

Louping Ill

*Ovine Encephalomyelitis,
Infectious Encephalomyelitis
of Sheep, Trembling-Ill*

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- OIE Collaborating Centres:
- Diagnosis of Animal Disease and Vaccine Evaluation in the Americas
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Importance

Louping ill is a zoonotic, tick-borne viral disease that is mainly significant in sheep and red grouse. Severe clinical signs can be seen in naive sheep flocks moved into endemic areas: many animals may develop neurological signs and up to 60% of the flock can die. In resident flocks, most losses occur in unvaccinated younger animals that are no longer protected by maternal antibodies. Louping ill can also cause high mortality in wild red grouse, especially chicks, which affects the grouse hunting industry. Clinical cases and fatalities are reported sporadically in other animals including livestock, captive wildlife and dogs. The commercial sheep vaccine for louping ill was recently withdrawn, which may make control more difficult until a new vaccine becomes available.

Etiology

Louping ill results from infection by louping ill virus, a member of the genus *Flavivirus* in the family *Flaviviridae*. This virus is closely related to tickborne encephalitis virus (TBEV) and is a member of the same viral complex. This close relationship may complicate diagnosis or surveillance by serology.

Several related viruses (Turkish sheep encephalitis virus, Greek goat encephalitis virus, Spanish sheep encephalitis virus and Spanish goat encephalitis virus) have been described in small ruminants outside the areas where louping ill is traditionally found. Although they were proposed as distinct species, some (or all) of these viruses are now considered to be variants of louping ill virus, as they have similar hosts, pathologies and vectors. Negishi virus, which was isolated in Japan in the 1940s, is very similar to a louping ill virus found recently in part of Russia.

Species Affected

Sheep are the major reservoir hosts for louping ill virus and the most commonly affected mammals. Clinical cases have also been documented sporadically in goats, cattle, horses, llamas, alpacas, pigs, dogs, farmed red deer (*Cervus elaphus*) and roe deer (*Capreolus capreolus*), and other mammals. Wild moose (*Alces alces*), red deer and roe deer were seropositive in Norway. Louping ill virus can also infect small mammals including shrews, wood mice, voles, rats, hares and rabbits. However, no mammals other than sheep seem to be involved in virus maintenance or amplification, except to serve as blood meals for ticks or as hosts during co-feeding transmission of the virus between ticks. Mountain hares (*Lepus timidus*) can help maintain the virus via the latter role.

The only birds known to become ill are naturally infected red grouse (*Lagopus lagopus scoticus*) and experimentally infected ptarmigan (*Lagopus mutus*) and willow grouse (*Lagopus lagopus*). Grouse can act as amplifying hosts.

Louping ill-related viruses (Turkish sheep encephalitis virus, Greek goat encephalitis virus, Spanish sheep encephalitis virus and Spanish goat encephalitis virus) have been reported in sheep, goats, or sometimes both species.

Zoonotic potential

Louping ill virus is zoonotic, but most clinical cases have been seen in laboratory workers or others who work with large amounts of virus.

Geographic Distribution

Louping ill occurs mainly in the U.K., where it is predominantly found in rough grasslands, especially in upland areas of Scotland, Ireland, northern England, and Wales. It has also been reported in Norway and one region in far eastern Russia, and on the island of Bornholm in Denmark. The virus in Russia is very similar to a louping ill virus (Negishi virus) that was isolated in Japan in the 1940s, but there are no recent reports of louping ill in Japan.

Louping ill and/or related viruses have been documented in the Basque region of Spain (Spanish sheep encephalitis virus), northwestern Spain (Spanish goat encephalitis virus), and Greece and Turkey (Greek goat encephalitis virus, Turkish sheep encephalitis virus, which are very similar). Louping ill virus or a similar virus was reported in Bulgaria in the 1960s.

Transmission

Infections in animals are mainly spread by ticks. The principal vector is the three-host tick *Ixodes ricinus*. Transstadial transmission and overwintering of the virus have been documented in this species, but transovarial transmission does not seem to occur. Other ticks (e.g., *Rhipicephalus appendiculatus*, *I. persulcatus*, *Haemaphysalis anatolicum*) may transmit the virus but are not significant in its epidemiology. Red grouse can become infected by eating ticks as well as via tick bites, and this seems to be an important route of transmission in young birds.

Only sheep and red grouse consistently develop viremia sufficient to infect ticks and amplify the virus. One report suggested that this might also be possible in some experimentally infected horses, but the viral titer was much lower than in sheep, and importance of this finding is uncertain. Mountain hares have been implicated as maintenance hosts via non-viremic transmission between co-feeding ticks.

Direct transmission seems to have a minor role in spreading louping ill between animals. For instance, the virus has been found in the milk of goats, and to a lesser extent, sheep, and small ruminants may transmit the virus to their offspring when they nurse. One group of pigs became ill after eating raw meat from infected lambs. Iatrogenic spread can occur on needles or surgical instruments.

Humans mainly seem to be infected by contact with the virus in tissues or laboratory cultures, but tick bites might be responsible for some cases where people had no obvious risk factors. Louping ill virus can enter the body through skin wounds, and aerosol exposure has been reported in laboratories. Humans might also acquire this virus by drinking unpasteurized milk from small ruminants, especially goats.

Disinfection

Flaviviruses are susceptible to most common disinfectants. They are also destroyed by heat or acidic conditions.

Infections in Animals

Incubation Period

The incubation period for louping ill ranges from 6 to 18 days in sheep. Parenterally inoculated red grouse developed clinical signs in 2-8 days.

Clinical Signs

In sheep, louping ill is characterized by an initial febrile stage, during which animals may have nonspecific signs such as depression and anorexia, followed in some animals by slight (e.g., transient ataxia) to severe neurological signs. Fever is not consistently present during the second (neurological) stage. Neurological signs are varied and may include muscle tremors and/or rigidity, incoordination,

ataxia, hypersensitivity, salivation, nervous nibbling and/or head pressing, progressing in some cases to posterior paralysis, recumbency, convulsions and/or coma. Affected sheep sometimes have an unusual hopping gait, called a louping gait (after an old Scottish term, 'loup,' which means to spring into the air), in which they move both hindlegs, then both forelegs, forward in unison. Animals with significant neurological signs often die within a few days. Sudden death can also be seen. Surviving animals may have temporary or persistent residual CNS deficits such as torticollis and paraplegia. When animals develop louping ill soon after infection with *A. phagocytophilum*, the illness is more severe and there may be additional signs such as dysentery. The disease caused by louping ill-related viruses is indistinguishable from louping ill.

Neurological signs have also been reported in other mammals including cattle, horses, South American camelids, dogs and cervids. The louping gait has not been documented in animals other than sheep; however, incoordination and ataxia are common, and exaggerated 'goose-stepping' of the hindlimbs was reported in a llama. Some clinical cases in cattle, dogs and other species are fatal, but it appears that the mortality rate in horses may be low.

Red grouse experimentally infected with louping ill virus had nonspecific signs of illness including depression, anorexia, regurgitation of the crop contents during handling, and muscle weakness, followed by death. There were no obvious neurological signs, though CNS lesions were found at necropsy. Decreased body weight and poor survival of chicks, as well as deaths in birds of all ages, have been reported in wild grouse. Some other species of grouse and ptarmigan developed a similar illness after experimental inoculation.

Post Mortem Lesions [Click to view images](#)

There are no significant gross lesions in the CNS of affected sheep, though congestion or mild hyperemia of the meningeal vessels or secondary pneumonia are sometimes noted. Microscopically, there is nonsuppurative meningitis and encephalomyelitis, with a combination of neuronal degeneration and necrosis, neuronophagia, multifocal gliosis and perivascular cuffing. In sheep, these changes occur primarily in the brainstem and cerebellum, and can also be present in the spinal cord. The microscopic lesions are not pathognomonic for louping ill.

Nonsuppurative meningoencephalitis was also reported in experimentally infected red grouse. The lesions occurred mainly in the cerebrum and optic lobes of the midbrain.

Diagnostic Tests

In sheep, louping ill virus can be found in blood samples for a few days during the initial fever, and the virus, its antigens or nucleic acids can be detected in the brain and spinal cord of animals with neurological signs. The most commonly used tests are immunohistochemical staining for viral antigens in the CNS and reverse

transcriptase polymerase chain reaction (RT-PCR) assays for nucleic acids. Virus isolation is now infrequently done but, if indicated, the virus can be isolated in porcine or ovine kidney cell lines or embryonated eggs. Intracerebral inoculation of suckling mice has also been used, mostly in the past. A RT-PCR assay specifically for Spanish goat encephalitis virus has been published.

Infections in sheep are also diagnosed by serology. Hemagglutination inhibition (HI) is the most commonly used assay, but other tests, such as serum neutralization and ELISAs, may be available in some laboratories. Cross-reactions can occur with other flaviviruses. Recent infections are indicated by the presence of virus-specific IgM in the HI test, or a rising titer in paired serum samples. However, IgG may become the major antibody in some sheep before the neurological signs develop.

Treatment

There is no specific treatment for louping ill, but supportive therapy including good nursing may be helpful.

Control

Disease reporting

Veterinarians who suspect louping ill should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal veterinary authorities should be informed immediately.

Prevention

There are currently few options to prevent louping ill in endemic areas. In the past, at-risk sheep could be immunized with an inactivated vaccine; however, it was recently withdrawn. Although a new vaccine is in development, when it will become unavailable is unclear. Acaricides may be of some benefit, though it may be difficult to protect animals by this method alone. Avoidance of *I. ricinus* habitats might also be feasible in some cases; however, this is likely to increase losses if the flock is later exposed. Attempts to protect wild red grouse populations, which are economically important in the U.K., have included vaccination and acaricide treatment of sheep, as well as other methods (e.g., culling of mountain hares). Acaricide treatment of grouse has been investigated.

If louping ill is introduced into a virus-free country, it is critical to prevent the virus from becoming established in ticks during stamping out. This virus was apparently eradicated from some Scottish islands by removing sheep for at least 2 years. The effectiveness of this approach may vary with the species present in the ecosystem.

Morbidity and Mortality

Most cases of louping ill occur in spring, early summer or fall, when *I. ricinus* ticks are more common. Morbidity and mortality are influenced by previous exposures, co-infections and other factors. In endemic areas, many sheep have mild or subclinical infections, most clinical cases

occur in animals that are less than 2 years old, and the mortality rate is about 5–10%. Lambs born in these areas are usually protected by maternal antibodies for the first few months of life, and older animals have developed immunity. However, mortality can be as high as 60% in newly introduced flocks and all ages are affected. Stressors and co-infection with *A. phagocytophilum* are thought to increase the severity of louping ill, probably by suppressing the immune system. Once a sheep has developed encephalitis, the case fatality rate is approximately 50%.

Louping ill is reported only sporadically in other mammals. Both fatal cases and recovery have been seen in cattle, but most horses seem to recover. Very few illnesses have been documented in dogs. Two fatal cases occurred in postparturient bitches, but a previously healthy, young adult male also died. Clinical cases seem to be uncommon in wild cervids and other wildlife but might be underdiagnosed. This disease was suspected in two wild Cantabrian chamois (*Rupicapra pyrenaica parva*), based on serology, though attempts to find viral antigens or nucleic acids in the brain were unsuccessful.

Louping ill is a significant issue in wild red grouse in the U.K., and there can be low survival in wild chicks and high seroprevalence (up to 84%) in adult birds where *I. ricinus* is common. The mortality rate can reach 80% in experimentally infected birds.

Illnesses caused by louping ill-related viruses seem to be uncommon in sheep and goats, though they might be underdiagnosed. These viruses have sometimes been found in small ruminants or ticks for decades, even in the absence of recognized clinical cases. Spanish goat encephalitis virus caused high mortality in a herd of Bermeya goats; however, this was probably related to unusual susceptibility of this rare, inbred breed and/or to their recent introduction to an endemic area, as other herds and flocks were unaffected and the disease was similar to louping ill in experimentally infected lambs and kids.

Infections in Humans

Incubation Period

The incubation period in humans is reported to be about 2-8 days.

Clinical Signs

In people, louping ill begins as a nonspecific, influenza-like illness with symptoms such as fever, headache, joint pain, muscle stiffness and malaise. Some cases resolve in about a week, but other patients develop meningoencephalitis, with signs such as fever, severe headache, neck stiffness and neurological signs including drowsiness, or a polio-like syndrome with mild to severe paralytic signs. Deaths seem to be rare, but convalescence can be prolonged.

Louping ill virus was also suggested to cause hemorrhagic fever in humans. This is based on a single report where blood samples from a sick laboratory technician, who had been working with Korean hemorrhagic fever, contained louping ill virus.

Diagnostic Tests

Some clinical cases in humans were diagnosed by isolating the virus, and others by rising antibody titers, the presence of IgM, or seroconversion. HI and complement fixation antibodies dropped rapidly after the illness in some patients, possibly due to poor sensitivity of these tests in humans. The use of RT-PCR on CSF samples has been proposed.

Treatment

Treatment of humans has been symptomatic and supportive.

Prevention

People who work with louping ill virus in the laboratory should wear appropriate personal protective equipment. The tickborne encephalitis vaccine has been recommended for this group, due to the close serological relationship between tickborne encephalitis virus and louping ill virus. Pasteurization kills the virus in milk, and vaccination of goats may reduce virus shedding in milk.

Morbidity and Mortality

Fewer than 50 clinical cases had been described in people as of 1991, and there is apparently only one suspected case since that time. Most cases occurred in laboratory workers, but a few were seen in people who worked with livestock or animal tissues (e.g., a farmer, a veterinarian, a butcher) or who had no apparent risk factors (a forestry worker, a physician). Deaths seem to be uncommon, with one reported fatality among 18 people with neurological signs and none in those with only a nonspecific febrile illness.

It is possible that louping ill is underdiagnosed, especially in cases without neurological signs. Serological evidence suggests that mild or subclinical infections might have been relatively common in high risk groups at one time, with old reports of antibodies in 8-18% of abattoir workers and 58-71% of laboratory workers who handled the virus. One study from 1962 found that up to 3% of the general population was also seropositive, depending on the test used. Cross-reactivity with tickborne encephalitis virus may complicate the interpretation of some of these results.

Internet Resources

United Kingdom. Department for Environment, Food and Rural Affairs
<https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs>

The Merck Veterinary Manual
<http://www.merckvetmanual.com/>

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