

LOUPING-ILL

(Ovine Encephalomyelitis, Infectious Encephalomyelitis of Sheep, Trembling-ill)

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Definition [top](#)

Louping-ill (LI) is an acute viral disease primarily of sheep that is characterized by a biphasic fever, depression, ataxia, muscular incoordination, tremors, posterior paralysis, coma, and death. Louping-ill is a tick-transmitted disease whose occurrence is closely related to the distribution of the primary vector, the sheep tick *Ixodes ricinus*.

Etiology [top](#)

Louping-ill is caused by a neurotropic single-strand RNA virus of 40-50 nm that has been classified in the Flaviviridae family, *Flavivirus* genus (20). It belongs to a subgroup of antigenically related viruses known as the tick-borne encephalitis complex whose members also include tick-borne encephalitis virus of Europe, the Omsk haemorrhagic fever virus of Russia, the Kyasanur forest disease virus of

India, Langkat virus of Malaysia, Negishi virus of Japan, and Powassan virus of North America (2). This complex of viruses is found throughout the northern temperate latitudes. The LI virus has been shown to be most closely related antigenically to strains of the Western European subtype of tick-borne encephalitis virus (17). Although there is no evidence of any significant variation in pathogenicity between strains of LI virus from a variety of vertebrate species and from ticks (11), monoclonal antibody analysis has revealed antigenic heterogeneity among isolates of the virus (8).

In tissue suspensions, LI virus will remain viable for at least 82 days when stored in 50 percent glycerol or at temperatures of -20° C or lower. It is rapidly inactivated in saline or broth — especially in dilute or acid suspensions.

Host Range [top](#)

Louping-ill is of greatest veterinary medical significance as a disease of sheep. All ages of sheep can be affected with LI, depending on their immune status and the severity of virus challenge.

Infection with LI virus has been demonstrated in other domestic species and wildlife; namely, cattle, horses, pigs, dogs, deer, and humans as well as in a range of species of small mammals such as shrews, woodmice, voles, and hares. Because none of these species develop a high-titered viremia, they are regarded as unlikely to play a significant role in the maintenance of LI virus in nature (11). Most recently, the influence of low or nonviremic hosts such as hares, both in the multiplication of vectors and the amplification of virus through nonviremic transmission, is now considered significant for virus persistence (9). Humans, though susceptible to infection with LI virus, are considered an accidental or tangential host of the virus.

Investigation of European grouse species has revealed marked variation in susceptibility to experimental infection with LI virus. Whereas two woodland or forest species, pheasant and capercaillie, were found to be resistant to disease, both of the mountain or tundra species of birds studied, red grouse and ptarmigan, were highly susceptible and developed high viremias and succumbed rapidly to the infection. If available, both red grouse and ptarmigan may act as amplifying hosts of the virus in endemic areas.

Geographic Distribution [top](#)

Louping-ill is endemic in rough upland areas in Scotland, Northern England, Wales and Ireland. A disease of sheep very closely related to LI has been reported in

Bulgaria (10), Turkey (17), the Basque region in Spain (6) and Norway (4).

Transmission [top](#)

Although many ixodid ticks have been shown to be capable of transmitting LI virus, including *Rhipicephalus appendiculatus*, *Ixodes persulcatus*, and *Haemaphysalis anatolicum*, *I. ricinus* is considered the natural vector of this disease. *I. ricinus* is a three-host tick with a life cycle from egg to engorged adult of 3 years. Occurrence of LI in those countries in which it is endemic can be correlated closely with the distribution of the tick vector, which requires an environment with a high relative humidity. All stages of ticks, larva, nymph, and adult, acquire the virus by feeding on a viremic host. Because transovarial transmission of the virus has never been established, transmission appears to be entirely transstadial (11). None of the known vectors of LI virus currently occur in the United States.

A significant feature of the bionomics of *I. ricinus* that has a major impact on the epidemiology of LI is the annual periodicity of tick activity. Peak tick activity occurs in the spring (the "spring rise"), and a minor resurgence of activity is experienced in some areas in the fall. Although cases of LI can occur at any time of the year, the disease is most prevalent during the periods of maximal tick activity between April and June and again in September.

On the basis of the level and duration of viremia that develops in sheep following infection with LI virus, this species appears to be the essential maintenance host for the virus (11). Irrespective of clinical outcome, sheep consistently develop viremias of sufficient magnitude to transmit the virus to the tick vector.

Experimentally, LI virus has been shown to be shed in the milk of goats and ewes following infection with the virus. Although titers of virus in the milk of both species were similar, virus was shed for a longer period in goats (13). Transmission of virus, presumably through the ingestion of infective milk, was demonstrated in kids that suckled infected goats. Similar attempts to transmit the infection in sheep were unsuccessful.

Louping-ill virus has been transmitted experimentally to various animal species by several parenteral routes of inoculation and following exposure to infective aerosols. Accidental infection of humans has occurred following tickbite, penetration of the virus through skin wounds, or by aerosol exposure in the laboratory.

Incubation Period [top](#)

Under conditions of natural exposure to the virus, the incubation period of LI ranges from 6 to 18 days. This is shortened in sheep experimentally infected by certain unnatural routes of challenge such as intracerebral inoculation.

Clinical Signs [top](#)

Exposure to LI virus may result in subclinical or clinical infection, depending on a range of host-related and environmental factors. Initial clinical signs in naturally infected sheep are nonspecific and include fever, which may reach 42° C (107.6° F), depression, anorexia, and possibly constipation. The fever is biphasic, with the second rise occurring about the fifth day after the appearance of clinical signs, at which point the virus may invade the central nervous system. If it does not, the animal will recover rapidly and develop a durable protective immunity. Involvement of the central nervous system is associated initially with evidence of cerebellar dysfunction characterized by muscular tremors and incoordination, ataxia, hyperaesthesia, and development of the characteristic louping gait. At this stage of the disease, sheep are often hypersensitive to noise and touch and will go into convulsive spasms if disturbed. Progression of the disease leads to cerebrocortical involvement. Affected animals exhibit head-pressing, paraplegia, convulsions, opisthotonos and coma. In many cases, death supervenes after a clinical course ranging from 7 to 12 days. Animals that survive never regain full health and display residual central nervous system deficits of variable severity.

Intercurrent infection of sheep with *Cytoecetes phagocytophila* or *Toxoplasma gondii* can influence the clinical outcome of infection with LI virus. Concurrent infection with either of these agents can enhance the pathogenicity of the virus — apparently by exerting a profound immunosuppressive effect on the animal's defense system. Viremias are markedly greater and more prolonged in such animals compared with those in sheep exposed to LI virus alone (14, 15).

Although no differences in susceptibility to LI virus have been demonstrated between a variety of breeds of sheep, the clinical course of the disease may vary in very young lambs versus older sheep. Lambs born to nonimmune ewes that are exposed to the virus may develop a peracute terminal illness with death supervening within 48 hours after the onset of clinical signs.

Naturally occurring cases of LI in cattle, horses (18) and pigs (1) present clinical features broadly similar to those observed in sheep. Evidence of neuromuscular dysfunction is seen. Affected cattle frequently have a staggering gait, hyperexcitability, head-pressing, recumbency, and convulsions and then die. Young piglets infected with LI virus can have a range of nervous signs, including aimless movement, head-pressing, ataxia, muscular spasms, and convulsions.

Natural cases or outbreaks of LI in horses are very uncommon, and most cases of infection with the virus are apparently subclinical.

Gross Lesions [top](#)

With the exception of possible congestion of meningeal vessels, there is no pathognomonic gross lesion.

Morbidity and Mortality [top](#)

All ages of sheep can be affected with LI, depending on their immune status and the severity of virus challenge. Typically, however, lambs born of immune dams are passively protected in their first year of life but then become susceptible. Replacement breeding stock are vulnerable to infection at 1 year of age (hoggets), and it is in this age group that losses from the disease are most frequently observed. Mortality rates as high as 60 percent can occur, however, in lambs whose passively acquired immunity has declined and which are introduced onto heavily tick-infested pastures for the first time. The incidence of LI in mature sheep is usually low unless they have recently been moved from a non-LI endemic area into an area in which the disease is endemic. Whereas the prevalence of infection may be as high as 60 percent, the case fatality rate is low and uncommonly exceeds 15 percent. Intercurrent tick-borne fever or toxoplasma infection or a range of environmental stress factors can predispose to the development of encephalitis and a higher mortality.

Diagnosis [top](#)

Field Diagnosis [top](#)

A diagnosis of LI must remain tentative or provisional until corroborated by confirmatory laboratory evidence. The disease should be strongly suspected, however, in sheep having signs of central nervous system disturbance consistent with those seen in typical cases of LI virus infection and where there is a flock history of recent introduction onto tick-infested pastures in an endemic area. Diagnosis of LI in other domestic species similarly cannot be based on clinical grounds alone.

Specimens for the Laboratory [top](#)

Heparinized blood should be collected during the acute viremic phase of the disease and preferably during the first 3 to 4 days after the onset of fever, which

is best for virus isolation. In the majority of cases, virus isolation is attempted on the brain and spinal cord of animals that died. Although this is frequently successful in sheep, results in cattle have been variable. Unfixed portions of brain and spinal cord are best transported to the laboratory in 50 percent glycerol and normal saline or frozen on dry ice and dispatched in a closed, insulated container using an overnight delivery service. Paired serum samples, acute and convalescent, should be submitted for serologic examination. Half of the brain and portions of spinal cord should be submitted in 10 percent formalin.

Laboratory Diagnosis [top](#)

A definitive diagnosis of LI is based on isolation and identification of the virus, virus detection by a reverse transcriptase polymerase chain reaction assay (RT-PCR), and confirmatory serological evidence. Where LI is suspected, isolation of virus can be attempted from the blood during the acute viremic phase of the disease. Virus isolation from the blood is not feasible, however, after the onset of central nervous system signs, for at this point the viremia has ceased because of the appearance of neutralizing and hemagglutinating-inhibiting antibodies in the blood. In the majority of cases, virus isolation is attempted on the brain and spinal cord from animals that died. Although this is frequently successful in sheep, results in cattle have been variable.

Although not yet widely in use, an automated RT-PCR assay followed by nucleotide sequencing of the cDNA product has been used successfully in the rapid detection and identification of LI virus in field specimens (5).

Serological confirmation of a diagnosis of LI virus infection is based on the demonstration of seroconversion or a significant (fourfold or greater) rise in antibody titer to the virus between acute and convalescent sera. Hemagglutination-inhibition antibodies appear 5 to 10 days after infection and decline after 6 to 12 months; serum neutralizing antibodies persist for years. The complement fixation test is of very limited value in the diagnosis of this disease in sheep because these antibodies appear late in the course of infection and are transient. A standardized tick-borne encephalitis virus antigen is now commercially available for use in an enzyme-linked immunosorbent assay (ELISA) test for this disease, which obviates the need to prepare in-house antigen reagents. Demonstration of specific IgM antibody in serum is also confirmatory of infection.

An avidin-biotin-complex (ABC) immunoperoxidase technique has successfully been applied to the detection of LI virus in formalin-fixed brain material from experimental and natural cases of infection.

Differential Diagnosis [top](#)

Louping-ill in sheep may be confused clinically with a range of other infectious and noninfectious diseases, including scrapie, pregnancy toxemia, hypocalcemia, tetanus, listeriosis, tick pyemia, hypocuprosis ("swayback"), rabies, hydatid disease, and various plant poisons. Cases of the disease in cattle must be differentiated from malignant catarrhal fever, listeriosis, pseudorabies, bovine spongiform encephalopathy, rabies, hypomagnesemia, hypocalcemia, acute lead poisoning, and certain plant poisons. With the exception of the need to distinguish LI from other viral encephalomyelitides, a differential diagnosis for LI is not provided for the other domestic animals because of the infrequency of reported occurrences of the disease in those species. In humans, LI virus infection may be confused with a range of other agents that can cause septic or aseptic meningitis and meningoencephalitis.

Treatment [top](#)

There is no specific treatment for encephalitic cases of LI virus infection. Unlike sheep, cattle affected with LI may respond favorably to good nursing and symptomatic treatment.

Vaccination [top](#)

A formalin-inactivated commercial vaccine is available that has been used successfully for many years in endemic areas (16). Two doses of vaccine with an interval of 2 to 8 weeks between injections are recommended to achieve optimal protection to natural infection. Vaccination of pregnant ewes during the last trimester is advocated to ensure that lambs receive maximal levels of passively acquired antibodies and are protected during the initial critical months of life. Vaccination of lambs after weaning when maternal immunity has waned may be advisable in areas where there is a secondary "fall rise" in tick activity (19). The same LI vaccine has been used in cattle with reasonable success based on annual revaccination against the disease.

Control and Eradication [top](#)

Preventive Measures

It is very doubtful whether measures aimed at reducing the tick population on infected pastures are a practical approach to controlling LI in areas endemic for the disease. Certainly, such measures are out of the question where rough upland or mountainous terrain is involved. Frequent acaricidal dipping or spraying of

sheep, and where appropriate, cattle, during the period(s) of maximal tick activity is a valuable means of controlling the level of tick infestation and transmission of the virus.

The single most important means of controlling LI in areas endemic for the disease is vaccination. This should be applied initially to all stock and subsequently to all replacement animals introduced from an area in which the disease is nonendemic. Vaccination should take place at least 1 month before exposure to infection. Because LI virus is likely to be maintained in a tick/sheep cycle, systematic vaccination of a flock over a period of years may result eventually in elimination of the virus. This should not, however, prompt discontinuation of vaccination because the potential for further outbreaks of LI remains as long as the tick vector is present.

Public Health [top](#)

Louping-ill virus is transmissible to humans. Humans can develop any one of four clinical syndromes: either an influenza-type illness, a biphasic encephalitis, a poliomyelitis-like illness or a hemorrhagic fever following infection with LI virus (3). Transmission can take place by tick bite, exposure to aerosolized infective material, or through skin abrasions or wounds. Nonlaboratory-acquired infections most frequently result from handling infected carcasses in abattoirs. The potential for oral transmission of LI virus to humans also exists where milk for human consumption is obtained from goats or sheep that are in the acute phase of the infection (12).

GUIDE TO THE LITERATURE [top](#)

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