VIROLOGY - CHAPTER TWENTY ONE

ARBOVIRUSES

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INTRODUCTION

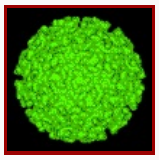
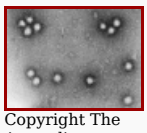
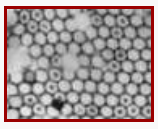
Zoonotic viruses are viruses which are transmissible from animals (arthropods, vertebrates) to man. Many are transmitted by means of an infected, blood-sucking, arthropod vector (**ar**thropod **bo**rne = arboviruses). Others may be transmitted by inhalation, or conjunctival contact with infected excretions, or by direct contact with infected animal (e.g. rabies).

Constant vigilance and surveillance are important components in reducing the public health impact of these viruses

TEACHING OBJECTIVES

Introduction to viral zoonoses
Brief overview of general features of togaviruses, bunyaviruses, reoviruses, arenaviruses and flaviviruses
Discussion of ecology, epidemiology and public health
Arbovirus encephalitis, febrile and hemorrhagic disease
Rodent borne hemorrhagic fever, hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome.
Flavivirus-associated hemorrhagic fevers

ARBOVIRUSES

FAMILY	ENVELOPE	SYMMETRY	GENOME	IMAGE	SIZE*
Togaviridae Flaviviridae	yes	icosahedral	single strand RNA (+ve)	 Computer generated model of the surface of an alphavirus derived by cryoelectron microscopy. CDC	
Bunyaviridae	yes	helical	single strand RNA (-ve) segmented	 Copyright The Australian National University	
Reoviridae	no	icosahedral	double strand RNA segmented	 Transmission electron micrograph of reovirus type 3. Both inner and outer capsid shells are present. Some virions are penetrated by negative stain. CDC/Dr. Erskine	

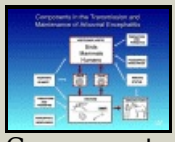
* Relative size adapted from *White and Fenner , Medical Virology, 1994*

The term arboviruses is used to describe viruses from various families which are transmitted via arthropods. Diseases caused by arboviruses include encephalitis, febrile diseases (sometimes with an associated rash), and hemorrhagic fevers.

ARTHROPOD VECTORS

The virus replicates in the vector but usually does not harm it. In the mosquito-borne diseases, the virus establishes a persistent infection in the salivary glands and there is sufficient virus in the saliva to infect another host during feeding. Each virus usually only grows in a limited number of mosquito species.

The natural habitat of the vector (rural or around dwellings), its diurnal activity patterns and its preferred targets for a blood meal, affect the transmission pattern of the disease. Many vectors are only active during part of the year and so this will affect the seasonal incidence of the disease. Insect vectors may over-winter as eggs; in this case the virus must either be transmitted transovarially (which happens in some cases), or survive the winter in the vertebrate host and infect the vector the following year.



Components in the transmission and maintenance of Arboviral Encephalitis
CDC

VERTEBRATE HOSTS

The virus is usually maintained in a vertebrate host. There is often a persistent viremia and the host can act as a long term reservoir. In many cases the reservoir host is not severely affected by the viral infection. If the vertebrate reservoir is migratory, this will affect the timing of infections in a particular locale.

DEAD END HOSTS

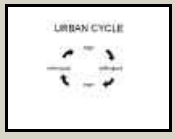
In many cases, if the virus is transmitted to an animal other than its normal host, viremia is low or transient and there is little chance of the infected animal being able to pass enough virus to a blood sucking arthropod to establish an infection. In this case, the animal is said to be a dead-end host. Man is a dead-end host in the case of most arbovirus diseases (exceptions include yellow fever and dengue fever).

PREVENTION

Methods include surveillance, vector control, public education about reducing breeding sites for vectors and reducing exposure to vectors (by wearing suitable clothing, using insect repellents, timing activities for low risk time of day, etc.), and use of vaccines in few cases where available.

LIFE CYCLES OF ARBOVIRUSES

Sylvatic life cycle



Urban life cycle

There are several types of life cycles, but many arboviruses have a sylvatic cycle while some also have an urban cycle.

1. Sylvatic cycle (sometimes known as the jungle cycle). In this the virus cycles between an arthropod and a mammalian host with man usually a dead-end host infected by the arthropod

2. Urban cycle. In this the virus cycles between man and an arthropod species.

There is an urban cycle for yellow fever and dengue fever (both of these also have a sylvatic/jungle cycle). If there is an urban cycle, using window screens, bed nets, etc. to prevent access of mosquitos to viremic patients may reduce transmission.

ARBOVIRUS DISEASE

Diseases caused by arboviruses include:

- encephalitis
- febrile diseases (sometimes associated with rash)
- hemorrhagic fevers

There is some overlap of symptoms between various virus types; for example viruses not usually classed as encephalitis viruses may cause CNS symptoms, etc.

More than 100 arboviruses are known to infect man but only a few will be mentioned here.

Disease outbreaks caused by arboviruses are sporadic and unpredictable. Usually, infection is followed by replication in endothelial cells and macrophage/monocyte lineage cells. Frequently, these infections are associated with flu-like symptoms since these RNA viruses are good inducers on interferon. Often the infection stops here but it may produce enough virus for secondary viremia which can then cause a major infection of target organs (brain, endothelial cells, liver). Which organs are targeted depends on the tropism of the virus. Access to the brain tends to be via infection of the endothelial cells in the blood vessels supplying the brain.

RECOVERY

Recovery involves the cell-mediated immune system. The arboviruses are generally good inducers of interferon, which may partially explain early influenza-like symptoms common to so many of these viruses (fever, headache, fatigue, myalgia). Antibody can be important in controlling the secondary viremia and limiting disease.

DIAGNOSIS

Diagnosis is difficult because many other agents cause similar symptoms. Arbovirus infection is usually confirmed by immunological methods (complement fixation, ELISA, immune fluorescence assay, etc) or by PCR of the viral nucleic acid. The tests are usually done in a State Laboratory or at the Centers for Disease Control. Awareness of an arbovirus associated disease in a particular area enables risk reduction procedures to be put in place (vector-control, insect repellents, protective clothing, change in human activity patterns).

RESISTANCE

Resistance to arboviruses is mediated by antibodies and recovery involves the cell-mediated immune system.

ARBOVIRUS ENCEPHALITIS DISEASES

ARBOVIRUSES - ENCEPHALITIS - Viruses currently important in the USA				
NAME	**DISEASE**	**OCCURRENCE**	**VECTOR**	**RESERVOIR**
Flaviviridae Family				
St Louis Encephalitis Virus	encephalitis	North America	Mosquito 	Birds
West Nile Virus	encephalitis	East and Central North America, parts of Europe and Africa	Mosquito	Birds
Bunyaviridae Family				
La Cross Virus (California serogroup)	encephalitis	North America	Mosquito	Small mammals
Togaviridae Family				
Eastern Equine Encephalitis Virus	encephalitis	Eastern U.S., Canada	Mosquito	Birds
Western Equine Encephalitis Virus	encephalitis	Western U.S., Canada, Mexico, Brazil	Mosquito	Birds
Venezuelan Equine Encephalitis	encephalitis	Central and South America, Texas, Florida	Mosquito	Small mammals Horses

All of the arboviruses in the above table are transmitted by mosquitoes; however, some arbovirus encephalitides are transmitted by ticks or other insect vectors such as sandflies.

For all of the viruses listed below, most infections are sub-clinical, but if clinical cases do occur, the consequences may be very serious. Initial symptoms are flu-like including fever, but can progress to encephalitis. The following are the most frequently reported in humans in United States

La Crosse Encephalitis / California serogroup
La Crosse Virus - Bunyavirus family

The reservoir for La Crosse virus is small mammals (chipmunks and squirrels) and the virus is transmitted by mosquitoes (*Aedes triseriatus*, Easter Treehole mosquito). Humans are "dead end" hosts as they do not develop a sufficiently high viremia to reinfect a mosquito.

The incubation period is one to two weeks after a bite by an infected mosquito.

Symptoms include:

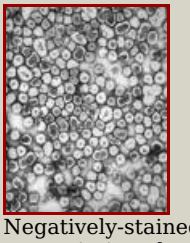
- fever
- headache
- nausea
- lethargy

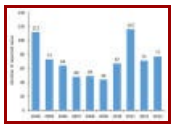
Children more often develop symptoms than adults and are more prone to neuroinvasive disease (resulting in seizures) but morbidity and fatality are low (case fatality rate is less than 1%). Severe neuroinvasive disease may result in repeated seizures, partial paralysis and neurobehavioral changes.

Recent cases have been predominantly in the Eastern United States where there are about 80 La Crosse virus neuroinvasive cases per year.

There is no vaccine and treatment is supporive including seizure control.

Bunyaviridae


Negatively-stained transmission electron micrograph showing the presence of La Crosse encephalitis virus ribonucleoprotein particles. CDC/ Dr. J. Obijeski


A

B
California Serogroup Virus Neuroinvasive Disease* Cases Reported by Year, A: 1964-2010 B: 2004-2013
CDC


California Serogroup Virus. Neuroinvasive Disease Cases Reported by State, 2004-2013 CDC

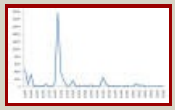
St. Louis Encephalitis
St. Louis Encephalitis virus - Flavivirus family


St Louis encephalitis virus transmission cycle CDC

The elderly are most severely affected by a St. Louis Encephalitis Virus (SLEV) infection since they often have weaker immune systems. The case fatality rate varies from 3-25%. The reservoir is birds and the virus is transmitted by mosquitoes with humans as a "dead end host". This virus can have an urban cycle as well as well as a sylvatic cycle. Infections occur in the northern parts of the United States in the late summer and early fall but in the south, infections occur all year. The geographic range of this virus is most of North and South America but most cases of human disease have occurred in the United States. The most extensive epidemic of SLEV infections occurred in 1975 in the Ohio-Mississippi river basin.


Negatively-stained transmission electron micrograph (TEM) showing the presence of numerous St. Louis encephalitis virions that were contained within a mosquito salivary gland tissue sample. CDC/ Dr. Fred Murphy; Sylvia Whitfield


St. Louis Encephalitis Virus Neuroinvasive Disease Cases* Reported by State, 2004-2013 CDC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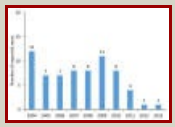
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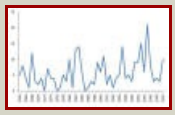
St. Louis Encephalitis Virus Neuroinvasive Disease Cases* Reported by Year, A: 1964-2010. Note peak in 1975 B: 2004-2013. CDC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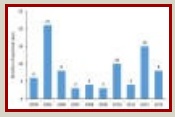

B

Eastern Equine Encephalitis Virus Neuroinvasive Disease Cases Reported by Year. A: 1964-2010 B: 2004-2013 CDC


Eastern Equine Encephalitis Virus Neuroinvasive Disease Cases Reported by State, 2004--2013
CDC

WEB RESOURCES
St Louis Encephalitis
CDC Information - St Louis Encephalitis

Western Equine Encephalitis

In many cases of SLEV infection, mild infections occur without apparent symptoms other than fever and headache. In more severe cases, there are:

- high fever
- neck stiffness
- stupor
- disorientation
- coma
- tremors
- occasional convulsions (which occur mainly in infants)
- spastic (but rarely flaccid) paralysis

The symptoms are therefore similar to West Nile encephalitis which is also caused by a flavivirus (see below). The number of cases seen in the United States varies widely with more than 100 annually but only 1 to 12 cases of St Louis Encephalitis Virus neuroinvasive disease reported between 2004 and 2013.

There is no vaccine for this virus for use in humans but infection seems to cause life-long immunity.

Flaviviridae


St. Louis Encephalitis Virus Neuroinvasive Disease* Average Annual Incidence by County, 1996-2010

* Neuroinvasive disease includes cases reported as encephalitis, meningoencephalitis, or meningitis. CDC


The geographic distribution of the Japanese encephalitis serocomplex of the family Flaviridae, 2016 CDC

Eastern Equine Encephalitis

Eastern Equine Encephalitis Virus - Alphavirus genus of Togavirus family

The reservoir of Eastern Equine Encephalitis virus (EEEV) is birds and it is transmitted by mosquitoes. *Culiseta melanura* mosquitoes transit the virus between birds and a variety of mosquito species transmit the virus from birds to humans and other mammals. Humans and horses are "dead end hosts". Many cases result in mild flu-like symptoms or no symptoms at all but children are more likely to have severe clinical symptoms that adults. The incubation period is about 4 to 10 days. People under 15 or older than 50 are more likely to have severe clinical symptoms. Disease that does not involve the brain is systemic and results in:

- chills, fever, muscle and joint pain and a general feeling of malaise

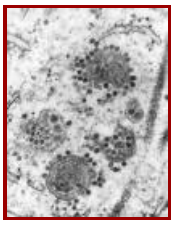
The symptoms resolve in a few weeks

The encephalitic form, involving the central nervous system, is somewhat different according to age. In infants, the disease is manifested abruptly while older children exhibit symptoms of systemic disease first. Symptoms of encephalitic disease include:

- Headache
- Fever
- sleepiness
- Irritability
- anorexia

- nausea
- diarrhea
- cyanosis
- convulsions
- coma

If there is clinical disease, death may occur relatively frequently (Case fatality rate is about 35%). Sequelae (mild to severe neurologic deficits) are common in survivors. The disease is quite rare and there have been about 250 confirmed human cases of Eastern Equine encephalitis in the United States since 1964. Mostly EEEV disease is seen in the Atlantic and Gulf Coast states.


Transmission electron micrograph showing the presence of a number of Eastern Equine Encephalitis (EEE) virus virions that happened to be in a specimen of central nervous system tissue. CDC/ Dr. Fred Murphy; Sylvia Whitfield

Western Equine Encephalitis

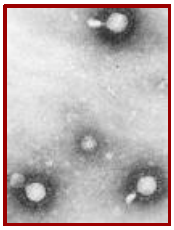
Western Equine Encephalitis Virus - Alphavirus genus of Togavirus family

Again the reservoir is birds and the virus is transmitted by mosquitoes. Humans and horses are a dead end hosts. As with eastern equine encephalitis, children are more likely to have severe clinical symptoms that adults. The case fatality rate is 3-7%. In the young, death or sequelae (mild to severe neurological impairment) are more common. There have been 639 confirmed cases in the U.S. since 1964; however the number has dropped off in recent years.

Venezuelan Equine Encephalitis

Venezuelan Equine Encephalitis - Alphavirus genus of Togavirus family

This virus is predominantly a problem in central and South America, but it periodically occurs in the southern United States (Texas, Florida). Its reservoir is small mammals and horses.


Negative stain electron micrograph showing the presence of a number of Venezuelan equine encephalitis virus virions. CDC/ Dr. Fred Murphy; Sylvia Whitfield

Alphaviridae

West Nile Encephalitis

West Nile Encephalitis Virus - Flavivirus family

West Nile virus is closely related to St. Louis encephalitis virus and until 1999 was found in Africa, west Asia/eastern Europe and the Middle East. In 1999 it was detected in North America, initially on the east coast, and has subsequently spread across both the United States and Canada.

Most (75%) of people who become infected show no symptoms and mount a successful immune attack against the virus. Most of the remainder (1 in 5 infected persons) have flu-like symptoms (fever, headache and general malaise) with an incubation period of 3 to 14 days. Sometimes there is swelling of the lymph glands (lymphadenopathy) and there may also be a rash. In less than 1% of patients, the infection is life-threatening as a result of encephalitis or meningitis. The initial symptoms are:

- high fever
- headache
- stiff neck

These are followed by:

- confusion
- tremors
- convulsions
- paralysis
- coma
- and, in some cases, death

Recovery can take weeks or months. Persons over 50 years of age are most severely affected by West Nile encephalitis and the case fatality rate is approximately 10%.

People with certain diseases of immunocompromization and those with cancer, diabetes, kidney disease and hypertension are more at risk for overt disease.

Some people who become infected with West Nile Virus can develop acute flaccid paralysis. This is a sudden onset of weakness in the limbs and/or breathing muscles. In most persons, this syndrome is due to the development of West Nile poliomyelitisan inflammation of the spinal cord that causes a syndrome similar to that caused by the poliovirus. West Nile poliomyelitis was first widely recognized in the United States in 2002. Persons with West Nile poliomyelitis may develop sudden or rapidly progressing weakness. The weakness tends to affect one side of the body more than the other, and may involve only one limb. The weakness is generally not associated with any numbness or loss of sensation, but may be associated with severe pain. In very severe cases, the nerves going to the muscles that control breathing may be affected, resulting in rapid onset of respiratory failure. It is important to recognize that this weakness may occur in the absence of meningitis, encephalitis, or even fever or headachethere may be few other clues that the weakness is due to West Nile Virus infection.

The natural reservoir of the virus is birds and the virus is transmitted by mosquitoes (most likely by *Culex pipiens*, in the North of the US and *Culex quinquefasciatus*, in the South; however, West Nile virus had been detected in many North American mosquito species). The first human cases in the United States were in 1999 in New York but in 2002, there were 4156 reported cases of West Nile virus human infection including 284 deaths, with the virus reaching 44 states. In 2003, it spread into all parts of the United States except Oregon, Washington and Idaho and in 2004 it was found in all states except Washington. The peak incidence of human West Nile virus disease is in late summer (late August and early September). The spread of the virus is likely to be due to migration patterns of birds. In 2003, the number of human cases of the disease was much higher in western states than in the eastern states in which the disease was found predominantly in earlier years; for example, Colorado reported over 1500 cases while South Carolina has reported only one. This is probably because the bird population in eastern states has developed immunity against the virus.

It is also probable that West Nile virus has been transmitted to humans in blood transfusions, organ transplants and during pregnancy, delivery and breast feeding (vertical transmission) but these cases are extremely rare.

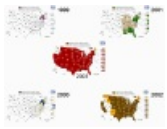
Treatment for West Nile virus infection is supportive although it has been suggested that ribavirin may be active against the virus. In an outbreak in Israel, however, patients treated with ribavirin had a higher mortality than those not treated, although this could have been due to other factors. There is no vaccine.

The best control for West Nile is reducing the incidence of mosquitoes by spraying (methoprene) or bacterial larvicides such as *Bacillus thuringiensis var. israelensis* and *Bacillus sphaericus*. Reduction of mosquito breeding sites such as pools of stagnant water is useful, as is the use of DEET-containing insect repellents.

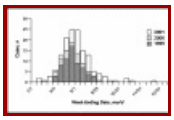
Spread of West Nile Virus 2003-2005 in humans	Spread of West Nile Virus 2003-2005 in birds	Spread of West Nile Virus 2003-2005 in mosquitoes

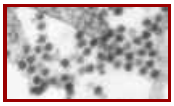
Flaviviridae

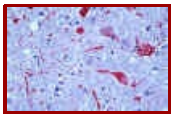
 A  B  C  D  E
States reporting confirmed West Nile virus infection in birds, mosquitoes, animals, or humans. A: 1999-2001 B: 2002 C: 2004 D: 2011 E: 2014 CDC

 Spread of West Nile Virus in the United States CDC

 A  B
West Nile virus neuroinvasive disease incidence, by state, United States, A: 2011 B: 2014

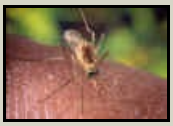
 Week of symptom onset for persons reported to have West Nile virus infection, 19992001. Annals of Internal Medicine

 West Nile virus is a flavivirus commonly found in Africa, West Asia, the Middle East. and, more recently, in North America. It is closely related to St. Louis encephalitis virus found in the United States. CDC/Cynthia Goldsmith

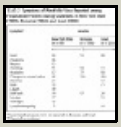

Brain tissue from a West Nile encephalitis patient, showing antigen-positive neurons and neuronal processes (in red) CDC/W.-J. Shieh and S. Zaki

 US national case definition

 West Nile virus transmission cycle CDC

 *Culex quinquefasciatus* Mosquito on a Human Finger CDC

 Genus Culex. Note the distinguishing features of the Culex mosquitoes: cross veins on narrow wings, blunt abdomen, short palpus, and no prespiracular or postspiracular setae CDC

 Symptoms of West Nile infection. Annals of Internal Medicine

 Japanese encephalitis Risk Areas CDC

Japanese Encephalitis

Japanese Encephalitis Virus - Flavivirus Family

Japanese encephalitis is a mosquito-borne (*Culex tritaeniorhynchus* and other *Culex* species) disease spread by Japanese Encephalitis (JE) Virus. It is not found in North America but travelers to rural areas of south and east Asia may become infected. In temperate areas, the level of infected mosquitoes and JE virus disease is highest in the summer months but in tropical areas, highest incidence is associated with the rainy season.

JE virus infects pigs and birds while humans are "dead-end hosts".

Most people who are infected by JE virus show no symptoms but in 1% of infected people severe symptoms may arise after an incubation time of five days to two weeks.

The initial symptoms are:

- fever
- headache
- nausea

These are followed by neurological symptoms:

- weakness

- movement disorders
- seizures, usually in children

When the infection causes encephalitis, the mortality rate is 20 - 30% and 30% of survivors will continue to have neurological and psychiatric problems.

Treatment is supportive but there is a good vaccine which should be considered by people visiting areas where JE virus is endemic. It is licensed in the United States and may be given to people over the age of 2 months.

ARBOVIRUSES FEVER AND HEMORRHAGIC FEVER			
NAME	**DISEASE**	**OCCURRENCE**	**VECTOR**
Flaviviridae Family			
Dengue Fever	fever, hemorrhagic fever	Worldwide - tropic regions	Mosquito
Yellow Fever	hemorrhagic fever	South and Central America and Africa	Mosquito
Zika	fever, also causes microcephaly in fetus	Africa, Asia, South and Central America. Spreading into North America	Mosquito
Reoviridae Family			
Colorado tick fever	fever	North America	Tick
Alphaviridae Family			
Chikungunya fever	fever encephalitis (rare)	Worldwide in tropical areas	Mosquito
Bunyaviridae			
Heartland Virus	fever with Thrombocytopenia	Missouri and Tennessee	Tick

ARBOVIRUS DISEASES ASSOCIATED WITH FEVER

Colorado Tick Fever
Colorado Tick Fever Virus - Reovirus family

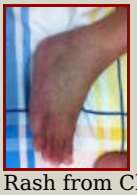
This occurs in the Rocky Mountain States (at elevations above 4000 feet). It is a mild disease resulting in:

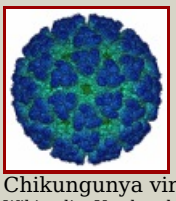
- fever (some patients exhibit a biphasic fever in which they have a fever for a few days, recover and then have another bout of fever
- headache
- myalgia
- rash (often seen)
- sore throat (sometimes)
- nausea

after an incubation period of 1 day to two weeks. Fatigue may last for a few weeks after the other symptoms resolve.

In very rare cases, there may be central nervous system involvement resulting in confusion; however, the disease is rarely life-threatening.

The virus is transmitted by ticks and is mostly seen in the summer when contact


Rash from Chikungunya infection
Wikipedia. Used under Creative Commons


Chikungunya virus
Wikipedia. Used under Creative Commons


Local transmission of Chikungunya in the Americas
CDC


States in the US in which Chikungunya has been identified. Local transmission from mosquitoes to humans has only be observed in Florida
CDC


Countries and territories where chikungunya cases have been reported* (as of October 20, 2015)
*Does not include countries or territories where only imported cases have been documented.
CDC

with ticks is most common. In diagnosis, the physician must consider the much more serious Rocky Mountain spotted fever (rickettsial disease) which may have similar initial symptoms and should be treated promptly. See also Ticks

There is no specific treatment other than supportive care.

Chikungunya Fever

Chikungunya Virus - Alphavirus family

Chikungunya virus is a single, positive strand RNA virus in the Alphavirus family of the Togaviridae. It has spread rapidly around the world. Chikungunya means *that which bends up* in the East African Makonde language, describing the contorted posture assumed by people affected as a result of the severe joint pain and arthritic symptoms associated with this disease. The disease was first described in 1955, as a result of an outbreak in 1952 on the Makonde Plateau, near the border between Mozambique and Tanzania.

Chikungunya virus fever is usually found in warmer regions of Africa and Asia with some incidence in Europe and other areas imported from endemic areas. In 2013, transmission from mosquitoes to humans (local transmission) was seen in the Caribbean. In 2014, Chikungunya cases were reported in the United States in people returning from the Caribbean and by 2015, local transmission from mosquitoes to humans had been observed in central America, northern South America and the United States. Most people in the Americans are not immune to the virus since it has only arrived recently. Thus, infections are expected to increase and to spread geographically.

Transmission

The vectors for Chikungunya virus are two mosquito species: *Aedes aegypti* and *Aedes albopictus*. The virus can also be spread by infected blood and rarely *in utero*. The newborn can also be infected from the mother at the time of delivery.

Symptoms

About 3 to 7 days after infection, most patients experience:

- fever (over 39C (102F))
- polyarthralgia (joint pain)
- sometimes joint swelling.

Other symptoms include:

- headache
- myalgia
- conjunctivitis
- arthritis
- nausea
- maculopapular rash

In the laboratory, lymphopenia, thrombocytopenia, high creatinine and high hepatic transaminases may be observed.

Most symptoms, which are usually mild, resolve within a week although polyarthralgia may persist. Some patients, however, experience more severe disease including infants infected at birth, older people and patients with chronic conditions. Rare complications include relapse of rheumatological symptoms and joint pain may last for years. Chikungunya infection is rarely fatal but has occurred in older patients.

Treatment

There is no vaccine and no specific treatment other than supportive care.

Chikungunya can cause a fatal encephalitis

There was an outbreak of Chikungunya on the island of Reunion in 2005. In all, over 300,000 people were infected. Although, symptoms are usually mild, there were rare cases in which the central nervous system was involved and some were fatal, particularly in newborns and patients over 65. The overall case rate of encephalitis (24 in all) was 8.6 per 100,000 infected people. In newborns, the rate was 187 per 100,000 and in people over 65, it was 37 per 100,000 The death rate for patients who contracted Chikungunya-associated encephalitis was 16%. Many surviving patients also had long term neurological problems.

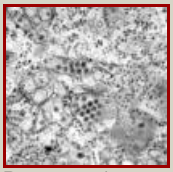
ARBOVIRUSES ASSOCIATED WITH HEMORRHAGIC DISEASE

Dengue Fever

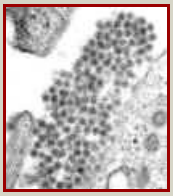
Dengue virus - Flavivirus family

Laboratory-confirmed cases of Dengue Hemorrhagic Fever in the Americas before 1981 and 1`981-2003
CDC

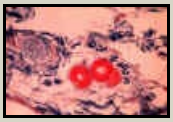
Dengue Fever risk areas around the world
CDC



Dengue virus particles. Transmission electron micrograph. CDC



Mature Dengue-2 virus particles replicating in five day old tissue culture cells. The original magnification is 123,000 times. CDC



High-power view of heavy fibrin depositis in small arteries, almost occluding the lumen. From a section of pancreas of a patient who died from dengue hemorrhagic fever. (Image courtesy of the Wellcome Trust/WHO)

Symptoms

Acute onset symptoms, which last about a week, include

- high grade fever
- headache
- rash
- retro-orbital pain
- myalgia
- arthralgia
- macropapular rash (sometimes)
- change in taste sensation (sometimes)
- mild bleeding from nose and gums and easy bruising
- bone pain (hence the name: "breakbone fever")

In these ways, Dengue may be clinically indistinguishable from influenza, measles or rubella

The infection can sometimes progress to encephalitis/encephalopathy.

The symptoms of Dengue are usually milder in children compared to adults. During the convalescence period there may be prolonged weakness and anorexia.

Treatment

There is no vaccine and treatment is supportive. The mortality rate is around 1%.

Dengue Hemorrhagic Fever

Dengue Hemorrhagic Fever is potentially a deadly complication of dengue and is most severe in children under 15 years of age. Globally, there are several hundred thousand cases per year.

It appears to be an immunopathological consequence of infection of a person who has already developed immunity to one serotype of Dengue virus with a virus of another serotype, although the mechanism is not fully understood. It may well involve an immune enhancement whereby there is increased uptake of virus coated with non-neutralizing antibody (developed during an earlier infection with a different serotype) into macrophages via the Fc receptor. Virus replicates in macrophages resulting in an increased virus load. In addition, macrophages become activated and release inflammatory cytokines. The immune enhancement by non-neutralizing antibody complicates prospects for vaccine development but one is in development. The disease is more severe in children; moreover, the presence of maternal antibody in infants may result in Dengue Hemorrhagic Fever even in a first infection with Dengue virus.

In Dengue Hemorrhagic Fever, increased vascular permeability is a major problem.

Symptoms

During the initial stages of Dengue Hemorrhagic Fever, the symptoms of those of classical Dengue. However, after a week or so, as the fever subsides, the patients shows:

- restlessness
- lethargy
- persistent nausea
- signs of circulatory failure
- severe abdominal pain
- breathing difficulty
- skin hemorrhages: petechiae and purpura or ecchymoses

In most patients this is followed by:

- thrombocytopenia
- hemoconcentration resulting from leakage of plasma from the circulatory system into the peritoneum and pleural cavity

The patients who develop these symptoms are in profound circulatory shock, in this case known as Dengue Shock Syndrome, which can rapidly lead to death.

Signs of Dengue Shock Syndrome are:

- cold clammy skin
- rapid weak pulse
- narrowing of pulse pressure
- hypoptension

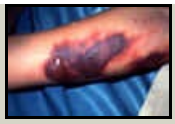
Treatment

If the patients with hemorrhagic fever is given suitable supportive treatment (especially fluid replacement and rest), the mortality rate is low (2 to 5%) but if left untreated, mortality can be very high (as high as 50%). The key to survival of the patient is early diagnosis. CDC recommends that patients thought to have dengue should be given acetaminophen preparations rather than aspirin, because the anticoagulant effects of the latter may aggravate the bleeding tendency associated with dengue infection.

WEB RESOURCES

Dengue Fever

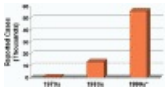
CDC Information - Dengue Fever


A large subcutaneous hemorrhage on the upper arm of a patient with dengue hemorrhagic fever. (Image courtesy of the Wellcome Trust/WHO)


Aedes albopictus mosquito feeding. This mosquito is a secondary vector for dengue in South-east Asia. It recently extended its range into Africa, the New World and Australia, increasing the risk of the spread of arbovirus infections. (Image courtesy of the Wellcome Trust)


World distribution of dengue fever CDC

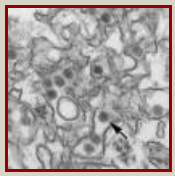

Distribution of *Aedes aegypti* (red shaded areas) in the Americas in 1970, at the end of the mosquito eradication program, and i*n 1997.* CDC


Reported cases of Dengue hemorrhagic fever - 1970's to 1990's


Areas with Risk of Yellow Fever Virus Transmission in Africa. CDC


Areas with Risk of Yellow Fever Virus Transmission in South America CDC


Yellow fever virus (magnification: 234,000x) CDC


Transmission electron micrograph of Zika virus, which is a member of the family *Flaviviridae*. Virus particles are 40 nm in diameter, with an outer envelope, and an inner dense core. The arrow identifies a single virus particle. CDC

Yellow Fever (Hemorrhagic Fever)

Yellow Fever Virus - Flavivirus family

This is a disease that is only found in Africa and South America. In South America, the disease is sporadic and occurs in forested areas. In Africa, yellow fever occurs mostly in the rainy season in the west and central areas of the continent. This disease is transmitted by mosquitoes. Natural hosts of the virus include monkeys and man. It has an urban and a sylvatic cycle.

Symptoms

Most people infected with yellow fever virus have no illness or only mild illness but some people develop symptoms, after an incubation period that is typically 36 days. Mild illness includes:

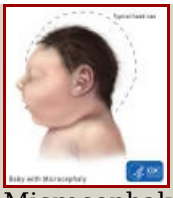
- fever
- chills
- severe headache
- back pain
- malaise (fatigue)
- nausea
- vomiting

Most patients improve after the initial presentation. However, after a brief remission (hours to a day), about 15% of patients develop more severe symptoms. This severe systemic disease is characterized by hemorrhages, degeneration of the liver, kidney and heart and failure of multiple organs. The case-fatality rate can be 50%.

Treatment

There is no specific treatment but there is an effective vaccine (attenuated strain called 17D). There are sometimes mild effects (head ache, malaise) of the vaccine within days of administration in a few recipients (less than 5%) but there have been reports of severe illness (fever, hepatitis and multiple organ failure) in seven patients in the past six years.

Yellow Fever Vaccine


Microcephaly
CDC


Location of known Zika virus infections: Early 2016
CDC

OTHER ARBOVIRUSES

Heartland Virus - Bunyavirus family
Severe Fever with Thrombocytopenia Syndrome Virus

Heartland virus which is a phlebovirus, a member of the *Bunyavididae*, was discovered in 2009 when two farmers from northwestern Missouri became ill with fever, fatigue, diarrhea, and low levels of blood platelets and white blood cells. Both men had been bitten by ticks and were hospitalized. One had malaise after two years while the other initially had fatigue and memory problems. It is not known if the ticks and the presence of the virus were related as ticks harboring Heartland virus have not been detected.

As of March 2014, eight cases of Heartland virus disease have been identified among residents of Missouri and Tennessee. It is unknown at this time if the virus may be found in other areas of the United States.

Zika Virus - Flavivirus Family

Zika virus, named after the place in Uganda (Zika Forest) where it was initially identified in 1947, is a small icosahedral positive strand RNA virus in the *Flaviviridae* family that has caused recent widespread alarm. There have been small outbreaks of Zika virus infections for decades in Africa and Asia. The virus spread to Micronesia in the western pacific in 2007 and then to French Polynesia in 2013. In late 2014, an outbreak of Zika virus infections occurred first in Easter Island and then on the South American mainland, particularly Brazil. The occurrence of Zika virus in Brazil was correlated with a large increase in infant microcephaly in which an infant is born with an abnormally small head and an incompletely developed brain. It is thought that infection of the pregnant mother with the virus is the cause of the abnormal fetal development. In addition, Zika virus infection may result in some cases of Guillain-Barré syndrome in adults.

Symptoms

Most people do not show any symptoms of a Zika virus infection but about 20% will experience some mild symptoms which may last up to a week. These include:

- Exanthum (rash)
- Fever
- Arthralgia
- Myalgia
- Conjunctivitis
- Headache

Diagnosis

There are specialized tests available to distinguish Zika from other viral infections that cause similar symptoms (including Dengue and Chikungunya, see above). These tests include reverse transcriptase-PCR which detects viral RNA in the blood. There are also antibody tests to detect anti-viral IgM. Neutralizing antibodies usually arise about a week after infection. People who experience symptoms and have traveled to an area in which Zika outbreaks have occurred (particular South and Central America) should consult a health care provider. The virus usually persists in the blood for a week or more and can be spread by mosquitoes to another person.

Transmission

Zika virus, like Dengue and Chikungunya, is mostly transmitted by mosquito bites usually by Aedes species mosquito (*Aedes aegypti* and *Aedes albopictus*). Therefore, it is likely to spread to all areas of North America where these mosquitoes are found.

There are other, rarer routes of transmission:

- In 2011 in Senegal and 2013 in Tahiti, there were cases of male to

female sexual transmission of Zika virus. There have also been several reports of sexual transmission in the United States in 2016. In the case of sexual transmission in Tahiti, semen and urine of the infected male contained the virus but it was not detected in his blood. Zika virus has also been found in saliva although whether it can be spread by kissing is debatable.

- The virus can be spread by blood transmission from an infected person.

- Mother to child transmission has occurred. This is rare and probably occurs at the time of delivery. There is no evidence at present for transmission via breast milk.

WHO estimates that up to 4 million people may become infected by the virus

Treatment

Treatment of the mild symptoms is supportive including drinking fluids to prevent dehydration and using an analgesic such as acetaminophen. Non-steroidal anti-inflammatory drugs and aspirin should not be taken. The best way of avoiding a Zika infection is to avoid mosquito bites. This can be done by using body-covering clothing, wearing permethrin-treated clothes, sleeping under mosquito nets or using insect repellents (such as DEET). Probably the most effective short term response to the wave of Zika virus infections will be mosquito control. There is no anti-Zika vaccine, although it is hoped that there might be one in a few years. Another possible avenue of treatment of pregnant mothers is monoclonal anti-Zika antibodies which will take a much shorter time to develop than a vaccine.

Viral range

Zika outbreaks have been reported from some African countries, Southeast Asia and some Pacific Islands. In 2015, Zika infections were reported from Brazil, possibly arriving with infected persons attending the World Cup. The virus has spread to other South American countries, Central America, Mexico and the Caribbean (including Puerto Rico and the US Virgin Islands). It has also been reported from Cape Verde, an island of the northwest African coast.

Cases have been found in the United States in people returning from South America. It is likely that the virus will spread to all areas of the United States where the mosquito vectors are present.

Microcephaly

Although most people experience no or mild symptoms of a Zika infection, there is considerable concern about the effect of the infection during pregnancy. There have been many reports of an increase in microcephaly in South American countries and these have coincided with the Zika virus epidemic. Originally, only a small number of microcephaly cases showed identifiable Zika virus infection; however, more recent studies using RT-PCR showed that in most, if not all, cases of microcephaly, all of the infants were infected by the virus. Nevertheless, several other viruses (including Cytomegalovirus and Chikungunya) can result in aberrant brain and cranial development.

Microcephaly (small head) is a rare condition. In Brazil, prior to 2015, only a few hundred cases of microcephaly were reported each year but since the Zika virus outbreak began there have been thousands of cases. Some, indeed perhaps the majority, of these cases may be false positives since there are other reasons that children are born with small heads, including as noted above, other viral infections. However, it is clear that infants infected *in utero* by Zika do develop microcephaly. Unfortunately, it now appears that complications in the infant can occur if the pregnant mother is infected at any time in the pregnancy. Some fetuses have died when mothers were infected late in pregnancy (25 - 32 weeks) and exhibited brain calcifications.

Microcephalic infants, besides having a small head and underdeveloped brain can exhibit seizures, loss of vision and blindness, loss of hearing,

WEB RESOURCES

Yellow Fever
CDC Information

Chikungunya
CDC Information

Zika
CDC Information

poor balance, learning disabilities and developmental delays. Microcephaly can be diagnosed *in utero* using ultrasound. It cannot be cured and there is no standard protocol for treatment. Some babies with a mild form of microcephaly have no problems; however, for many there will be lifelong disabilities, including blindness.

How infection by Zika virus leads to brain malformation in the fetus is not known but the virus seems to destroy cortico neural progenitor cells that will form the brain cortex.

In the United States, the incidence of microcephaly is 2 12 per 10,000 live births (CDC figures)

Miscarriage

Zika also appears to result in miscarriages. Because of this, CDC has advised pregnant women not to travel to countries where Zika infection is a risk and El Salvador has suggested that because of the outbreak, potential mothers should delay their pregnancies (which may be difficult as birth control is not widely available).

Guillain-Barré syndrome

Guillain-Barré syndrome is a rare autoimmune disease in which nerve cells become damaged, leading sometimes to paralysis and death. In the United States, there are between 3,000 and 6,000 cases per year. Most patients, however, completely recover. It is not known what causes Guillain-Barré syndrome but it often follows a viral or bacterial infection. It is not established that an infection by Zika virus can cause Guillain-Barré syndrome since it is always difficult to find any cause in a particular patient. Rather there are correlations and in Brazil there has been an increase in Guillain-Barré syndrome at the same time as the rise in Zika virus infections.

Guillain-Barrč Syndrome

Flaviviridae

 Return to the Virology section of Microbiology and Immunology On-line

This page last changed on Sunday, March 06, 2016
Page maintained by Richard Hunt