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Japanese Encephalitis
Japanese B Encephalitis, Arbovirus B




Japanese encephalitis is a mosquito-borne viral infection of horses, pigs and humans. It is also referred to as Japanese B encephalitis, arbovirus B, and mosquito-borne encephalitis virus.

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Overview

- Economic impact
- Epidemiology
- Transmission
- Clinical Signs
- Diagnosis and Treatment
- Disease in Humans
- Prevention and Control
- Actions to Take



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In today's presentation we will cover information regarding the organism that causes Japanese encephalitis and the epidemiology of the disease. We will also talk about the economic impact the disease has had in the past and could have in the future. Additionally, we will talk about how it is transmitted, the species it affects, the clinical signs and necropsy findings, as well as the diagnosis and treatment of the disease. Finally, we will address prevention and control measures for the disease as well as actions to take if AHS is suspected. Photo of *Culex* mosquito laying eggs, from CDC website at www.cdc.gov/ncidod/dvbid/jencephalitis.

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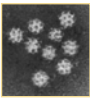
The Organism



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Japanese Encephalitis

- Flaviviridae
 - Flavivirus
- Enveloped
- Single stranded RNA virus
- Morphology not well defined
- The name is Latin for flavus
 - Flavus means "yellow"
 - Refers to yellow fever virus



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JE is in the family Flaviviridae and the genus *Flavivirus* (related to St. Louis encephalitis virus, Murray valley virus and West Nile virus). It is an enveloped single stranded RNA virus. Currently, the morphology of the virus is not well defined. Two subtypes of the virus exist, Nakayama and JaGar 01. The name of the family (flavus) is Latin meaning yellow, which refers to yellow fever which is also a member of this family. Photo: Flaviviridae.

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Importance



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History

- 1870's: Japan
 - "Summer encephalitis" epidemics
- 1924: Great epidemic in Japan
 - 6,125 human cases; 3,797 deaths
- 1935: First isolated
 - From a fatal human encephalitis case
- 1938: Isolated from *Culex tritaeniorhynchus*

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The first historic mention of Japanese encephalitis occurred during the "summer encephalitis" outbreaks in the late 1870's. The next documented epidemic in Japan occurred in 1924 with 6,125 human cases resulting in 3,797 human deaths (62% case-fatality rate). The virus was first isolated in Japan in 1935 from a fatal human case of encephalitis. In 1938, the virus was first isolated from its primary vector species, *Culex tritaeniorhynchus*.

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History

- 1940-1978
 - Disease spread with epidemics in China, Korea and India
- 1983: Immunization in South Korea
 - Started as early as age 3
 - Endemic areas started earlier
- 1983-1987: Vaccine available in U.S. on investigational basis

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In 1940, JE was first identified in China and in 1949 it was identified in Korea during a major epidemic that resulted in 5,548 human cases. In 1954 the virus was recognized in India and a major epidemic occurred in 1978 with over 6,000 human cases occurring. In 1983, in South Korea, JE immunizations started in children as young as age 3 except in endemic areas where the vaccine was recommended in children even younger. From 1983 to 1987 the JE vaccine was available in the U.S. on an investigational basis.

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Economic Impact

- Animals
 - Porcine
 - High mortality in piglets
 - Equine
 - Up to 5% mortality rate
- Humans
 - Medical cost for immunization and medical treatment

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The mortality rate in piglets can be quite high from JE. This reduction in number of offspring can have an great economic impact for the swine market. Additionally, equine deaths due to an outbreak of JE can result in a 2-5% mortality rate. These losses can impact the income potentially provided by these animals. Although JE is not currently found in the U.S., the transmitting vectors are, as is the potential for the disease. Since humans are also quite susceptible to JE, the need for immunization of the population and treatment of affected persons can lead to an great economic demand to the public and the medical community. Additionally, vector control measures will be needed to aid and protect the population.

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Epidemiology



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Geographic Distribution

- Endemic in temperate and tropical regions of Asia
- Reduced prevalence in Japan
- Has not occurred in U.S.



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JE virus infection occurs throughout the temperate and tropical regions of Asia. Although initially prevalent in Japan in the late 1800's, control methods (vaccination and pesticides) have reduced the incidence of the disease in this country. Currently, the disease occurs in China, India, Nepal, the Philippines, Sri Lanka and Northern Thailand. Occasionally sporadic cases of disease occur in Indonesia and northern Australia. The disease has not occurred in the rest of the world. Photo shows distribution of Japanese encephalitis from 1970-1998, from CDC website at www.cdc.gov/ncidod/dvbid/jencephalitis.

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Morbidity/Mortality

- Swine
 - High mortality in piglets
 - Death rare in adult pigs
- Equine
 - Morbidity: 2%, during an outbreak
 - Mortality: 5%
- Humans
 - Mortality: 5-35%
 - Serious neurologic sequela: 33-50%

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JE in pigs causes high mortality for newborn piglets. However there is close to zero mortality for adult pigs. Death from JE in equines is rare; when outbreaks occur, mortality rates of 5% or less have been reported. JE can be quite severe for humans. One in 250 infections results in symptomatic disease and mortality rates can vary from 5-35% depending on intensive care facilities of the region. Approximately 33-50% of the patients with symptomatic disease, who survive, have major neurologic sequelae within 1 year. This can include seizures, paresis or movement disorders. Children (ages 2-10 years) and the elderly are at the highest risk.

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Transmission



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Transmission

- Vector-borne disease
- Enzootic cycle
 - Mosquitoes: *Culex* species
 - *Culex tritaeniorhynchus*
 - Reservoir: Ardeid (wading) birds
 - Amplifying hosts
 - Pigs, bats
 - Possibly reptiles and amphibians
 - Incidental hosts
 - Horses, humans, others

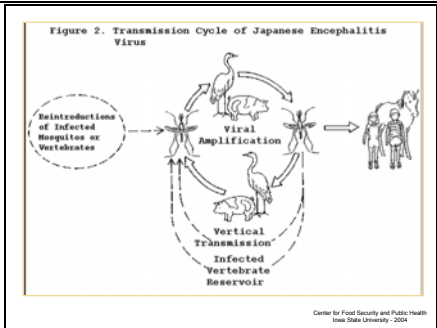



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JE is a zoonotic disease that affects humans and several species of animals. It is transmitted by mosquitoes. The most important vectors are *Culex* species (top picture), with *Culex tritaeniorhynchus* being the primary vector. The enzootic cycle involves mosquitoes and an amplifying host (also known as reservoir hosts). Known amplifying hosts include domestic pigs and wading bird species i.e., egrets, herons (bottom picture). Studies have demonstrated that bats are susceptible to infection with JE and that their levels of viremia are also sufficient to infect mosquitoes, thereby serving as a reservoir as well. There have also been limited studies done on snakes and frogs. Their importance at this point is unclear but more research may provide interest. Several additional species can become infected with JE but are incidental hosts since they do not achieve high enough viremias to cycle the virus in nature. Incidental host species include horses, donkeys, cattle, water buffalo, sheep, dogs, chickens and ducks. Humans are also incidental hosts.

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Enzootic cycle for Japanese encephalitis. From Tsai, TF. Japanese Encephalitis Vaccines. Accessed at www.cdc.gov.

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Animals and Japanese Encephalitis




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Clinical Signs: Equine

- Late summer to early fall
- Incubation period: 8 to 10 days
- Usually subclinical
- Fever, impaired locomotion, stupor, teeth grinding
- Blindness, coma and death rare



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JE in animals is most commonly seen in late summer to early fall. The incubation period in horses with JE disease is 8 to 10 days. Most infections are subclinical. Affected horses will show fever, impaired locomotion, stupor and teeth grinding. Blindness, coma and death are possible but mortality is typically low.

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Clinical Signs: Swine

- Incubation period not known
- Exposure early in pregnancy more harmful
- Birth of stillborn or mummified fetuses
- Piglets: Neurological signs, death
- Boars: Infertility, swollen testicles



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The incubation period in swine has not been clearly established, but it is known that the earlier the exposure occurs in pregnancy, the more harmful the sequela to the fetuses. Swine that are infected with JE commonly show few clinical signs except those associated with pregnancy. Pigs infected with JE will give birth to litters of stillborn or mummified fetuses, at term. If infected piglets are born alive, they will have tremors, convulsions and die soon after birth. Adult pigs are typically asymptomatic. Experimentally, boars infected with JE have shown swollen testicles and decreased fertility. Photo from Photo: Affected litter at farrowing showing mummified fetuses and stillborn piglets with deformities from Australian Veterinary Journal 2001;79:192-8.

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Post Mortem Lesions

- Horses
 - Non-specific
 - Nonsuppurative meningoencephalitis
- Swine
 - Fetuses
 - Mummified and dark in appearance
 - Hydrocephalus
 - Cerebellar hypoplasia
 - Spinal hypomyelination

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Post mortem lesions in horses are typically non-specific and similar to those seen with EEE and WEE. Histologically, nonsuppurative meningoencephalitis may be seen, but is not diagnostic. In pigs, fetuses are mummified and dark in appearance. Defects such as hydrocephalus, cerebellar hypoplasia and spinal hypomyelination may be seen.

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Differential Diagnosis

- Equine
 - WEE, EEE, other viral encephalitides, Hendra, rabies, neurotoxins, toxic encephalitis
- Swine
 - Myxovirus-parainfluenza 1, coronavirus, Menangle virus, porcine parvovirus, PRRS

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Differentials for equines include Western equine and Eastern equine encephalitis, as well as other viral encephalitides, Hendra virus, rabies, neurotoxins, and toxic encephalitis. In swine, differentials to consider include Myxovirus-parainfluenza 1, coronavirus, Menangle virus, porcine parvovirus, and possibly porcine reproductive and respiratory syndrome.

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Sampling

- Before collecting or sending any samples, the proper authorities should be contacted
- Samples should only be sent under secure conditions and to authorized laboratories to prevent the spread of the disease

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Before collecting or sending any samples from animals with a suspected foreign animal disease, the proper authorities should be contacted. Samples should only be sent under secure conditions and to authorized laboratories to prevent the spread of the disease.

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Diagnosis

- Clinical
 - Horses: Fever and CNS disease signs
 - Swine: High number of stillborn piglets
- Laboratory Tests
 - Definitive: Viral isolation
 - Blood, spinal cord, brain, CSF
 - Rise in titer
 - Neutralization, HI, IF, CF, ELISA
 - Cross reactivity of Flaviviruses

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Clinical diagnosis of JE should be suspected in horses demonstrating fever and signs of central nervous system disease. In swine a tentative diagnosis of JE is based on the birth of litters with a high percentage of stillborn and weak piglets. Definitive diagnosis of JE in animals is by virus isolation. Samples of blood, cerebral spinal fluid (in horses), spinal cord and portion the brain can be used for this process. The brain should be submitted as one half fixed in 10% buffered formalin and one half unfixed. JE diagnosis can be tentatively diagnosed by the demonstration of a rise in titer (paired samples 14 days apart) by neutralization, hemagglutination inhibition (HI), immunofluorescence (IF), complement fixation (CF) and ELISA tests. These tests are not definitive for JE due to cross reactivity of Flaviviruses.

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Treatment

- No effective treatment
- Supportive care

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There is no effective treatment for JE. Supportive care is recommended.

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JE in Humans



Every year approximately 35,000-50,000 symptomatic cases occur worldwide. From 1978-1993, 12 cases occurred in the United States. Fewer than 1 case/year occurs in U.S. Most U.S. cases are among military personnel, expatriates and rarely, in returning travelers. The incubation period of JE in humans is 6 to 8 days and disease varies from a febrile headache to an acute and possibly fatal encephalitis. The majority of cases are asymptomatic or have mild clinical signs, such as fever and headache. Children and the elderly are at the greatest risk for severe disease and elderly persons acquiring the infection have the highest case-fatality rate (30%). Only one in 250 infections of JE results in symptomatic disease, but mortality rates can vary from 5-35% depending on intensive care facilities of the area.

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Clinical Signs

- 35,000-50,000 cases annually
- Less than 1 case/year in U.S.
 - Military, travelers
- Incubation period: 6 to 8 days
- Most asymptomatic or mild signs
- Children and Elderly
 - At highest risk for severe disease
 - Elderly: High case fatality rate (30%)

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Clinical Signs: Severe

- Acute encephalitis
 - Headache, high fever, stiff neck, stupor
- Severe encephalitis
 - Paralysis, seizures, convulsions, coma and death
- Neuropsychiatric sequelae
 - 30-50% of survivors
- In utero infection possible
 - Abortion of fetus

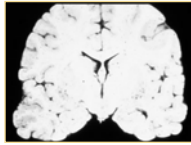
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Serious clinical signs for JE include those of an acute encephalitis, headache, high fever, stiff neck and stupor, this can progress to severe clinical signs such as, paralysis, seizures, convulsions, coma and death. Approximately 33-50% of the patients with symptomatic disease, who survive, have major neurologic sequelae at 1 year. This can include seizures, paresis or movement disorders. In utero infection can also occur in humans, which can result in the abortion of the fetus.

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Post Mortem Lesions

- Pan-encephalitis
- Infected neurons scattered throughout CNS
- Occasional microscopic necrotic foci
- Thalamus generally severely affected



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Post mortem lesion in humans are a pan-encephalitis. Infected neurons are scattered throughout the CNS. Occasional microscopic necrotic foci are present with the thalamus being affected severely. The photo shows a section of brain taken from a patient with Japanese encephalitis. This gross pathology can be found in all of the arbovirus encephalitides. The perivascular congestion and hemorrhage, may be diffuse or focal, and is seen predominantly in cortical gray and deep gray matter. Photo from Gary Baumbach, MD., Department of Pathology, University of Iowa, College of Medicine, <http://www.vh.org/adult/provider/pathology/CNSInfDisR2/Text/203.html>.

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Diagnosis and Treatment

- Clinical
- Laboratory Tests
 - Tentative diagnosis
 - Antibody titer: HI, IFA, CF, ELISA
 - JE-specific IgM in serum or CSF
 - Definitive diagnosis
 - Virus isolation: CSF sample, brain
- No specific treatment
 - Supportive care

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Human cases of JE may be suspected in persons visiting endemic areas and demonstrating neurological sign accompanied by a fever. A tentative diagnosis of JE can be based on a four-fold rise in antibody titer using several methods, such as hemagglutination inhibition (HI), immunofluorescent antibody titer (IFA), complement fixation (CF) or IgG ELISA. Caution should be used when interpreting these results since cross-reactivity can occur with other flaviviruses. Additionally, the antibody response may have already peaked by the time the patient presented for care and there for fail to demonstrate a rise in titer. Additionally, demonstration of JE specific IgM in serum or CSF may be useful in acute phases of the disease. Definitive diagnosis of JE is done by viral isolation. Samples of CSF can be used. Brain tissue can be used for virus isolation in post-mortem situations. There is no specific treatment for JE and supportive care is recommended.

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Public Health Significance

- Vectors in U.S.
- Disease has spread in last 100 years
- Reservoirs: swine and birds
- Human mortality
- Animals deaths
 - Lost income


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JE has significant public health impact. Swine and birds can serve as reservoirs, as well as, amplifiers of the virus. This contributes to the spread of the disease, as has been occurring over the last 100 years. Although JE is not currently found in the U.S., the transmitting vectors are. Additionally, importation of infected, amplifying swine is always possible. Rapid identification and diagnosis will be important for protecting the public and our livestock from this disease.

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Prevention and Control



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Recommended Actions

- Notification of Authorities
 - Federal:
 - Area Veterinarian in Charge (AVIC)
 - www.aphis.usda.gov/vs/area_offices.htm
 - State veterinarian
 - www.aphis.usda.gov/vs/sregs/official.htm
- Quarantine

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If JE infection is suspected, state or federal authorities should be notified immediately. Animals suspected with JE or any arboviral encephalitides should be isolated and the farm should be quarantined until definitive diagnosis is determined.

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Disinfection

- Biosafety Level 3 precautions
- Chemical
 - Ethanol, glutaraldehyde, formaldehyde
 - Sodium hypochlorite (bleach)
 - Iodine, phenols, iodophors
- Physical
 - Deactivation at 133°F (for 30 minutes)
 - Sensitive to ultraviolet light and gamma irradiation

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Biosafety level 3 precautions and practices are recommended for investigators working with this virus. Areas and equipment that have been potentially contaminated with JE infected tissues or blood can be disinfected with chemical agents such as 70% ethanol, 2% glutaraldehyde, or 3-8% formaldehyde. Additionally, 1% sodium hypochlorite (bleach), iodine, phenol iodophores and organic solvents or detergents may be used. Physical deactivation occurs in 30 minutes at 133°F (56°C). The virus is also sensitive to ultraviolet (UV) and gamma radiation, however the virus can survive for long periods in mosquito eggs (the virus can be maintained over winter in eggs).

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Prevention

- Vector control
 - Eliminate mosquito breeding areas
 - Adult and larval control
- Vaccination
 - Equine and swine
 - Humans
- Personal protective measures
 - Avoid prime mosquito hours
 - Use of repellants containing DEET

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Prevention measures are very important for minimizing JE infection. Vector control should include measures such as eliminating potential mosquito breeding areas. This should include the removal of sources of standing or pooled water around homes and barns. Additionally, adult and larvicidal programs should be implemented to reduce mosquito numbers. This may have limited overall effect due to the high cost of retreating areas and resistance of the mosquitoes over time. Equine and swine in affected areas should be vaccinated. For humans in endemic areas, vaccination should be implemented, as well as personal protective measures. This can be done by avoiding the outdoors during prime mosquito hours, having windows and screens on homes and by using insect repellants containing DEET according to recommendations on labels.

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Vaccination

- Live attenuated vaccine
 - Used in equine and swine
 - Successful for reducing incidence
- Inactivated vaccine (JE-VAX)
 - Used for humans
 - Japan, Korea, Taiwan, India, Thailand
 - Used for endemic or epidemic areas
 - Recommended for travelers
 - Visiting endemic areas for > 30 days


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A vaccine for JE is available for horses and swine. The live attenuated vaccine is used in most JE endemic regions. It has been successful in reducing the incidence of the disease in endemic regions. Formalin inactivated vaccine (JE-VAX) is licensed in Canada and recommended for those of increased risk such as laboratory workers and travelers spending more than one month in endemic/epidemic areas during the transmission season; 3 doses of the vaccine scheduled on days 0, 7 and 30 are required for a good protection; vaccine is contraindicated for women who are pregnant and those who are immunocompromised. Two live vaccines are licensed for use in China.

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Additional Resources



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Internet Resources

- World Organization for Animal Health (OIE) website
– www.oie.int
- USAHA Foreign Animal Diseases – “The Gray Book”
– www.vet.uga.edu/vpp/gray_book
- Centers for Disease Control and Prevention (CDC)
– www.cdc.gov/ncidod/dvbid/jencephalitis/facts.htm


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