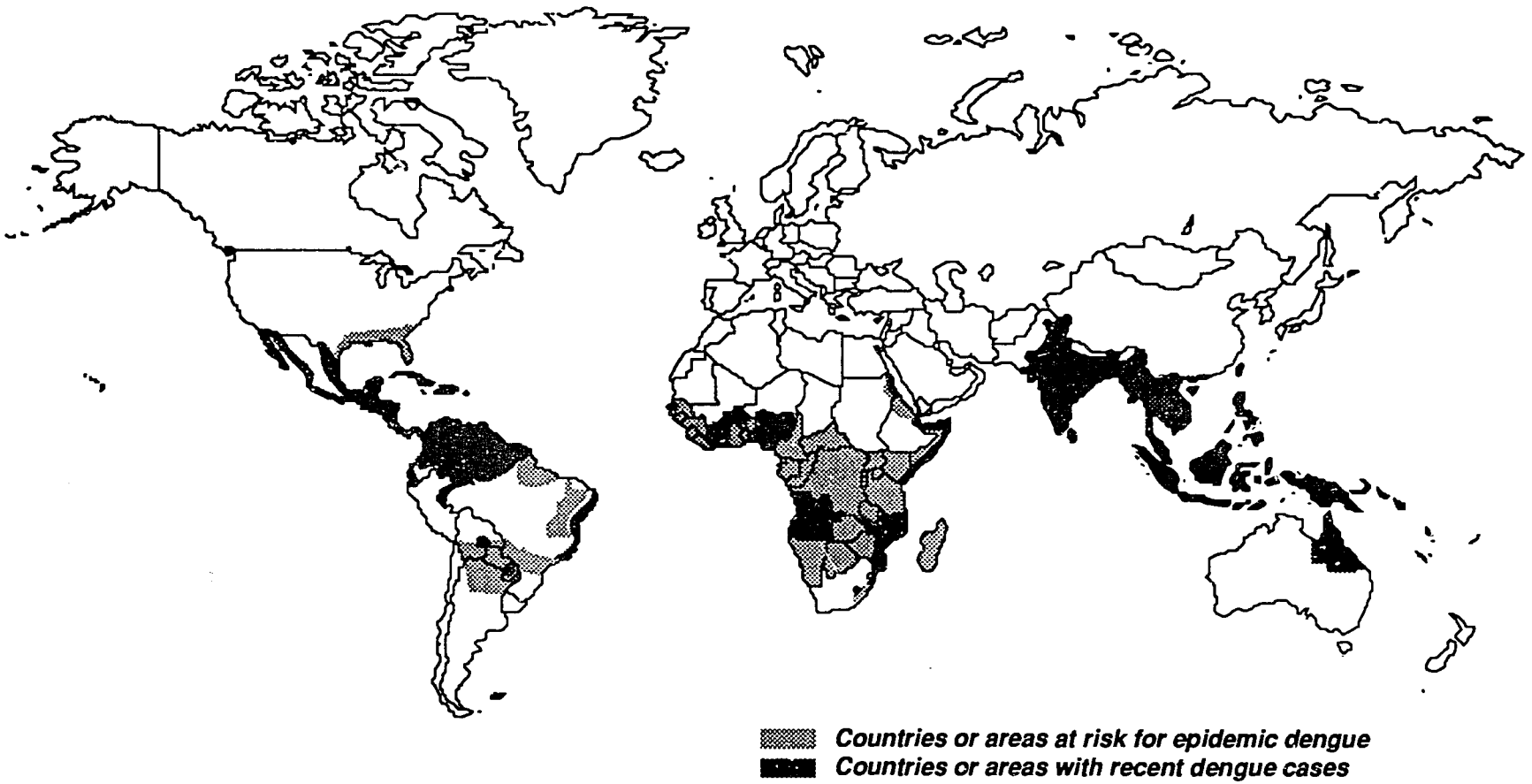
The diagnosis of dengue may be complicated by its resemblance to other viral, respiratory and influenza-like diseases. Early symptoms are also similar to those of malaria, scrub-typhus, hepatitis and leptospirosis. At least three other arbovirus infections (chikungunya, o'nyong-nyong and West Nile virus) are dengue-like and produce rashes. Clustering of cases in endemic transmission areas aids presumptive diagnosis, but confirmation depends on isolation of the virus or detection of antibodies in the blood. Because of the potential for child mortality, all cases should be suspected to be dengue until they are diagnosed by a physician.

c. Distribution of dengue

In the past, dengue outbreaks were widespread not only in Asia and the Americas, but in Europe and the eastern Mediterranean region. Between 1940 and 1970, the distribution of dengue contracted in many countries, particularly in the Americas, through the success of regional *Ae. aegypti* eradication programs. In Europe and a number of countries in the Middle East, the vector species disappeared as a result of ecological changes associated with economic development, including widespread provision of piped water supplies to houses and the disappearance of domestic water storage containers. However, *Ae. aegypti* have reappeared in many countries of the Americas and dengue transmission has also returned.

Map 1 shows the distribution of the disease. It is clear that a number of other countries where dengue has occurred have not reported the infection. It can be assumed that the distribution is underreported in Africa, where clinical recognition of the disease and serological surveys to detect viral antibodies are lacking.

Map 1. Global Distribution of Dengue, 1990



Prepared by the Vector Biology and Control Project
Source map: Centers for Disease Control, 1990

Surveys in areas where the vector is found in high densities would probably show that the virus was present and active transmission was occurring. Dengue transmission is likely to continue spreading, as it has in the last three decades, to geographical areas where vector density is high enough to support transmission.

Dengue is characteristically an urban disease, occurring in epidemics. Increasing urbanization heightens the risk of dengue in tropical cities.

d. Distribution of dengue hemorrhagic fever (DHF)

DHF was initially recognized as a disease syndrome in Manila in 1954. It appears to have spread to most of the countries where dengue is endemic, but has not been reported from Africa. The syndrome first appeared in the Americas in Cuba, when 344,203 cases were reported during an outbreak of dengue-2 in 1981. One-third of the cases resulted in hospitalization. There were approximately 10,000 shock cases and 158 of them were fatal. More than half of the deaths occurred in children younger than 15 years of age.

The epidemic had an enormous impact on the Cuban economy and medical service system. Almost 350,000 dengue cases occurred from June 6 to October 10 of that year. More than 16,000 cases were hospitalized in June, almost 52,000 in July and more than 46,000 in August. On August 6 alone, almost 4,000 people were admitted to hospitals and a total of 17,218 patients with dengue fever occupied hospital beds.

Since 1981, cases of DHF/DSS in the Americas also have been reported from St. Lucia in the Lesser Antilles, the Dominican Republic and Puerto Rico. A severe DHF epidemic in Venezuela caused at least 2,000 cases and 73 deaths between November 1989 and February 1990. Some severe cases of dengue reported from Mexico may have been DHF.

e. Vectors

Ae. aegypti is the vector of the virus that causes dengue and DHF/DSS in most parts of the world. Important epidemics have occurred in areas where this species is the only *Aedes* present. In other areas of the western Pacific and Southeast Asia, *Aedes*

albopictus has also played a role in transmitting dengue virus during epidemic outbreaks. Therefore, the recent finding of *Ae. albopictus* in the United States and Brazil, and the possibility of its infesting other countries in South and Central America, may have important epidemiological consequences.

In most areas of Southeast Asia, the western Pacific and the Americas, *Ae. aegypti* breed almost entirely in and around human habitations in freshwater containers. Larvae have been found in clay and ceramic water jars, water storage drums, flowerpots, water-filled ant traps under table legs, tires filled with rainwater and almost any other sort of man-made container that holds water. In Africa, on the other hand, the species is found in both natural containers, such as leaf axils and tree holes, and man-made containers.

In its Asian habitats, *Ae. albopictus* readily breeds in tree-holes, bamboo stumps and other natural containers and in many of the same man-made habitats where *Ae. aegypti* breeds. Several strains of *Ae. albopictus* recently found in the United States and Brazil, which were probably introduced through importation of tires from Asia, seem equally capable of maintaining themselves in natural habitats some distance away from human dwellings and in man-made habitats. Introduction of this species has complicated control efforts, which had been directed against *Ae. aegypti*. The threat for northern areas of the United States is increased by the fact that the introduced strain of *Ae. albopictus*, unlike *Ae. aegypti*, is able to survive freezing temperatures.

f. Reservoirs

Dengue transmission usually occurs through a man-mosquito-man cycle. There is evidence that monkeys may serve as a jungle reservoir in West Malaysia. African monkeys have also been found positive for dengue, but their role as reservoirs of the disease in that region is unknown.

g. Control

No specific chemotherapy is available for treating dengue or DHF/DSS. Efforts to develop an approved vaccine have been unsuccessful so far. The existence of four serotypes of dengue and their varied pattern of distribution makes the development of a vaccine extremely complicated.

In the absence of any chemotherapeutic agent or vaccine, control of dengue and DHF/DSS must depend on vector control. A combination of environmental sanitation and chemical control, or integrated control, is usually needed to control the vector.

Environmental sanitation

Control through environmental sanitation involves denying vectors access to man-made containers that can be used for breeding. In areas without adequate piped water supplies, people often store fresh water in containers that provide excellent larval habitats. The best way to prevent the vector from breeding in domestic water storage containers is to provide an adequate piped water supply to individual homes or at least to each city block, reducing or eliminating the need to store potable water. If improving the water supply is not economically feasible, health education efforts can encourage people to protect water supplies.

Even in places where adequate piped water has been provided, it is also necessary to deny the mosquitoes access to such alternative larval habitats as trash containers, used tires, or other waste containers capable of retaining rainwater. It is essential to work closely with community members and leaders to obtain their active participation in eliminating waste containers and preventing *Ae. aegypti* from breeding in water containers that cannot be destroyed.

Chemical control

Unless a high degree of community participation is achieved, either as a result of voluntary cooperation or legal pressure, chemical measures will also be necessary to reduce *Aedes* infestation to the lowest possible level. These measures can take the form of either larviciding or adulticiding.

Since breeding of *Ae. aegypti* and closely related species often occurs in water that may be used for domestic consumption, larvicides applied to the water containers must be of the lowest possible mammalian toxicity. Even after larviciding, adult population densities will decline only when the existing, untreated *Ae. aegypti* die and are not replaced. Therefore, larviciding is not an appropriate method for controlling epidemic outbreaks of arboviral disease.

Adulticides, particularly space sprays, are used to achieve a very rapid decline in the adult population densities of the

vector, usually during an epidemic situation. When cases of *Ae. aegypti*-borne disease first appear in a locality, an epidemic may be prevented by eliminating the adult female mosquitoes that are circulating the virus.

Integrated control

In most geographical areas where dengue transmission occurs, it will almost certainly be necessary to use both environmental control methods to reduce the breeding sites of *Ae. aegypti* or *Ae. albopictus* to the greatest extent possible and insecticides to control the remaining populations. This kind of program will require accurate monitoring of adult and larval population densities and a very thorough knowledge of the ecology of the species.

h. Constraints to control

By the early 1950s, most of the countries of the Americas had eradicated *Ae. aegypti*, but it has not been possible to sustain eradication in the face of constant reintroduction from the countries still infested. Virtually all countries in the Americas where *Ae. aegypti* had been eradicated have been reinfested. In fact, the species is now found in geographical and ecological areas where it had not been found before. Vector control will be further complicated by the introduction of *Ae. albopictus*.

Insecticide resistance, which is widespread in *Ae. aegypti* populations, also will make vector control more difficult. Susceptibility tests should be conducted to determine the nature and degree of this resistance before an insecticide is procured and applications are made.

After a major epidemic of DHF/DSS, Cuba succeeded in virtually eradicating *Ae. aegypti*, but only by applying considerable resources in manpower and materials, using health education, and enforcing laws to eliminate breeding sites. In most other countries, vector control programs are frequently ineffective because they lack public cooperation or adequate funding.

Effective control measures often involve high costs for labor, commodities and transport. Prevention through community-based source reduction is a promising alternative, but achieving and sustaining the necessary public cooperation is very difficult. It is becoming apparent to some governments that the cost of lost

working days during massive dengue epidemics and the expense of hospitalization and medical support for large numbers of DHF/DSS cases is so substantial that achieving effective vector control is imperative, if only as an economic necessity.

I. Current research

Research on dengue has been broad and well-funded. It has focused on the epidemiology of the disease, treatment of cases of DHF and DSS, viral detection, vaccine development and vector control.

Recent advances in microbiology and biomedical research have provided new tools for dengue research. To understand the cycles of disease outbreaks that have occurred in places like Thailand and Puerto Rico, scientists have used computer-assisted genetic techniques to study the microevolution of virus strains obtained between 1962 and 1986. Researchers have used molecular biological techniques to explore the relationship between previous dengue infections and DHF by examining the natural killer cells and white blood cells of children with dengue virus. They found that natural killer cells were active in defense against the virus, but subneutralizing concentrations of dengue antibody actually enhanced dengue virus infections in certain white blood cells. These findings may explain why successive dengue infections increase a person's risk of developing DHF.

WHO has been overseeing vaccine trails conducted by Mahidol University in Bangkok during the past five years, and U.S. military researchers have produced several candidate vaccines, which are in the initial phase of testing. A number of approaches to effective vector control have been field tested in recent years, including aerial ULV spraying of large urban areas, biological control using *Cyclops* in discarded tires and other artificial containers, and unique community participation activities in source reduction. In 1987, the Rockefeller Foundation in New York began a new initiative to support education and research associated with the control of the dengue/DHF vectors.

3. Japanese Encephalitis

a. Symptoms

Japanese encephalitis (JE) may take the form of an inapparent to acute infection characterized in human patients by fever, headache, prostration, stiff neck and neurological disorders, including encephalitis. In animals and birds, infection is common and usually inapparent. Horses may develop encephalitis and gestating swine may give birth to infected and often dead pigs.

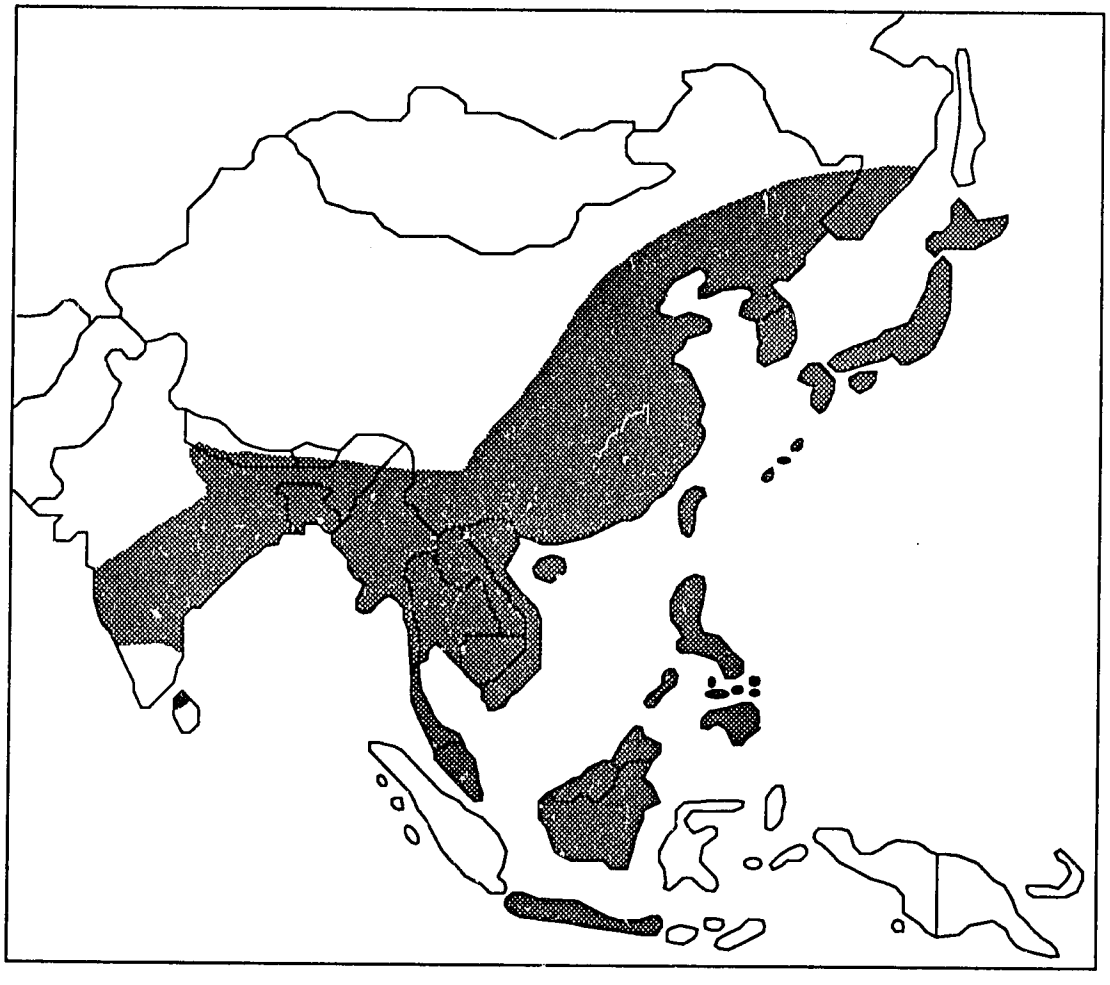
The onset of the disease in human is abrupt after an incubation period of seven to 10 days. Convulsions are common in children. Fever peaks at four to five days and gradually subsides. Patients who succumb usually go into a coma within seven to 10 days. Prognosis varies with the age of the patient, with a fatality rate of 20 percent or below in children to nearly 50 percent in patients older than 50. Some degree of mental impairment can be demonstrated in 30 to 40 percent of convalescent patients between the ages of 5 and 40. In children younger than four, the percentage is much higher. Diagnosis is considered to be fairly accurate only during large epidemics.

b. Distribution

Japanese encephalitis occurs as epidemics in the rice-growing areas of eastern Asia from eastern Siberia to Taiwan (Map 2). The incidence of the disease appears to be subsiding in China, Japan and the Republic of Korea, but it has been increasing and spreading over parts of Bangladesh, Burma, India, Nepal, Sri Lanka, Thailand and Vietnam. Changes in the epidemiology of JE in many countries may be the result of increased rice paddy cultivation and pig rearing, and the effects of vaccination.

JE was first reported in Thailand in 1969. Incidence has increased markedly, with more than 1,500 cases a year reported for the past several years. Between 1978 to 1984, more than 25,000 cases of JE and 9,260 deaths were reported in India. JE occurs throughout most of China, where more than 10,000 cases are reported every year with a fatality rate of about 10 percent. In India, China and Thailand, children younger than 15 are at greatest risk.

Map 2. Japanese Encephalitis Endemic Areas



Prepared by the Vector Biology and Control Project
Source Map: World Health Organization, 1989

Sri Lanka has been reporting JE cases in small numbers for years, but in 1985-1986 an epidemic occurred in the north-central province, with 410 cases and 74 deaths. Another epidemic in late 1987 resulted in at least 254 cases and 65 deaths. The incidence of JE in Nepal has increased progressively since the first documented epidemics in 1978. Successively larger epidemics have occurred at approximately two-year intervals. The case fatality rate in Nepal has been high, ranging from 14.8 percent in 1983 to 46.3 percent in 1982 (unconfirmed by serology).

Once an infection of considerable importance in Japan, JE has become increasingly uncommon in that country, with fewer than 100 cases reported every year. This reduction has been the result of extensive vaccination of people and pigs in high-risk areas, use of pesticides and fungicides in farms, and changes in irrigation and pig-rearing practices.

c. Vectors and reservoirs

The ricefield-breeding mosquitoes *Culex tritaeniorhynchus*, *Cx. gelidus* and *Cx. fuscocephala* are the most important vectors of the JE virus. Pigs are the major vertebrate host in the northern areas of the disease's distribution. In some areas, 100 percent of pigs are infected with JE. Because infected pigs help circulate the virus without displaying any symptoms of illness, they are considered amplifying hosts. The role of other animals as reservoirs in the tropical areas remains unknown.

d. Control

There is no specific therapy for JE. Control of the disease must be achieved either through immunization or vector control. Protecting pigs and other amplifying hosts from infection or minimizing their contact with people is also important.

Immunization

There are two kinds of JE virus vaccine: killed or inactivated and live attenuated vaccines. In Japan and Korea, vaccination programs for children have been conducted using inactivated vaccine made from infected mouse brain. Inactivated vaccines have been tested in other areas. A monovalent mouse-brain vaccine is made from the JEV virus strain Nakayama-Yoken and a bivalent vaccine is made by adding the Beijing-1 strain. The Biken (Nakayama) vaccine costs about U.S. $2.30.

Less expensive inactivated and live attenuated vaccines produced in tissue culture have been used successfully in China. Live vaccines were developed in Japan primarily for immunizing pigs.

Environmental management

Water management in rice fields and other changes in agricultural practices have helped reduce JE vectors in Japan, China and other countries. The most common form of environmental management in rice fields is intermittent irrigation, or providing water long enough to sustain optimal growth of rice plants without allowing it to stand long enough to permit mosquito breeding. Where rainfall or irrigation permit a shift in planting times, farmers can select rice varieties that can be planted before the JE transmission season. Planting a wide belt of dry land crops between rice fields and human dwellings may help reduce JE transmission.

Breeding pigs near rice fields increases the risk of JE transmission. Keeping pigs indoors or bringing them indoors during the early evening hours may help reduce JE infection rates in the amplifying host and people. Pig shelters should not be built near human dwellings. Screens or nets can help protect humans and pigs from JE-infected mosquitoes.

e. Constraints to control

Although vaccination programs have helped reduce incidence in some countries, technical, economic and logistical problems present serious constraints to controlling JE through immunization.

Only 80 to 90 percent vaccination coverage of the population at risk will lower the morbidity rate. Even if a country can muster the financial and administrative support necessary to mount a successful vaccination campaign, it may be difficult to identify the populations at greatest risk. Such a program would have to be continued indefinitely because vaccination would not affect the level of JE virus transmission among amplifying hosts.

Studies in Nepal and the United States using the Biken vaccine indicate that a three-dose regimen may be required to produce a protective antibody response in more than 90 percent of recipients. Antigenic variants of JE virus have been found in different areas, raising the question of whether a monovalent vaccine from one area can protect against infection in others.

Chemical vector control is expensive and often is not feasible because of the extremely large areas covered by the rice fields

where the vectors breed. Adulticiding by aircraft has only a temporary effect on vector densities and there is no evidence that it reduces disease transmission. Larviciding is economically feasible only in restricted areas or rice fields closely surrounding human settlements.

Persuading farmers to change their agricultural practices can be a very difficult task. The agricultural changes that can help control JE vectors are not considered acceptable or feasible in many high-risk areas.

f. Research

The ecology of the vectors of JE is being studied in Japan and other parts of Asia.

Field trials of vaccines are conducted in India, China and other parts of Asia. An extensive trial in Thailand during the 1980s found a 91 percent efficacy in children who received two doses of either the monovalent Biken vaccine or the bivalent Nakayama-Yoken-Beijing-1 vaccine, compared to children who received a placebo. Chinese investigators have demonstrated that the live SA 14-14-2 vaccine can produce immunity and is safe for children.

4. Yellow Fever

Yellow fever has been called yellow jack, typhus amaril and black vomit. The virus exists in two cycles: an urban cycle involving human-to-human transmission through *Aedes aegypti* and a sylvatic or jungle cycle involving forest primates and forest canopy mosquitoes, with accidental human infections. African primates are relatively tolerant of yellow fever infection, whereas fatal infections are generally the rule in Central and South American monkeys and marmosets.

a. Symptoms

Mild cases of yellow fever last one to three days and are clinically indeterminate. Moderate to severe cases may last one to two weeks. Typical attacks are characterized by a dengue-like illness, with sudden onset of fever, headache, backache, prostration, nausea and vomiting. As the disease progresses, the pulse slows and weakens, even though the temperature may be elevated. Production of urine may be completely shut down and white cells counts may drop to less than 20 percent of normal levels. Common hemorrhagic symptoms include bleeding from the nose and mouth, and vomiting blood. Jaundice is moderate early in the disease and intensifies later.

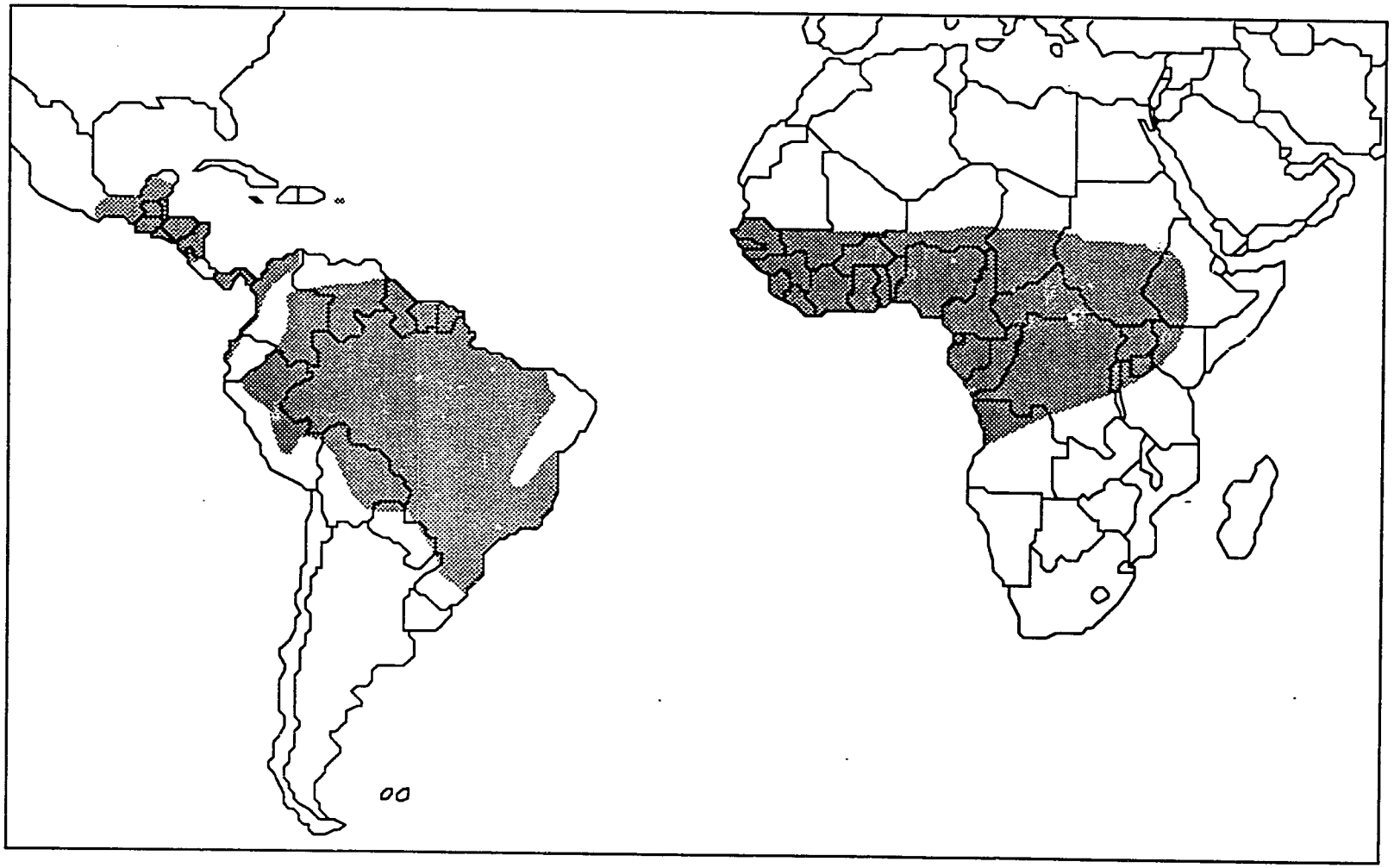
The fatality rate among indigenous populations of endemic regions is generally less than five percent, but the death rate may reach 50 percent among nonindigenous groups or during epidemics. Clinical symptoms are sufficient to define a case during an epidemic. Laboratory confirmation of diagnosis is accomplished by isolating the virus from lab animals or detecting antibodies in a patient's blood.

b. Distribution

Yellow fever is endemic in tropical Africa between 15 °N and 15 °S and in northern and eastern South America (Map 3). Epidemics occur in parts of Central America. The disease has never been reported from Asia.

In 1988, Africa and South America reported 2,058 cases of yellow fever and 1,709 deaths, a case fatality rate of 83 percent. Between 1986 and 1988, a worldwide total of 5,395 cases and 3,172 deaths were reported. This is the largest number of cases

Map 3. Yellow Fever Endemic Areas



Prepared by the Vector Biology and Control Project
Source Map: World Health Organization, 1989

reported for any three-year period since WHO began collecting data on yellow fever in 1948 (WHO 1990).

Numerous epidemics of yellow fever have been recorded in Africa during the last 30 to 40 years. The virus is endemic among animals in Burkina Faso, Cameroon, the Central African Republic, Cote d'Ivoire, Ghana, Guinea, Mauritania, Nigeria, Senegal, Sudan, Togo and Zaire. It is probably circulating in a number of other countries where occasional human cases occur.

In 1988, almost all of the 1,511 cases of yellow fever reported from Africa occurred in Nigeria as part of a major epidemic, which probably represented a continuation of the epidemic that began in 1986. Since 1984, the number of cases in Nigeria has risen every year and the fatality rate also appears to be rising.

Studies have shown that only a small percentage of yellow fever cases in Africa are reported. In seven epidemiological studies of outbreaks in Africa during the past 25 years, the numbers of cases and deaths reported were 10 to 500 times less than the actual numbers (WHO 1990). A survey in nine villages in Benue State, Nigeria, showed that about 20 percent of the population had been infected during the 1986 outbreak. These data suggest that there were some 30,000 subclinically infected individuals, 9,000 clinical cases and 5,400 deaths in just one of the two epidemic centers. The epidemic occurred in a typical emergence zone for yellow fever, a humid and semi-humid savannah next to a rain forest where the sylvatic cycle of yellow fever was maintained in a large monkey population (WHO 1987).

South America reported 629 cases and 540 deaths from yellow fever from 1986 to 1988, the highest morbidity and mortality reported since 1952. More than 85 percent of cases were in males older than 15. The majority of cases occurred in Peru, but reports were also received from Bolivia, Brazil, Colombia, Ecuador and Peru. An outbreak began in late 1988 in Cochabamba, Bolivia, raising concerns that yellow fever could be introduced into Santa Cruz and other nearby towns. A vaccination campaign was initiated and more than 150,000 people were immunized. Vaccination teams made house-to-house visits in the endemic zone and unimmunized travelers to the endemic zone were vaccinated at highway roadblocks.

In the Americas, most yellow fever cases are in males aged 15 to 45 who are working in agriculture or forestry. Because the disease remains endemic in its jungle cycle, all virus-infected countries face the threat of yellow fever outbreaks.

c. Vectors

Several species of *Aedes* mosquitoes are of practical epidemiological significance in the transmission of yellow fever virus in Africa. In forest and savannah areas, wild populations of *Ae. aegypti* breed in water holes and other water pockets in plants and trees, and the female mosquitoes take their blood meals primarily from animals. In villages or cities where breeding occurs in domestic water containers, the mosquito feeds almost exclusively on humans. *Ae. aegypti* is likely to be the main epidemic vector of yellow fever in its domestic form. In the rain forest, the principal vectors are members of the *Ae. africanus* group, which transmit the virus between monkeys.

Recently, yellow fever virus has been isolated from naturally infected ticks in Africa. These have been shown to transmit the virus to their progeny, which can infect monkeys. The ticks may represent an alternative cycle and deserve further study.

Ae. aegypti has been the sole vector in urban outbreaks of yellow fever in the Western Hemisphere. In the jungle cycle in the Americas, the primary vectors for monkey-to-monkey transmission are mosquitoes of the genus *Haemagogus*. Human infections result almost entirely from exposure to infected forest canopy mosquito species, which breed primarily in tree holes. They may also breed in bamboo stumps or suitable sites in adjacent parks and even around houses. These species have been shown to follow people for several hundred meters away from the forests. Should one transmit the yellow fever virus to a human who goes to an urban area, transmission could then be taken up by *Ae. aegypti* and result in an epidemic.

Recent evidence points to the possibility of transmission from one mosquito generation to another in the uterus as an additional mechanism for maintaining the virus in nature.

d. Control

Treatment for a patient ill with yellow fever is mainly supportive. Personal protection from exposure is often difficult, so vaccination is the most important form of prevention.

The 17D vaccine was developed by Dr. Theiler at the Rockefeller Institute in 1937. The 17D strain is cultivated for vaccine production in embryonating chicken eggs. It is administered by

subcutaneous injection. Complications are extremely rare, except in children younger than seven months of age.

The French or Dakar vaccine for yellow fever was developed at the Institute Pasteur de Dakar, Senegal, and adapted to laboratory cultivation. It is cultivated for vaccine production in mouse brain and administered by cutaneous scarification. The Dakar vaccine is generally used only in people older than 14 because of the risk of post-vaccinal encephalitis.

With both vaccines, neutralizing antibodies appear within 10 days after vaccination and persist for at least 10 years. Vaccination is the only practical measure for protecting people entering zones where there is a high risk of infection. In a virus-endemic areas, where a variable portion of the older population will have acquired natural immunity, children older than six months should be vaccinated first during epidemics. Unless the populations at risk are precisely identified, the objective should be to obtain 100 percent vaccination coverage at the time of an epidemic. Twenty percent of the population may be considered at risk four to five years after a vaccination campaign.

e. Vector control

When an urban outbreak of yellow fever occurs, mass vaccination and space sprays to kill adult female mosquitoes should be conducted as promptly as possible. Should an outbreak occur in a large city or one that covers an extensive area, aerial applications of insecticides, particularly low-volume insecticide sprays, should be considered. Insecticides sprayed as ultra-low-volume (ULV) concentrates provide some control if applied at the proper concentrations and volumes by experienced pilots.

When equipped spray aircraft are not readily available, ULV ground applications should be made with either vehicle-mounted application equipment or hand-carried motorized sprayers. Thermal fogging can also be effective. All space sprays should be conducted under the supervision of experienced vector control personnel.

f. Constraints to control

Although there has been a safe, effective vaccine for yellow fever for more than 50 years, worldwide incidence has been

rising, and the risk of yellow fever epidemics has increased in many areas. Because of the expense of vaccination campaigns and the logistical problems that make it difficult to achieve adequate coverage, many countries have abandoned routine immunization programs for emergency immunization and vector control during outbreaks. Controlling these unpredictable epidemics is very difficult even when they are detected early.

A mandatory immunization program begun in francophone West Africa during the 1940s interrupted the pattern of epidemics in these countries and controlled yellow fever throughout the 1950s. This strategy was abandoned in 1960 for a post-outbreak, emergency control strategy. Since then, a series of epidemics have occurred. Yellow fever vaccination has been incorporated into some African countries' Expanded Programmes of Immunization to varying degrees, depending on available funds.

Chemical control of jungle species of mosquitoes or those in or on the edge of forests is unlikely to be successful because of the difficulty of ensuring that the insecticide droplets penetrate the forest canopy. Larviciding is of little use as a method of epidemic control because its effects will not become apparent for some time and transmission of the virus will continue in the interim.

g. Research

Despite extensive study of the epidemiology and the vectors and reservoirs of yellow fever, much remains to be learned. Studies on the role of virus transmission in the uterus from one mosquito generation to the next should be encouraged because they might result in a better understanding of how the virus persists in its natural foci.

The thermostability of yellow fever vaccine has been increased, enabling it to withstand higher temperatures without losing its efficacy. Trials of combined yellow fever and measles or hepatitis B vaccines have demonstrated no reduction in the percentage of immunizations that produce a protective antibody response. Operations research to develop more cost-effective vaccination programs is needed.

5. Arboviruses from the A.I.D. Perspective

Experience has shown that various arbovirus infections may wane and even disappear from countries where they were once prevalent. These "silent periods," however, may be followed by the explosive reappearance of the disease among humans or animals. An arbovirus infection previously thought to be absent from a country can appear suddenly and cause sizeable epidemics. DHF appeared as an apparently new syndrome in the Philippines in the early 1950s, but it spread throughout much of the western Pacific and Southeast Asia, and has now appeared in the Americas. Other infections may cause sharp local outbreaks with a limited number of cases but high mortality.

Dengue hemorrhagic fever and Japanese encephalitis are a serious threat to child survival in many A.I.D.-assisted countries. Many of the diseases considered in this paper have been the cause of considerable morbidity and mortality. Supportive treatment and control efforts during an epidemic can overwhelm a poor country's health services and divert scarce resources from other health problems.

A.I.D.'s greatest role in the prevention and control of arboviral diseases may be in assisting the development of effective surveillance systems, and helping countries prepare realistic contingency plans to control outbreaks. In endemic countries, support for regional training programs and assistance in planning and developing effective, well-supervised vector control programs would be of particular value.

a. The Horizon

During the next 10 years, field trials in Thailand on candidate dengue vaccines will probably be completed. If a safe and effective multivalent vaccine is approved for worldwide use, A.I.D. could become a major partner in its distribution in endemic areas. This vaccine could greatly reduce childhood morbidity and mortality due to DHF and DSS in Asia, Africa and the Americas.

Many technological spin-offs can be expected from the major research effort to combat the global HIV epidemic. New drugs for viral diseases will be discovered, which may cure certain arboviral diseases. New diagnostic tests may increase the speed, sensitivity and specificity of arbovirus detection in humans. Prediction models will incorporate the attributes of these methods, leading to quicker response times in fighting epidemics.

Control of arbovirus vectors will still be dependent upon the use of insecticides against the larvae or adults. Insecticide resistance will become a greater problem, and the cost of control will increase significantly. Community involvement in the prevention and control of arboviral disease will become much more important. A.I.D. can take the lead in advancing the strength of the social sector in arbovirus control.

b. Priorities for future action

- Development of regional dengue surveillance systems and contingency plans for dengue outbreaks.
- Vaccination programs in all A.I.D.-supported countries where yellow fever is endemic, especially those in West Africa, associated with support for expanded programs of immunization (EPI).
- Linking improved vector control in rice-growing areas to agricultural practices, particularly the use of intermittent irrigation and selected cultivars that do not require growing conditions conducive to mosquito breeding.
- Training of personnel involved in surveillance, laboratory diagnosis and control of arboviral diseases and development of appropriate career structures for those who have been trained.
- Training of public health personnel in early recognition and diagnosis of arboviral diseases.
- Assistance to national and regional training centers in arbovirology to improve surveillance capabilities, leading to more effective control of epidemics.
- Support of research on the development and distribution of more effective vaccines for Japanese encephalitis.
- Studies of the ecology of local vectors and the behavior of human populations to gain a better understanding of how to prevent transmission.

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ANNEXES

Annex 1

Table 1. Diseases in Man Caused by Arthropod-Borne Viruses

Togaviruses

Name of Virus	Vector	Disease in Man	Distribution
Alphaviruses (Group A)			
Chikungunya	Mosquito	Fever, arthralgia hemorrhagic fever	Africa, SE Asia, Phillippines Americas
Eastern equine	Mosquito	Encephalitis	South America
Mayaro	Mosquito	Fever, arthritis, rash	South America
Mucambo	Mosquito	Fever	Africa
O'nyong-nyong	Mosquito	Fever, arthralgia	Australia, S. Pac.
Ross River	Mosquito	Arthritis, rash	Africa, Asia
Semliki Forest	Mosquito	Fever	Africa, India, SE Asia, Pacific
Sindbis	Mosquito	Fever, rash	S. America to U.S. Americas
Venezuelan equine	Mosquito	Encephalitis	
Western equine	Mosquito	Encephalitis	
Flaviviruses (Group B)			
Banzai	Mosquito	Fever	Africa
Rio Bravo	Unknown	Encephalitis, aseptic meningitis	U.S.A., Trinidad
Bussuquata	Mosquito	Fever	South America
Dengue 1,2,3,4	Mosquito	Fever, rash, hemorrhagic fever	Africa, Asia, Pacific, S.&C. America, Carib.
Central European Encephalitis	Tick	Encephalitis	Europe S.&C. America
Ilheus	Mosquito	Fever, encephalitis	

Table 1 (cont.)

Name of Virus	Vector	Disease in Man	Distribution
Japanese	Mosquito	Encephalitis	Asia, Pacific Is.
Kunjin	Mosquito	Fever	Australia, Sarawak
Kysanur Forest	Tick	Hemorrhagic fever	India
Louping Ill	Tick	Encephalitis	Great Britain
Murray Valley	Mosquito	Encephalitis	Australia, New Guinea
Negishi	Unknown	Encephalitis	Japan
Omsk hemorrhagic	Tick	Hemorrhagic fever	U.S.S.R.
Powassan	Tick	Encephalitis	Canada, U.S.A.
Rocio	Unknown	Encephalitis	Brazil
Russian spring-summer	Tick	Encephalitis	Europe, Asia
Spondweni	Mosquito	Fever	Africa
St. Louis	Mosquito	Encephalitis	Americas
Usutu	Mosquito	Fever	Africa
Wesselsbron	Mosquito	Fever	Africa, Asia
West Nile	Mosquito	Fever, encephalitis, rash	Africa, Asia, ME, Europe
Yellow fever	Mosquito	Hemorrhagic fever	Africa, S.&C. America
Zika		Fever	Africa, SE Asia
Bunyaviruses (Group C)			
Apeu	Mosquito	Fever	South America
Caraparu	Mosquito	Fever	South America
Itaqui	Mosquito	Fever	South America
Madrid	Mosquito	Fever	Panama
Marituba	Mosquito	Fever	South America
Murutucu	Mosquito	Fever	South America
Oriboca	Mosquito	Fever	South America
Ossa	Mosquito	Fever	Panama
Restan	Mosquito	Fever	Trinidad

Table 1 (cont.)

Name of Virus	Vector	Disease in Man	Distribution
Bunyamwere Group			
Bunyamwere	Mosquito	Fever	Africa
Germiston	Mosquito	Fever	Africa
Guaroa	Mosquito	Fever	S. America, Panama
Ileasha	Unknown	Fever	Africa
Restan	Mosquito	Fever	Trinidad
Wyeomyia	Mosquito	Fever	S. America, Panama
Bwamba Group			
Bwamba	Mosquito	Fever	Africa
California Group			
California	Mosquito	Encephalitis	U.S.A., Canada
LaCrosse	Mosquito	Encephalitis	U.S.A., Canada
Tahyna	Mosquito	Fever	Europe, Canada
Guama Group			
Catu	Mosquito	Fever	South America
Guama	Mosquito	Fever	South America

Table 1 (cont.)

Name of Virus	Vector	Disease in Man	Distribution
Sandfly Fever Group (Phlebotomus fever)			
Candiru	Unknown	Fever	South America
Chagres	Sandfly	Fever	Central America
Naples type	Sandfly	Fever	Europe, Africa, Asia
Punta Toro	Sandfly	Fever	Panama
Rift Valley	Mosquito	Fever, hemorrhagic encephalitis blindness	Africa, Middle East
Scilian type	Sandfly	Fever	Europe, Africa, Asia
Simbu Group			
Shuni	Mosquito, Culicoides	Fever	Africa
Oropouche	Culicoides	Fever	South America
Crimean-Congo Group			
Crimean-Congo hemorrhagic	Tick	Hemorrhagic fever	Europe, Africa, Central Asia
Nairobi Sheep Disease Group			
Nairobi Sheep Disease	Tick	Fever	Africa, India
Dugbe	Tick	Fever	Africa
Ungrouped			
Thogoto	Tick	Meningitis	Africa, Europe

Table 1 (cont.)

Name of Virus	Vector	Disease in Man	Distribution
Changuinola Group			
Changuinola	Sandfly	Fever	Central America
Kemerovo Group			
Kemerovo	Tick	Fever	Europe
Tribec-Lipovink	Tick	Fever	Europe
Colorado Tick Fever			
Colorado Tick	Tick	Fever	U.S.A.
Rhabdoviruses			
Vesicular Stomatitis Group			
Vesicular stomatitis	Sandfly	Fever	N.&C. America
Not Classified			
Quaranfil	Tick	Fever	Africa
Bhanja	Tick	Fever, encephalitis	India, Europe, Africa

Annex 2

Rift Valley Fever (RVF)

This disease was first described in sheep in the Rift Valley in Kenya. Until recently, the number of human cases associated with outbreaks was small and the disease was rarely fatal in humans. In 1977, however, an estimated 200,000 human cases and at least 600 deaths from encephalitis and hemorrhagic fever occurred in Egypt.

RVF is characterized by outbreaks in domestic animals. Humans may be infected by arthropods or secondarily through diseased animals. RVF is highly pathogenic for cattle and sheep, particularly for strains exotic to Africa. Many of the indigenous livestock strains have a relatively high level of resistance to infection and show only transient febrile reactions. Goats and water buffaloes are important hosts and camels may abort when exposed to RVF virus. Horses, donkeys and pigs are not susceptible. Outbreaks in herds and flocks result in widespread abortions and deaths in young animals. Mortality may approach 100 percent in susceptible breeds of wool sheep or cattle and reach up to 40 percent in other animals.

a. Symptoms

In humans, RVF has a short incubation period of about three days. The onset of fever is accompanied by severe depression, muscle and joint pains, vomiting, diarrhea, back and abdominal pain and a severe headache with eye pain. Other symptoms include a depression of white blood cell counts, and gastrointestinal discomfort and jaundice similar to the early stages of hepatitis. In a small proportion of human cases, a hemorrhagic syndrome is seen during the febrile phase, with an extremely high fatality rate. Encephalitis has been reported as a late complication. Recovery can be complete, but some loss of visual acuity is frequently observed.

b. Distribution

Since the initial isolation of the virus in Kenya in 1930, serological surveys have provided evidence of RVF infection in most countries of sub-Saharan Africa. A major outbreak of RVF occurred in Zimbabwe in 1978, affecting sheep and cattle as well

as a large percentage of abattoir workers. Serological surveys in Nigeria have shown antibodies for the virus in man, cattle, sheep, goats and camels. Human or animal antibodies to RVF virus have been detected in Madagascar, Somalia and Tanzania. In West Africa, the virus previously named Zinga virus has been identified as a strain of RVF and has been isolated in Senegal, Burkina Faso and Guinea. Serological surveys among animals have identified an important focus of RVF along the border between Mauritania and Mali. When additional serological surveys are conducted, the virus will probably be found elsewhere within the extremes of the known range.

The appearance of the disease in Egypt in 1977 represented an incursion into a climatically rainless zone that apparently had never before been seeded with the virus. Eighteen thousand human cases were reported in the first year, but the actual number may have reached 200,000. This epidemic was the first in which a large-scale outbreak in humans was associated with a substantial number of fatalities from encephalitis and hemorrhagic fever. Some 600 deaths from RVF were reported. In 1978, a smaller outbreak of the disease in Egypt caused about 90 human deaths. The virus now appears to have disappeared from the country and has not been detected again in extensive serological surveys of young animals.

c. Vectors

Approximately 23 species of mosquitoes have been implicated as possible RVF vectors. The virus has been isolated from *Culex*, *Aedes*, *Eretmapodites*, *Anopheles* and *Mansonia* species. In 1985, RVF virus was isolated in Kenya from male and female *Ae. mcintoshi* that had been reared from field-collected larvae and pupae. This suggests that transmission occurs in the uterus in this species, providing a survival mechanism for the virus between outbreaks.

d. Control

The control of RVF during periodic outbreaks in Africa has largely consisted of vaccinating the principal disease hosts. Usually human populations have not been affected to an extent that would require prophylaxis. Vaccination prevents or greatly reduces the economic loss of livestock deaths and the possibility of abortions in susceptible pregnant animals. It also reduces the

amplification of the RVF virus in livestock, limiting the danger of human infection by direct or vector transmission.

Two vaccines are available for veterinary use: a live attenuated vaccine and an inactivated or killed vaccine. Humans who have a high risk of infection, such as veterinarians or those working in laboratory diagnosis or field research on RVF, should be offered the option of being inoculated with the inactivated vaccine.

Another method of controlling the spread of the infection during an outbreak among animals is to strictly limit their movement from within the infected area to other areas.

e. Vector control

Vector control measures must be adapted to the habits of the target species. Larviciding is only feasible if the breeding habitats of the putative vector species are readily and economically accessible. The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) has used satellite imagery and aerial photography to identify savannah breeding sites of RVF vectors.

Annex 3

Venezuelan Equine Encephalitis (VEE)

VEE infections exist in two forms: a severe epidemic form in which horses and other equines are the principal hosts and an endemic form in which rodents appear to be the main hosts. A wide variety of other hosts may be infected by the virus. Its effects on a patient may be severe, but humans are relatively unimportant in the normal transmission cycle.

a. Symptoms

Human patients have influenza-like symptoms, with an abrupt onset of severe headache, chills, fever, muscle and eye pain, nausea and vomiting. Irritation of the eyes and throat are the only physical signs. Infections may cause relatively mild to severe respiratory illnesses with symptoms lasting three to five days. After a few days of fever, particularly in children, signs of central nervous system involvement may appear, ranging from somnolence to frank encephalitis with disorientation, convulsions, paralysis, coma and death. During an outbreak in Texas in 1971, three of 40 patients studied had severe neurologic damage resulting in personality change or paralysis.

The incubation period is three to 15 days and can be as short as one day. Mortality is usually very low, but mortality as high as 36 per 1000 has been reported in areas with inadequate medical care. Diagnosis is usually made by isolating the virus from whole blood drawn two or three days after the onset of symptoms.

b. Distribution

VEE is endemic throughout much of Central and South America and parts of North America. Epidemic strains of the disease are believed to have been involved in horse epidemics reported between 1939 and 1959 in Venezuela, Ecuador, Peru, Colombia, Argentina and Trinidad. In 1969, a rapidly spreading epidemic form was recognized in Ecuador, Peru and Colombia. The same strain spread north to Costa Rica, Nicaragua, El Salvador, Honduras, Guatemala, Mexico and finally to the southern United States.

An estimated 60,000 human cases of VEE were recorded in Colombia, Venezuela and Ecuador between 1962 and 1970 with more than 1,200 neurologic cases and approximately 500 deaths. During the 1969-1970 outbreak in Mexico, 16,922 human cases and 42 deaths were reported. In the Texas outbreak in 1971, 84 confirmed human cases were reported.

c. Vectors

In epidemic outbreaks of VEE involving horses and people, many species of mosquitoes of the genera *Culex* (*Melanoconion*), *Anopheles*, *Mansonia*, *Deinocerites*, *Psorophora* and *Aedes* have been shown to be infected. It is likely that many different species of these genera or subgenera have served as vectors in different parts of the wide geographic range of this virus.

d. Reservoirs

More than 150 different animal species have been found naturally infected with VEE virus or have been infected in the laboratory. Horses are of the greatest importance in the explosive spread of epidemics. A number of other animals, including dogs, other canines and swine, also develop high concentrations of circulating virus. Small rodents appear to be the reservoir hosts of endemic VEE. Among the important rodent reservoirs species are cotton mice, found only in the southern United States, and cotton rats, which are found in the Florida Everglades. Spiny rats and rice rats are important reservoir species in northern coastal areas of South America.

e. Control

There is no specific treatment for either human or equine cases except good supportive care. Effective control must be based on limiting the movement of viremic animals from infected to non-infected areas and using a vaccine to immunize horses. Mosquito control measures are essential in areas where the identity of the vector species is recognized, particularly during epidemic outbreaks of the disease.

Annex 4

Western Equine Encephalitis (WEE)

Also known as western equine encephalomyelitis, WEE is primarily an infection of wild birds. It produces acute central nervous system (CNS) disease in humans and equines. It is generally less virulent than EEE virus in horses. The case fatality rate in equines may be as high as 50 percent, but averages from 20 to 30 percent.

Inapparent WEE infections are relatively common in humans in endemic areas where clinically recognized cases of the disease occur. WEE antibody has been detected among 10.9 percent of a human population sampled in Colorado and 8.6 percent of a northern Utah population in years when no clinical cases were reported.

Wild birds, especially nestlings, are the amplifying host in the transmission cycle of this infection. Although equine outbreaks usually precede human epidemics, horses play no role in the cycle.

a. Symptoms

The same criteria for the diagnosis of EEE apply to WEE. Symptoms differ among various age groups. Children younger than one year may have fever and convulsions. Symptoms in one- to four-year-olds include fever, headaches, vomiting, drowsiness, irritability, restlessness, muscle rigidity, tremors and sometimes convulsions. In addition to these symptoms, five- to 14-year olds may have photophobia and limitation of neck and back flexion. Patients 15 and older suffer drowsiness, lethargy, malaise, fever, stiffness of back and neck, usually with severe headache, disturbance of vision, nausea, vomiting and vertigo. The case fatality rate is generally three to four percent. In a 1975 outbreak in the northeastern United States and Canada, the fatality rate was 7.7 percent.

WEE infections may result in neurological, intellectual and psychological problems. The disease is particularly severe in infants and young children. A strong correlation has been reported between the age of a patient at the time of the illness and the incidence and severity of permanent damage. In California, long-term studies of patients who were younger than one month at the onset of the disease showed residual brain damage among

55 percent of the survivors. Severe brain damage was found in 12 percent of those who were one month of age at onset, and in six percent of those infected at two to 11 months of age. Only five percent of stricken adults showed such sequelae.

b. Distribution

WEE occurs mainly in the central and western United States and Canada, with scattered foci further east. The virus has also been isolated in Argentina, Brazil, Guyana and Uruguay, and is occasionally responsible for equine deaths in these countries. Infections in Central America are extremely rare. Between 1955 and 1979, 947 cases of the disease were reported in the United States, with 346 suspected cases in the 1975 outbreak alone.

c. Vectors

The vector in the western United States and Canada, *Culex tarsalis,* is found in irrigated, agricultural areas and readily bites man. *Aedes dorsalis* is an important vector in California. The vector relationships in South America are unknown.

d. Control

Prevention of WEE in horses may be enhanced by annual immunizations with commercially available vaccines. No WEE vaccine is licensed for immunization of people but there is an investigational vaccine to protect laboratory workers. There is no specific treatment for WEE illness. Supportive nursing care is important, particularly in cases with neurologic involvement.

e. Vector control

Controlling vector mosquitoes is the most effective way of reducing the risk of WEE in humans. This is one of the main objectives of organized mosquito abatement districts in endemic areas of the United States and Canada. In the western and central United States, vector control is complicated by widespread insecticide resistance. No organized control exists in Latin American countries.

Annex 5

Eastern Equine Encephalitis (EEE)

Eastern equine encephalitis (EEE) is also known as eastern equine encephalomyelitis and horse sleeping sickness. The natural history of the disease is still not completely understood. Incidence depends on the relationships between the vertebrate hosts (birds and equines), the mosquito vectors and, in geographical areas where human cases appear, man.

EEE case fatality rates among both human beings and horses are characteristically high, but human cases are relatively rare. In an outbreak in 1947 in Louisiana, 11,927 deaths were reported among 14,334 equine cases.

a. Symptoms

The clinical symptoms of EEE in humans are indistinguishable from those of western equine encephalitis (WEE) but a higher percentage of symptomatic infections end in death. Fatality rates for EEE approach 80 percent, especially in children, whereas with WEE they range from five to 15 percent. Onset of EEE is abrupt, with high fever of 40° to 41°C, severe headache, a stiff neck, nausea, stupor, coma and convulsions. EEE virus infections often result in encephalitis.

Although fatal infections occur in the majority of clinically recognized EEE cases, mild and inapparent syndromes have also been described. Serological surveys suggest that there are 23 inapparent infections for every recognized case. This declines to eight to one among children younger than four.

b. Distribution

Retrospective evidence indicates that EEE was the cause of equine outbreaks in the United States as early as the 19th century. From 1935 (shortly after the first isolation of the virus in 1933) until 1970, the Animal Health Division of the USDA reported 533,269 cases of arthropod-borne encephalitis in equines in the United States, with 41,968 associated deaths from 1939 through 1970. These numbers probably include cases of WEE.

Cases of EEE, both equine and human, have also been reported from Canada, Panama, Trinidad, north-central Argentina and the northern part of South America from Brazil to Venezuela. Serological tests have shown EEE activity around the base of the Yucatan Peninsula and in Belize, Guatemala and Honduras. During an outbreak of EEE in Panama in 1973, at least 100 horses were affected by the disease and 40 died. The Caribbean is also a receptive area. Sporadic equine outbreaks have affected Cuba, Hispaniola and Jamaica. Migratory birds may play a major role in the observed distribution pattern.

Reporting and diagnosis of the disease is probably more accurate in the United States than in the countries to the south. Many cases that occur in equines and humans throughout the range of the disease probably are not diagnosed.

c. Vectors

Mosquito vectors of the disease appear to vary from one area to another. Mosquitoes associated with human outbreaks in the United States are thought to be *Aedes sollicitans*, *Ae. vexans and Coquillettidia perturbans*. *Ae taeniorhychus* and other species in Central and South America are vectors of equine and human cases.

d. Control

Effective vaccines for immunizing equines against EEE are available commercially. A bivalent vaccine containing both EEE and WEE virus antigen is usually used. There are no licensed vaccines for immunizing humans against EEE. An investigational vaccine is available under special circumstances of high exposure and is reported to be quite effective.

e. Vector control

Control of mosquito populations is the only available method for minimizing the risk of EEE infection. Most of the endemic or enzootic areas in the USA have well-organized mosquito abatement districts that can quickly respond to the occurrence of human or equine cases. In areas where routine control is not carried out, the most effective measure is reduction of adult mosquito populations by ultra-low-volume spraying.

Annex 6

Chikungunya

a. Symptoms

The name "chikungunya," a Swahili word meaning "that which bends up," describes the arthritic symptoms of the disease. The infection has a three- to 12-day incubation period. Chikungunya fever in man is often confused with dengue, but it has a more abrupt onset and the median duration of the fever is three days instead of five. A rash occurs with greater frequency in chikungunya than in dengue and a single episode of rash accompanies the crisis of fever on the second or third day after the onset of symptoms. Infections are frequently accompanied by arthritis, evidenced by redness, swelling and tenderness of inflamed joints. Pain may last for months or years. Unlike dengue patients, people with chikungunya have normal or slightly low white blood cell counts. Hemorrhagic manifestations may accompany chikungunya, particularly in Southeast Asia and India, but they are usually mild. Mortality is generally less than one percent.

Chikungunya may occur in epidemic outbreaks or as sporadic scattered cases. A specific diagnosis can be made by observing an increase in antibody titer in serum samples collected within five days of the onset of the fever.

b. Distribution

Chikungunya appears to be endemic throughout much of Africa south of the Sahara. The disease has been reported from Uganda, Tanzania, Zimbabwe, South Africa, Angola, Zaire, Nigeria and Senegal. It has caused large epidemic outbreaks in the American and Asian tropical areas, even extending at one time as far north as Philadelphia in the United States.

During the late 1950s and 1960s, chikungunya established itself as an endemic infection in Southeast Asia and was continuously transmitted among urban populations of Thailand, Cambodia and Vietnam, with sporadic outbreaks in Burma, Bangladesh, the Philippines, Hong Kong, Indonesia, Malaysia and Singapore. Major epidemics occurred in India and Sri Lanka. An epidemic of the disease in Madras in 1964 caused some 300,000 cases in a population of about 2 million. In 1986, three cases of chikungunya were diagnosed from

U.S. Peace Corps volunteers working in different parts of the Philippines.

c. Vectors

Almost all recorded chikungunya infections in humans have paralleled the distribution and abundance of *Aedes aegypti* mosquitoes. Virus has been recovered from wild-caught *Ae. aegypti* in Africa, India and Thailand, from *Ae. africanus* in Uganda and Bangui, and *Ae. luteocephalus* in Senegal. In urban areas, where most cases of this disease occur, *Ae. aegypti* is probably the most important vector. Other vector species probably maintain the zoonotic cycle by transmitting the disease among primate reservoirs.

d. Control

There is no commercial vaccine for preventing chikungunya, but an investigational vaccine is being tested. The only treatment for an infected person is supportive, with bed rest advised during febrile periods. Salicylates should be avoided because of their hemorrhagic potential. Children who have lost excessive fluids due to vomiting, fasting or thirsting may require intravenous replacement if they cannot take fluids orally.

e. Vector control

Controlling the predominant vector, *Ae. aegypti*, is the best way to control transmission. Control of this species has been discussed in detail under the section on control of dengue and dengue hemorrhagic fever vectors (Chapter 2).

Annex 7

St. Louis Encephalitis (SLE)

a. Symptoms

Infection with St. Louis encephalitis virus may cause an acute illness with a spectrum of nervous system problems, but in most people the disease is mild, with fever and a headache lasting for several days. A few patients may have life-threatening neurological disorders. Those older than 50 are most likely to develop a clinical illness. In urban epidemics of 30 or more laboratory-diagnosed cases, fatality rates have ranged from 2.6 to 19.4 percent. Diagnosis must be made by serological identification. If a clinical diagnosis is attempted, the disease must be differentiated from many other viral and some bacterial infections.

b. Distribution

SLE is widely distributed in the Western hemisphere, ranging from Canada in the north to Argentina in the south. Serological surveys frequently reveal human infections in Central and South America, but epidemics are rare. In one epidemic in northwestern Mexico in 1974, there were 51 hospitalized cases, an attack rate of 19 per 100,000 inhabitants, and a case fatality rate of approximately 20 percent. Incidence was higher in children than in adults. The virus is very widely distributed in the United States and relatively serious outbreaks have occurred in the east-central part of the country. The virus has caused as many as 10,000 cases of SLE and 1,000 deaths in North America since it was first recognized in 1933. The largest epidemics was in 1976, when more than 2,000 cases were reported in the United States.

c. Vectors

In the eastern United States, the principal vectors of SLE virus are mosquitoes of the *Culex pipiens* complex and *Cx. nigripalpus* is the epidemic vector in Florida. *Cx. tarsalis* transmits the disease in the western United States. The status of the vectors in central and South America is uncertain. The virus probably passes through a cycle

involving wild birds and domestic fowl, which serve as amplifying hosts. It may be transmitted from one area to another by migratory birds.

d. Control

There is no specific treatment for SLE or an approved vaccine to prevent infection, so control of the disease depends entirely on controlling its mosquito vectors. Measures employed depend on the ecology of the vector in the area of the outbreak. As is the case in most arboviruses epidemics, ground or aerial application equipment can be used to apply ultra-low-volume concentrates of insecticides to rapidly reduce the numbers of adult mosquitoes circulating the virus.

Annex 8

O'Nyong–Nyong Fever (ONN)

a. Symptoms

O'nyong-nyong fever in humans is characterized by sudden onset, with chills and nosebleeds, pain, stiffness in the back and joints, headaches, irritating rash and swelling of the lymph glands.

b. Distribution

ONN infection was first recognized in northwestern Uganda in 1959, when it was responsible for one of the largest and most well-documented arbovirus outbreaks ever recorded. From Uganda, ONN spread southeastward into Kenya, Tanzania, Mozambique and Malawi and westward into what is now Zaire. A strain of ONN was isolated as far west as Senegal. It has been estimated that as many as 2 to 5 million cases occurred in East Africa during this outbreak.

The clinical infection cause by ONN is quite mild. Its significance lies in the sudden appearance and dramatic spread of the virus. Obviously the human populations in the areas to which it spread were entirely nonimmune. The reasons for the subsequent disappearance of the disease are unknown. Its recent reappearance in Kenya in mosquitoes, with no evidence whatsoever of a natural reservoir, poses many unanswered questions about its natural cycle. The sudden appearance and rapid spread of ONN raises the possibility that other viruses that cause much more serious illness might follow the same pattern if introduced into nonimmune populations, creating major epidemics with high morbidity and mortality.

c. Vectors

ONN is the only major arbovirus transmitted solely by anopheline mosquitoes. During the epidemic, the major malaria vectors *An. funestus* and the *An. gambiae* complex were incriminated as vectors. Since then, no vertebrate host other than man has ever been demonstrated, nor has the virus been isolated from mosquitoes or man, except for one isolation from *An. funestus* collected in Kenya in 1978.

Annex 9

Ross River Virus

The disease caused by this viral infectious agent is also known as arthropod-borne viral arthritis, epidemic polyarthritis, and Ross River Fever. The Ross River syndrome of joint paints and rash was first recognized in Australia in 1927. A number of epidemics involving the same syndrome subsequently occurred in various parts of that country and elsewhere in the southern Pacific. Ross River virus is not known to cause fatal cases or encephalitis.

a. Symptoms

The onset of this benign disease is usually rapid, with a slight fever, often not more than 38 °C, a sore throat and swelling of joints, especially the small joints of the hands and feet. Some patients also have a rash on the trunk and limbs and a mild headache. Most people recover completely within two weeks. A minority have persistent or relapsing joint swellings for up to a year after onset. Specific diagnosis of human cases depends on serological tests. Ross River fever is usually inapparent in young children.

b. Distribution

Major outbreaks have occurred in the Murray Valley, Northern Territory and Queensland areas of Australia, with sporadic, widespread cases occurring elsewhere in coastal areas of Australia, the Solomon Islands and New Guinea. In 1979, a major outbreak occurred in Fiji with an estimated 30,000 to 40,000 cases. The disease spread to Rarotonga in the Cook Islands and later to Tonga and American Samoa, where there were 15,000 cases in 1979-1980.

c. Vectors

In the outbreak that occurred in the Cook Islands in 1979, Ross River was isolated from six pools of *Aedes polynesiensis*. It appears that this species may be the vector on Rarotonga, the most populous island of the group. In Australia, *Aedes vigilax* and

Culex annulirostris are considered major vectors of the virus. Serological surveys in Australia have shown that a large number of wild and domestic animal species, particularly marsupials, are positive for antibodies to Ross River. Birds may not be significant hosts.

The reservoirs of the disease, if any, are as yet unknown. Cases continued to occur 15 months after the onset of the 1979 epidemic in Fiji, where the disease probably became enzootic among domestic animals and possibly in wild rodent populations.

d. Control

No specific vaccines or chemotherapy exist for this virus, so prevention of transmission must depend on mosquito control. No efforts have been made to control the mosquito vectors, except in Fiji during the major outbreak. Travelers to infected areas should use insect repellents and other methods of personal protection to avoid mosquito bites.

Annex 10

Oropouche Virus (ORO)

Oropouche (ORO) virus is the leading cause of urban epidemics of arthropod-borne viral disease in the Amazon Basin. This virus was first isolated in 1955 in Trinidad. The first urban outbreak of ORO was not recognized until 1961, when an estimated 11,000 residents in Belem, Brazil, were infected. From 1961 to 1978, seven epidemics of ORO have been documented in Para State, Brazil. Although no fatalities have been attributed to this virus, which is transmitted by a tiny biting fly (*Culicoides paraensis*), it has infected thousands of persons of all age groups and caused severe illness.

a. Symptoms

Oropouche virus infection in man causes an acute febrile illness with a sudden onset, usually four to eight days after exposure to the bite of an infected fly. Temperatures generally exceed 39 °C. Chills, severe headache, joint and muscle pain, dizziness, and photophobia are the most common symptoms. Nausea may occur and may be followed by vomiting and diarrhea. Although some patients become severely ill, no fatalities or irreversible effects have been attributed to the disease. Clinical illness usually lasts from two to five days, but recurrence of some symptoms, particularly a persistent headache, has been reported.

b. Distribution

ORO virus has a wide geographical distribution in the Amazon Basin. The major epidemics of the disease caused by this virus have occurred in Para State, Brazil, south of the Amazon River. This may reflect the greater human population in this part of the Amazon Basin. Antibodies to ORO virus have been detected in human populations living in the following states or territories of Brazil: Amazonas, Maranhao, Goias, Mato Grosso, Acre, Roraima and Amapa. Distribution of the virus in cities has been markedly uneven, but has been spread throughout affected village populations. All age groups are affected, but the female: male ratio of attack rates varied in some of the outbreaks. For example, it was 3:1 in Santarem in 1975.

c. Vectors

The primary vector of ORO virus in urban areas of the Brazilian Amazon Basin is *Culicoides paraensis*, a tiny biting midge that breeds primarily in banana plant refuse. Banana plants are commonly cultivated in the urban centers of Amazonia, bringing man and the midge in close contact. *Culicoides paraensis* is the most common diurnal man-biting insect in urban areas, with peak biting activity occurring between 5 and 6 p.m. A few virus isolations have been made from mosquitoes, primarily from *Culex quiquefasciatus*, which breeds in polluted waters associated with human populations. Although antibodies to ORO virus have been detected in domestic and wild birds, monkeys, wild carnivores and rodents, man is thought to be the only significant reservoir, at least during epidemics.

d. Control

There is no commercial vaccine available to prevent ORO virus infection in humans. Given its limited global distribution, it is doubtful that a commercial vaccine will be developed in the near future. The only treatment for an infected person is supportive.

e. Vector Control

Decaying banana plant materials and decomposing cacao hulls are the principal breeding sites of *Culicoides paraensis* in urban and peri-urban areas. Decayed banana stalks are thought to be useful as fertilizer, so a trunk is usually cut into several small stalks that are left to decompose. These stalks will serve as a breeding site for two to four months. Since cacao hulls have no commercial value, they are generally piled in large mounds near the harvester's residence and left to decompose. The hulls will also serve as breeding sites for several months. Destruction of the banana stalks or cacao hulls by burning is not feasible because of their high water content. Therefore, the refuse should be buried and not left exposed. Community participation aimed at cleaning up this refuse will be necessary to control vector populations and the transmission of ORO virus.