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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 Japanese encephalitis is suspected.

(Photo of *Culex* mosquito laying eggs, from CDC website at www.cdc.gov/ncidod/dvbid/jencphalitis)

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The Organism

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Japanese Encephalitis

- Genus *Flavivirus*
- Name derived from the Latin *flavus* meaning "yellow"
- Single stranded, enveloped RNA virus
- Morphology not well defined

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Japanese Encephalitis (JE) virus belongs to the genus *Flavivirus* in the family Flaviviridae (related to St. Louis encephalitis virus, Murray valley virus, and West Nile virus). The name of the family is derived from the Latin 'flavus' meaning yellow, which refers to the yellow fever virus, also a member of this family. JE virus 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.

(Photo: Flaviviridae)

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Importance

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History

- 1870s: Japan
  - "Summer encephalitis" epidemics
- 1924: Great epidemic in Japan
  - 6,125 human cases; 3,797 deaths
- 1935: Virus first isolated
  - Fatal human encephalitis case
- 1938: Virus isolated from mosquito *Culex tritaeniorhynchus*

The first historic mention of Japanese encephalitis occurred during the "summer encephalitis" outbreaks in the late 1870s. 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 to 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 to 1987: Vaccine available in U.S. on investigational basis

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. 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

- Porcine
  - High mortality in piglets
- Equine
  - Up to 5% mortality rate
- Humans
  - Cost for immunization and medical treatment
  - Vector control measures

The mortality rate in piglets can be quite high from JE. This reduction in number of offspring can have a great economic impact for the swine market. Additionally, equine deaths due to an outbreak of JE can result in a 2 to 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. Since humans are also quite susceptible to JE, the need for immunization of the population and treatment of affected persons can lead to a 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
- Disease control by vaccination
- Disease has not occurred in U.S.

JE virus infection occurs throughout the temperate and tropical regions of Asia. Countries which have had major epidemics in the past, but which have controlled the disease primarily by vaccination, include China, Korea, Japan, Taiwan and Thailand. Other countries that still have periodic epidemics include Viet Nam, Cambodia, Myanmar, India, Nepal, and Malaysia.

(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
  - Mortality high in piglets; rare in adults
- Equine
  - Mortality rare (<5%)
- Humans
  - Mortality: 5 to 40%
  - Serious neurologic sequelae: 45 to 70%

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 in humans. One in 250 infections results in symptomatic disease, and mortality rates can vary from 5 to 35% depending on intensive care facilities of the region. The infection is usually most severe in infants and the elderly where mortality ranges from 5 to 40%. Parkinsonism, convulsive disorders, paralysis, neuropsychiatric sequelae, or mental retardation are seen after 45 to 70% of severe cases.

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Transmission

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Transmission

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

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 host). 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 been limited studies done on snakes and frogs; their importance at this point is unclear. Several additional species can become infected with JE but are

incidental hosts since they do not achieve viremia sufficient enough 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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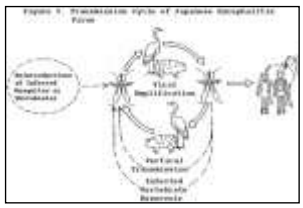

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This figure demonstrates the enzootic cycle for Japanese encephalitis.

(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

- Incubation period: 8 to 10 days
- Usually subclinical
- Fever, impaired locomotion, stupor, teeth grinding
- Blindness, coma, 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 unclear
- 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 sequelae 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 at term to litters of stillborn or mummified fetuses. If infected piglets are born alive, they will have tremors and convulsions and die soon after birth. Adult pigs are typically asymptomatic. Experimentally, boars infected with JE have shown swollen testicles and decreased fertility.

(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
  - Hydrocephalus, cerebellar hypoplasia
  - Spinal hypomyelinogenesis

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Post mortem lesions in horses are typically non-specific and similar to those seen with Eastern or Western equine encephalomyelitis (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 hypomyelinogenesis may also occur.

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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 and Eastern equine encephalomyelitis 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
  - 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 portions of 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 other flaviviruses.

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Treatment

- No effective treatment
- Supportive care


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

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Japanese Encephalitis in Humans

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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
  - Highest risk for severe disease

Every year approximately 35,000 to 50,000 symptomatic cases occur worldwide. From 1978 to 1993, 12 cases occurred in the United States. Fewer than 1 case/year occurs in the U.S. Most U.S. cases are among military personnel, expatriates, and, rarely, 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 to 35% depending on intensive care facilities of the area.

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Clinical Signs: Severe

- Acute encephalitis
  - Headache, high fever, stiff neck, stupor
  - May progress to paralysis, seizures, convulsions, coma, and death
- Neuropsychiatric sequelae
  - 45 to 70% of survivors
- *In utero* infection possible
  - Abortion of fetus

Serious clinical signs for JE include 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 45 to 70% of the patients with symptomatic disease who survive have major neurologic sequelae. This can include seizures, paresis, movement disorders, or mental retardation. *In utero* infection can also occur in humans, which can result in abortion of the fetus.

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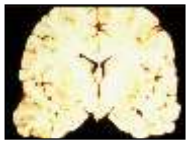
Post Mortem Lesions

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



Post mortem lesions in humans consist primarily of 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 with 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

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

Human cases of JE may be suspected in persons visiting endemic areas and demonstrating neurological signs accompanied by 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), immunofluoresent 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 presents for care, and therefore fails to demonstrate a rise in titer. 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; 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
- Animal deaths
  - Lost income

JE has a 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. 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

- IMMEDIATELY notify authorities
- Federal
  - Area Veterinarian in Charge (AVIC)
    http://www.aphis.usda.gov/animal_health/area_offices/
- State
  - State veterinarian
    http://www.usaha.org/StateAnimalHealthOfficials.pdf
- 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 encephalitis 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 UV light, gamma radiation

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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 iodophors, 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 larvae control
- Vaccination
  - Equine, 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 elimination of potential mosquito breeding areas such as standing or pooled water around homes and barns. Additionally, adult and larvacidal 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
  - Equine and swine
  - Successful for reducing incidence
- Inactivated vaccine (JE-VAX)
  - Humans
  - Japan, Korea, Taiwan, India, Thailand
  - Used for endemic or epidemic areas
  - Travelers, military, laboratory workers

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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 is recommended for those at increased risk, such as laboratory workers and travelers spending more than one month in endemic/epidemic areas during the transmission season or those planning to visit rural areas or engage in outdoor activities. Three 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

- World Organization for Animal Health (OIE)
  - www.oie.int
- U.S. Department of Agriculture (USDA)
  - www.aphis.usda.gov
- Center for Food Security and Public Health
  - www.cfsph.iastate.edu
- USAHA Foreign Animal Diseases ("The Gray Book")
  - www.usaha.org/pubs/fad.pdf

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