Annex B. **Human and animal health affected by mosquitoes**

This annex deals with the pathogens and diseases transmitted by mosquitoes to humans and animals. The main arbovirus infections of humans in the diverse regions of the world are summarised. More details are given on the dengue virus including its four viral serotypes, the range of symptoms affecting humans, the past and current epidemics of dengue (mainly vectored by Aedes aegypti *and other aedine species) including its increasing spread over the past fifteen years. Few elements are also provided on virus transmission to animals by* Ae. aegypti*, and on vertical transmission.*

Pathogens and diseases

An arthropod-borne virus or arbovirus is defined as a virus that is maintained in nature principally through biological transmission between susceptible vertebrate hosts by haematophagous arthropods; arboviruses multiply and produce virus in the vertebrate host, multiply in arthropod tissues, and are passed on after a period of extrinsic incubation to other vertebrates once again by the bites of an arthropod (PAHO, 1979). Most arboviruses fulfil the criteria laid down in this definition, but the group is very heterogeneous, containing viruses which, because they have not been fully classified on morphological or physicochemical grounds, are included among the arboviruses for convenience. There are currently 490 known arboviruses and this very large group contains representatives from several different viral families, the most important of which are the families Togaviridae, Flaviviridae, Bunyaviridae, Reoviridae and Rhabdoviridae (Bishop et al., 1980; Rehle, 1989).

The extrinsic incubation period (EIP) is the time necessary for the development of arbovirus in the arthropod host. If the female mosquito longevity is lower than the viral EIP, then the potential for vector transmission is reduced. Average EIP is 15 days at 25°C and 6.5 days at 30°C (Chan and Johansson, 2012).

By definition, arboviruses have at least two different hosts, a vertebrate and an invertebrate arthropod, although many arboviruses have complex life-cycles involving several different vertebrates, and some are capable of transmission by more than one species of vector. All arboviruses, with perhaps very few exceptions, are current or potential zoonoses maintained in nature principally by wild animals and birds.

They have evolved to a state of mutual tolerance or symbiosis with their reservoirs. Since arboviruses rely only on virus production in the vertebrate host for successful transmission, disease in this host would be a disadvantage. Therefore, arboviruses seldom cause recognisable disease in maintenance hosts, and when disease is apparent in man or domesticated animals, it is only overt sign of the presence of these viruses.

Over 80 viruses produce significant human disease which ranges from mild febrile illness, which may or may not be accompanied by a skin rash and sometimes by polyarthritis, to severe and often fatal encephalitis or haemorrhagic fever. The same virus may produce different disease patterns in different subjects and illness often has a biphasic pattern. Mild fever, often not recognised, occurs during the initial viraemic stage. This may be followed by more serious symptoms, at which stage viraemia may have ceased and immunological responses, including antibody formation, have occurred. Frequently, only a small proportion of persons infected with potentially encephalitogenic arboviruses in epidemics develop encephalitis in this second phase. The great majority of infections do not develop past the first phase, which may even be asymptomatic.

Virus infection vectored by mosquitoes

There are 66 members in the flavivirus group, of which 31 are mosquito-borne. 26 flaviviruses can cause human disease but several of them have produced only laboratory-acquired infections or isolated cases of disease in man (Table A B.1). The range of clinical manifestations produced by flaviviruses is similar to those of the alphaviruses – febrile illnesses with or without a rash, or encephalitis. In addition, yellow fever, Kyasanur Forest disease, Omsk haemorrhagic fever, and dengue virus can

cause haemorrhagic symptoms. Only those viruses which produce substantial prevalence are discussed in detail.

The International Committee on Taxonomy of Viruses (ICTV) has assigned the dengue virus (DENV) to the genus *Flavivirus*, of the Flaviviridae family. Based upon biological, immunological and molecular criteria, there are four viral serotypes, namely DENV-1, DENV-2, DENV-3 and DENV-4, which have different antigenic characteristics and serology (Boshell, 1995; Klungthong et al., 2004). Each serotype creates specific lifelong immunity against homologous reinfection, as well as short-term cross-immunity against the other serotypes, which can last several months (Leitmeyer et al., 1999; Monath, 2004). Each serotype has been subdivided into several genotypes (clades): three genotypes for DENV-1 (I, II and III) although two other clades named IV and V have been proposed, six genotypes for DENV-2 (American, Asian/American, Asian I, Asian II, Cosmopolitan and Sylvatic), four for DENV-3 (I, II, III and IV) although a fifth has also been proposed (V) and finally four for DENV-4 (I, II, III and Sylvatic) (Holmes, 2006).

Classic dengue fever affects both adults and older children. Following an infective mosquito bite, there is an incubation period of five to eight days followed by the sudden onset of acute fever, which often becomes biphasic, with a severe headache, pain behind the eyes, backache, chills and generalised pain in muscles and joints. A maculopapular rash generally appears on the thorax between the third and fifth day of illness and may spread later to the face and extremities. Lymphadenopathy, anorexia, constipation and altered taste sensation are common. Occasionally, petechiae are seen on the dorsal surfaces of the feet and the legs, hands, axillae and palate late in the illness. In young children, upper respiratory tract symptoms predominate and dengue fever is rarely suspected. The illness generally lasts for about ten days, after which recovery is usually complete, although convalescence may be prolonged. Laboratory findings reveal leukopenia, a mild thrombocytopenia, and slight lymphocytosis (Brathwaite et al., 2012).

Concerning the dengue haemorrhagic syndrome, fever, upper respiratory symptoms, headache, vomiting and abdominal pain may be present in the initial phase of the disease. Myalgia and arthralgia are uncommon. These symptoms (which are not severe enough for confinement) may last two to four days and many recover without any further symptoms. However, in a proportion of these cases, the initial phase is followed by an abrupt systemic collapse with hypotension, peripheral vascular congestion, petechiae, and sometimes a rash. Different degrees of shock may be evident, with the patient often restless, sweating, and febrile, clammy extremities, and a hot, feverish trunk. The fourth and fifth days are critical and purpura, ecchymoses, epistaxis, haematemesis, melaena, coma, convulsions and severe shock indicate a poor prognosis. Should the patient survive this period, however, recovery is usually complete. Laboratory studies often reveal thrombocytopenia, a prolonged bleeding time, an elevated prothrombin time, a raised haematocrit, hyperproteinemia and a positive tourniquet test. The liver is often enlarged, soft, and tender (Brathwaite et al., 2012). Several hypotheses have been proposed to explain why DENV now causes devastating epidemics, although it previously caused relatively mild illness. The two principal proposals are that either there is an unusual response to infection in the host, or there is an increase in the virus' virulence. Haemorrhagic manifestations are thought to be due to secondary infection with different DENV, with a critical interval of six months between the two infections. The first infection probably sensitises the patient, whereas the second appears to produce an immunological catastrophe (WHO, 2009).

Table A B.1. Some important arbovirus infections of humans in geographic regions of the world

Disease	Geographic region(s)	Vectors	Vertebrate host(s)	DISEASE FEATURES IN HUMANS			Control measure
				Disease pattern	Description of diseases	Diagnosis	
Yellow fever urban	New World and Africa	*Ae. aegypti*	Man	Epidemic	Acute onset, high fever, prostration, later jaundice, proteinuria; fatalities common, although ratio of inapparent/apparent infection is high	Virus isolation, CF, HI, N, ELISA test	Vaccination with 17D vaccine, *Ae. aegypti* control
Yellow fever jungle	New World and African tropics	Mosquitoes haemagogus and aedines	Forest primates	Endemic	As above; cases occur sporadically in people exposed in forested regions in Africa and New World	Virus isolation, CF, HI, N, ELISA test	Vaccination with 17D vaccine, mosquito control not practicable
Dengue	New World and Old World tropics and subtropics	*Ae. aegypti* and other aedines	Man, possibly a jungle cycle in primates	Endemic and epidemic	Acute onset with rash in many cases and joint pains; simulates as influenza-like syndrome	Virus isolation, CF, HI, N, ELISA test	Vaccination with Dengvaxia, under conditions[1] Mosquito control and protection against mosquito bites
Dengue haemorrhagic fever	Southeast Asia and South America	*Ae. aegypti*	Man	Endemic and epidemic	Serious illness with haemorrhagic complicates, shock syndrome and high mortality almost exclusively in children and following a second infection with a different DENV	CF, HI, N, ELISA test, cell-culture system	Mosquito control
Japanese encephalitis	Korea to India and East Indies	*Culex tritaeniorhynchus* and other culicines	Wild birds, pigs can serve as amplifying host	Endemic and epidemic	Infection usually mild but encephalitic complications can be serious in young and in elderly, very important disease in the Orient	CF, HI, N, ELISA test	Mosquito control, vaccination with an inactivated vaccine
Murry Valley encephalitis	Australia	*Culex annulirostris*	Birds	Endemic, sporadic, over wide areas	Infection usually mild but encephalitis may occur with greatest probability in children and high fatality rates in the young	CF, HI, N test	Mosquito control measures and protection against mosquito bite

Disease	Geographic region(s)	Vectors	Vertebrate host(s)	DISEASE FEATURES IN HUMANS			Control measure
				Disease pattern	Description of diseases	Diagnosis	
Chikungunya	Africa and Asia, tropics and subtropics Cases of autochtonous transmission in Europe	*Ae. aegypti*and *Ae. albopictus*	Possibly primates	Epidemic	Acute onset often with rash, rarely with haemorrhagic manifestations; joint aching and swelling are prominent features	CF, HI, N, ELISA test and virus isolation	Mosquito control
Kyasanur Forest disease	India (Mysore State)	Ticks mainly *Haemaphysalis*	Monkey, possibly also small mammals	Endemics and epidemic	Sudden onset, fever, headache, severe myalgia; there may be a diphase course with second phase	Virus isolation, CF, HI, N ELISA test	Protection against tick bite
Crimean-Congo haemorrhagic fever	Southern former USSR, Bulgaria, Central and South Africa, Pakistan, Iraq	Ticks - *Hyalomma marginatum*	Probably small mammals	Endemics	Sudden onset, chills, fever, headache, nausea, vomiting; haemorrhagic manifestations common; mortality rate 5%-10%	Virus isolation, CF test	Protection against tick bite
Venezuela equine encephalitis	Central and South America and southern United States	Mosquito of several species	Horses, possibly small mammals	Probably endemic, sharply epidemic	Fever, encephalitic signs, usually mild fatalities rate	Virus isolation, CF, HI, N, ELISA test	Mosquito control and protection against mosquito bites; attenuated vaccine exists for equines

Note: [1]WHO recommends that vaccine against dengue should only be used after testing on individuals to assess whether they have ever been exposed to the infection. (WHO Website, 2018)

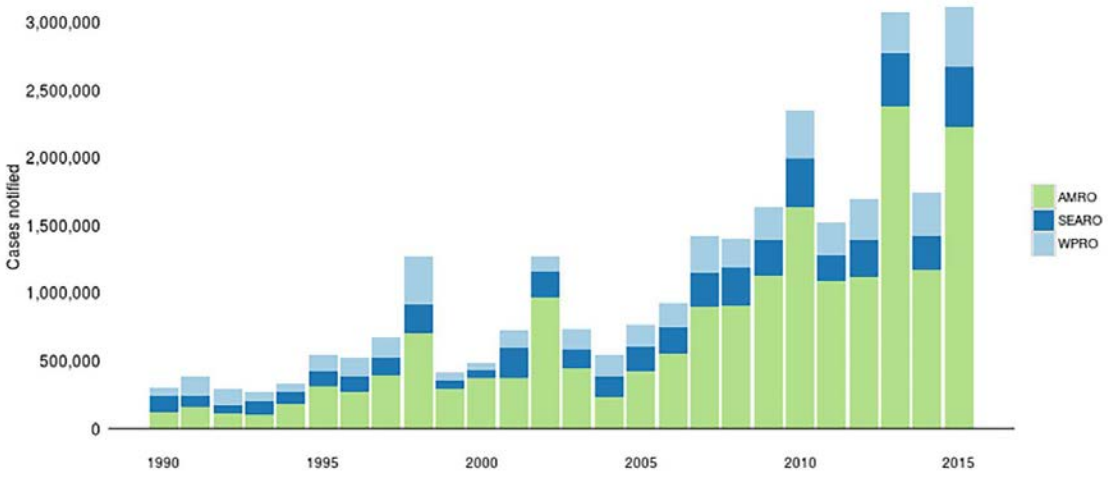
Source: Adapted from Evans, A.S. (Ed.) (1982), Viral Infections of Humans: Epidemiology and Control. Second Edition, Plenum Medical Book Company, New York and London.

Dengue virus serotypes, health effects and epidemics

The dengue disease may be endemic (which is often undiagnosed) or epidemic. In the Americas, there have been four epidemics during the 1963-83 period. The first epidemic in 1963 was caused by DENV-3 in the Caribbean and Venezuela. The second was in 1969, caused by DENV-2, affecting the Caribbean islands and also Colombia. The third epidemic began in 1977 in Jamaica, was caused by DENV-1 and affected more than 60 000 inhabitants, spreading to other Caribbean islands, Mexico, Central America, and Venezuela (Figueroa et al., 1982). In 1981 the fourth epidemic, resulting from DENV-4, began in Saint Barthélemy (French Antilles) and spread to other Caribbean Islands and Belize (PAHO, 2005).

Puerto Rico was seriously affected during all four epidemics, and after relatively high dengue activity in 1981 and 1982, the first epidemic of dengue in Brazil in 50 years began. Most countries reported only sporadic cases during 1983, however, Colombia, El Salvador and Mexico had significant localised outbreaks in 1983 (PAHO, 2005). *Ae. aegypti* reinfestation (1971-99) was caused by the failure of eradication programmes leading to increased dispersal of the mosquito and DENV circulation and a corresponding clear increase in the number of outbreaks over the 2000-10 period. During 2010, more than 1.7 million dengue cases were reported, with 50 235 severe cases and 1 185 deaths (Brathwaite et al., 2012). The epidemic seemed to continue extending globally in the following years; in 2015, the total number of suspected or laboratory-confirmed dengue cases notified to WHO for the Americas, South-East Asia and Western Pacific regions, exceeded three million (Figure A B.1).

Figure A B.1. Number of suspected or laboratory-confirmed dengue cases notified to WHO, 1990-2015



Note: a) AMRO: WHO Regional Office for the Americas
b) SEARO: WHO Regional Office for South-East Asia
c) WPRO: WHO Regional Office for the Western Pacific
Source: WHO (2018), Programmes – Dengue Control – Epidemiology Page, Website, www.who.int/denguecontrol/epidemiology/en/.

Zika virus infection

Zika virus (ZIKV) belongs to *Flavivirus* genus of the Flaviviridae family and it is transmitted to humans by mosquitoes (Gould and Solomon, 2008). However, sexual transmission between humans is another potential form of infection (Moreira et al., 2017). In 2015, ZIKV was shown to be associated with microcephaly and birth defects in children exposed *in utero* following infection of mothers during their pregnancy in Brazil (Zanluca et al., 2015; Calvet et al., 2016; Mlakar et al., 2016). Other studies evidenced the link between ZIKV infection during pregnancy and congenital cerebral malformations in newborns as microcephaly and other dysfunctions (Besnard et al., 2016; Driggers et al., 2016), and this was experimentally supported (Cugola et al., 2016). Moreover, the infection consequences in newborns can cause a range of different pathologies, which were described as the congenital Zika syndrome (Martines et al., 2016). ZIKV may additionally be associated with other neurological complications affecting adults, such as Guillain-Barré Syndrome (Dos Santos et al., 2016). Beyond to newborn disorders, the main symptoms of ZIKV infection are maculopapular rash, fatigue, lethargy, asthenia, fever, arthritis, arthralgia, myalgia, conjunctivitis and headache. The suspected patients can be submitted to RT-PCR assays or serological tests to confirm the ZIKV infection (Musso and Gubler, 2016).

The recent burden of Zika virus outbreaks in many countries is alarming. Although the virus is known since 1947 when it was first isolated from a sentinel *Rhesus* monkey exposed in the Zika Forest (Uganda) (Dick, Kitchen and Haddow, 1952), fewer reports of human infections were described until 2007. In that year, a ZIKV outbreak was first registered in Yap Islands, Federated States of Micronesia and since then, subsequent epidemics were reported in several islands in different Pacific regions between 2013 and 2014. This fast geographic expansion of the viral distribution was achieved in the Americas in 2015, causing important epidemics, mainly in Brazil. Currently, autochthonous transmission of ZIKV is occurring in many countries around the world where potential mosquito vectors are endemic (Musso and Gubler, 2016). The ZIKV emergent scenario caught the attention of the main health authorities mainly because congenital microcephaly and other neurological disorders in newborns were correlated with ZIKV infection in pregnant women, as described above. The WHO declared a state of public health emergency of international concern during almost the entire year of 2016 and launched a document named "Zika Strategic Response Plan" to guide the viral prevention and management by the national governments and communities where activities related to detection, prevention, research, care and support were recommended. This strategical document is constantly updated to provide the key information and progress achieved against ZIKV infections (WHO, 2016).

Entomological studies have demonstrated that Brazilian and other American populations of *Ae. aegypti* and *Ae. albopictus* mosquitoes are competent to ZIKV, but they present different levels of susceptibility (Chouin-Carneiro et al., 2016). Moreover, well-known laboratory strains of *Ae. aegypti* also show vector competence to this pathogen, which can sustain vector-pathogen studies to clarify the interactions between this virus and its invertebrate host (Costa-da-Silva et al., 2017). Recently, a field study demonstrated the occurrence of naturally-infected *Ae. aegypti* in the city of Rio de Janeiro (Brazil), confirming the species potential to transmit ZIKV to humans (Ferreira-de-Brito et al., 2016). The entomological surveillance in endemic regions is an essential activity to monitor the circulation of ZIKV and the potential of new outbreaks to occur.

Ae. Aegypti other characteristics

Transmission to animals

In addition to being a vector for human pathogens, *Ae. aegypti* is capable of spreading disease among animal species that associate with humans, such as cattle and dogs. *Ae. aegypti* female mosquitoes are capable of the mechanical transmission of lumpy skin disease virus (LSDV) from infected to susceptible cattle (Chihota et al., 2001). Canine heartworm is transmitted by *Ae. aegypti* to dogs, which are companion animals frequently associated with the home environment.

Vertical transmission

The virus is transmitted to humans through the bite of the mosquito *Ae. aegypti* as principal vector and *Ae. albopictus* as a secondary vector. The mechanism of transmission of the virus that occurs most commonly involves the human-to-mosquito-to-human cycle.

However, it has been observed that vertical transmission of the virus can occur whereby infected females naturally transmit the virus to their progeny (transovarial transmission), the virus being in this case transmitted to the next generation without an intervening human host. Vertical transmission allows the virus to persist in nature during adverse weather conditions that limit mosquito reproduction, resulting in the appearance of virus-infected mosquitos once desiccated eggs hatch following a subsequent rainfall. Thus, vertical transmissions in vectors could play a role in the endemic maintenance of the viruses. Vertical transmission of dengue viruses in *Ae. aegypti* is documented by several studies (see below) and appears to vary with the vector geographical strains and virus serotypes (Rodhain and Rosen, 1997).

The first findings suggesting that transovarial transmission of DENV can occur in nature was reported by Khin and Than (1983). In this study, DENV-2 serotype was recovered from three of 123 pools of *Ae. aegypti* larvae (6 200 specimen) collected from water containers in Rangoon, Myanmar; the virus was also isolated from two of the 76 pools (7 730 mosquitoes) of male *Ae. aegypti* collected as larvae and reared in the laboratory to adults. In Trinidad and Tobago, the isolation of DENV-4 from adult *Ae. aegypti* reared from eggs and larvae collected in nature was documented by Hull et al. (1984): the virus was recovered in one out of the 158 mosquito pools tested from 10 different localities (10 957 adults processed for virus isolation), giving further evidence that transovarial transmission of DENV occurs in nature. In southern India, DENV-2 and DENV-3 were detected in vertical transmission to males in summer months when dengue infections were high in humans, suggesting how DENV adopted a novel strategy of surviving adverse climatic conditions (Thenmozhi et al., 2000). In Juchitán and Tuxtepec, Oaxaca, Mexico, vertical transmission of DENV in *Ae. aegypti* mosquitoes was recorded in two endemic localities. Although the presence of DENV in larvae could not be demonstrated, DENV- 2, - 3 and -4 serotypes were detected in four out of 43 pools of in-cage born mosquitoes (Günther et al., 2007). In Acapulco, Guerrero, only two (0.9%) of 226 pools of *Ae. aegypti* adults (one pool of adults emerged from field-collected larvae, and another of indoor-collected adults) were positive for DENV-1. This appears to be the first report of evidence on the vertical and transovarial transmission of DENV-1 in field-caught *Ae. aegypti* in Mexico (Martínez et al., 2014).

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