

Rabbit Hemorrhagic Disease and Other Lagoviruses

Viral Hemorrhagic Disease of Rabbits, Rabbit Calicivirus Disease, European Brown Hare Syndrome

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Importance

Rabbit hemorrhagic disease is a serious and extremely contagious viral disease of the European rabbit (*Oryctolagus cuniculus*). Morbidity and mortality rates are high in unvaccinated animals; on some farms, most or all naive rabbits may die. Rabbit hemorrhagic disease virus (RHDV) is thought to have emerged in the 1970s or 1980s in Europe. In 1984, a major outbreak in China killed 14 million domestic rabbits within 9 months. By the late 1990s, outbreaks had been seen in forty countries, and RHDV had become endemic in a number of locations where European rabbits also exist in the wild. The disease caused dramatic declines in some wild rabbit populations, particularly when it was first introduced. This has had a detrimental effect on some ecosystems in Europe, where wild rabbits are an important food source for certain endangered predators such as Iberian lynx (*Lynx pardinus*) and Spanish imperial eagle (*Aquila adalberti*). Conversely, RHDV has been used to help control excessive numbers of non-native European rabbits in Australia.

A new virus, RHDV2, emerged around 2010 in Europe and caused outbreaks in animals that had immunity to RHDV. Although early variants of RHDV2 appeared somewhat less pathogenic than RHDV, some recent isolates can be just as virulent. RHDV only seems to affect European rabbits, but RHDV2 also causes disease in hares (*Lepus* spp.), and its full host range might not yet be known. Like classical RHDV, RHDV2 spread to many countries within 10 years and became endemic in some. In some areas, it is now more common than RHDV. A closely related virus, European brown hare syndrome virus (EBHV), causes a similar disease in wild and farmed hares but does not affect European rabbits. The origins of RHD viruses and EBHSV are not completely understood, but they might have emerged from avirulent caliciviruses that circulate asymptotically in lagomorphs. This suggests that other virulent lagoviruses might emerge in the future.

Etiology

The genus *Lagovirus* (family Caliciviridae) contains several viruses pathogenic for lagomorphs. RHDV and RHDV2 (which is also known as RHDVb) cause rabbit hemorrhagic disease, while EBHSV causes European brown hare syndrome. Because the illness caused by RHDV2 in hares is indistinguishable from European brown hare syndrome, some sources have suggested that the latter disease should be renamed hare hemorrhagic disease, hare lagovirus disease or hare lagoviral hepatitis. RHDV and RHDV2 belong to different serotypes, and there is little or no cross-protection between them. The original RHD virus, which is known as classical RHDV, has given rise to antigenic variants including a subtype called RHDVa, which has become widespread. Unless otherwise specified, 'RHDV' in this factsheet refers to classical RHDV and all its variants, including RHDVa.

Related lagoviruses called rabbit caliciviruses or hare caliciviruses circulate in healthy rabbits and hares, respectively. While most rabbit caliciviruses do not seem to cause any illnesses, two potentially pathogenic strains have been reported. One virus identified in the U.S. (Michigan rabbit calicivirus) was found during a 2001 outbreak that resembled rabbit hemorrhagic disease, although an attempt to reproduce the disease in experimentally infected rabbits resulted in little or no illness. A related strain, the Ashington strain of rabbit calicivirus, was recovered from dead wild rabbits during an outbreak in Europe.

Note on the changing virus taxonomy

As of 2020, the officially recognized scientific names of the pathogenic viral species are still *Rabbit hemorrhagic disease virus* and *European brown hare syndrome virus*. However, a proposed new classification system is used in many recently published research papers. In this system, all lagoviruses belong to a single virus species, *Lagovirus europaeus*, which contains two genogroups, GI and GII. RHDV, RHDVa and nonpathogenic rabbit caliciviruses belong to GI, while EBHSV and nonpathogenic hare caliciviruses have been placed in GII. Each individual virus has a comprehensive name, which includes detailed information about its origins. For instance, the comprehensive name for one RHD virus, which was first found in

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European rabbits ('O cun') in France (FR) in 2003, is *Lagovirus europaeus*/GI.1d/O cun/FR/2003/03–24. The common name of this virus and other genetically related viruses is GI.1d. As a reminder to those not familiar to this naming convention, the common name may include the virus's historical name, i.e., GI.1d/ RHDV. It is still unclear whether this naming system will be adopted by most veterinarians and diagnostic laboratories.

The current and proposed common names of the pathogenic and nonpathogenic lagoviruses are:

CURRENT NAME	NEW NAME
RHDV (classical)	GI.1 (contains GI.1b, GI.1c, GI.1d)
RHDVa	GI.1a
RHDV2	GI.2
Rabbit caliciviruses (nonpathogenic)	GI.3, GI.4
EBHSV	GII.1
Hare caliciviruses (nonpathogenic)	GII.2, GII.3*, GII.4,* GII.5*

* Provisional designations for three recently described hare caliciviruses in Australia

Species Affected

RHDV

RHDV only seems to affect wild and domestic European rabbits (*Oryctolagus cuniculus*). Experiments generally found that European brown hares (*Lepus europaeus*), varying (snowshoe) hares (*L. americanus*), eastern cottontail rabbits (*Sylvilagus floridanus*), black-tailed jackrabbits (*L. californicus*) and volcano rabbits (*Romerolagus diazzi*) were not susceptible to infection. However, classical RHDV was found in dead wild Iberian hares (*L. granatensis*) that had been collected during an outbreak in the 1990s.

Whether rodents might be infected with RHDV is currently uncertain. Viral RNA was found in certain internal organs of wood mice (*Apodemus sylvaticus*) and Algerian mice (*Mus spretus*) collected near warrens that contained infected wild rabbits. The liver and/or feces of asymptomatic wood mice and Algerian mice also contained viral RNA for at least 10 days and occasionally up to 2 months after exposure to infected rabbits in the laboratory, but the presence of infectious virus and viral replication has

not yet been evaluated. Experiments in immunocompetent and immunosuppressed laboratory mice (*Mus musculus*) found no evidence for viral replication, though trace amounts of viral RNA were detected in the liver or spleen for up to 7 days.

RHDV2

RHDV2 is known to affect European rabbits and at least some species of hares, including the European brown hare, Cape hare (*L. capensis* var. *mediterraneus*), Italian hare (*L. corsicanus*) and mountain (varying) hare (*L. timidus*). Rabbits are reservoir hosts for RHDV, but whether hares can maintain the virus long term is currently uncertain. Infectious RHDV2 was detected in the liver of a Mediterranean pine vole (*Microtus duodecimcostatus*) and two white-toothed shrews (*Crocidura russula*) that died in the vicinity of affected rabbits in Europe.

European brown hare syndrome

European brown hare syndrome only seems to affect hares (*Lepus* spp.); European rabbits are not thought to be susceptible. Species known to develop clinical signs include European brown hares, mountain hares, Cape hares and Italian hares. In some areas, this virus seems to circulate mainly in European brown hares, with occasional spillover into other species of hares. Eastern cottontails were susceptible to experimental infection, and some wild Eastern cottontails in Italy had antibodies that suggested they had been infected with EBHSV.

Zoonotic potential

There is no indication that any lagoviruses infect humans.

Geographic Distribution

Classical RHDV and/or RHDVa are endemic in some areas with wild European rabbits, including Australia, New Zealand, some islands (e.g., Cuba), parts of Asia and Africa, and most of Europe. Susceptible wild lagomorphs do not exist in most of North America, though feral European rabbits do occur in a few locations. RHDV was found in both domestic and wild rabbits in South America (Uruguay) in 2005 but there are no reports of its occurrence since that time, and Uruguay reported itself to be free of rabbit hemorrhagic disease as of 2012.

As of 2020, RHDV2 has become established in wild lagomorphs in a number of European countries, Australia and parts of Africa. In some locations, RHDV2 has largely replaced classical RHDV or RHDVa. Outbreaks have also been reported in New Zealand and some countries in the Middle East, Asia and North America, but whether the virus will persist in some of these locations is not yet certain. In North America, this virus was found in both domestic and feral rabbits.

European brown hare syndrome has been documented in Europe. Viral antigens were also detected in some wild European hares in Argentina, though there were no signs of disease. Whether this organism was EBHSV or a less

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pathogenic relative was uncertain. Some other countries (e.g., Australia) also have susceptible wild hares but have never found EBHSV.

Michigan rabbit calicivirus was found in a single outbreak in a Michigan (U.S.) rabbit facility in 2001.

Transmission

Most studies on virus shedding and transmission have been done with RHDV, but RHDV2 and EBHSV are thought to spread similarly. RHDV can enter the body through the oral, nasal or conjunctival routes, though oral transmission is thought to predominate. Most or all secretions and excretions from infected rabbits, including urine, feces and respiratory secretions, are thought to contain virus. There do not seem to be any published reports of transplacental transmission of RHDV; however, viral nucleic acids of EBHSV and mild hepatitis were found in the fetuses of some infected hares. Whether the virus contributed directly to fetal deaths was uncertain.

Surviving rabbits can continue to shed RHDV for at least a month after they recover. Long-term persistence of viral RNA has been reported in apparently healthy rabbits for at least 15 weeks, but whether this represents true persistence or slow clearance of viral nucleic acids is still uncertain. Viral antigens or infectious virus have not been detected in these animals, even in laboratory experiments where they were immunosuppressed. RHDV can remain viable in carcasses for long periods. Even rabbit fur alone can be infectious.

RHDV is readily spread on various fomites including contaminated food, and insects might transmit this virus long distances. Flies seem to be very efficient mechanical vectors; infectious virus can persist in flies for up to 9 days, and only a few virions are needed to infect a rabbit by the conjunctival route. Viruses might also be deposited on vegetation in fly feces or regurgita, then eaten by a rabbit. Fleas and mosquitoes could also transmit RHDV mechanically in the laboratory. Birds and mammals that prey on lagomorphs may be mechanical carriers and excrete infectious viruses in feces after eating infected rabbits. Nucleic acids of RHDV and EBHSV have been found in the feces of various carnivores, and fecal shedding of infectious virus was demonstrated in a dog fed RHDV.

Rabbit lagoviruses are very resistant to inactivation when they are protected within tissues. RHDV can survive for 7.5 months in tissue suspensions stored at 4°C (39°F), and for more than 3 months in dried organ homogenates at 20°C (68°F). In one study, RHDV remained viable in decomposing rabbit carcasses kept at 22°C (72°F) for up to 20 days, but there was insufficient infectious virus after 26 or 30 days to cause clinical signs in rabbits. However, virus-inoculated bovine liver left to decompose in New Zealand fields (to simulate infected carcasses) remained infectious for at least 3 months. Unprotected viruses shed in excretions are not thought to remain viable for more than a few weeks, and may lose some of their infectivity within 1-

2 weeks. RHDV is also reported to survive exposure to pH 3.0, heat of 50°C (122°F) for an hour, and freeze-thaw cycles.

Disinfection

RHDV can be inactivated with 4-10% sodium hydroxide or 1-2% formalin. Other disinfectants that have been suggested include 0.5% sodium hypochlorite (10% household bleach) and 2% One-stroke Environ® (Vestal Lab Inc., St. Louis, MO). Some other commercial disinfectants effective against caliciviruses might also be useful. RHDV resists degradation by ether or chloroform.

Incubation Period

The incubation period is reported to be 1-3 days for classical RHDV/RHDVa, and estimated to be slightly longer, 3-5 days, for most cases of RHDV2. Clinical signs appeared 3-9 days after inoculation with RHDV2 in early experiments; however, some recent isolates killed rabbits as quickly as classical RHDV. The incubation period for EBHSV is likewise short in hares, which may die as soon as 2 days after exposure.

Clinical Signs

Classical RHDV/ RHDVa

RHDV infections are usually subclinical in rabbits less than 4-8 weeks of age. However, some of these animals may have elevated temperatures, and subclinical signs of liver disease were noted in experimentally infected 4-week-old rabbit kittens. Deaths have been reported, though rarely. In one study, experimentally infected 4-week-old rabbits died rapidly if they were immunosuppressed with corticosteroids.

Peracute and acute disease are the most common syndromes in older rabbits. Peracutely affected animals develop a fever and die suddenly within 12 to 36 hours of its onset. The only clinical signs may be terminal squeals, quickly followed by collapse and death. Animals with acute RHD survive somewhat longer, with nonspecific signs such as depression, anorexia, congestion of the conjunctiva and/or prostration, and, in some cases, respiratory signs (e.g., dyspnea, cyanosis and a terminal, bloodstained, frothy nasal discharge), lacrimation, ocular hemorrhages or epistaxis. Some rabbits also have neurological signs such as incoordination, opisthotonos and paddling. Affected animals sometimes turn and flip quickly in their cages, resembling convulsions or mania. Rabbits that survive longer (subacute cases) can develop severe jaundice, with weight loss and lethargy, and often die from liver dysfunction, typically within few weeks. Diarrhea or constipation and abdominal dilatation were sometimes seen just before death. Milder signs or subclinical infections have also been reported occasionally in adult rabbits.

Iberian hares infected with classical RHDV were found dead but had lesions consistent with a disease caused by a lagovirus.

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RHDV2

RHDV2 affects young rabbits as well as older animals; clinical cases have been reported in rabbits as young as 11 days of age. The clinical signs are indistinguishable from the illness caused by RHDV. However, at least some isolates seem to cause fewer peracute and acute cases, and rabbits may survive longer. A captive Italian hare infected with RHDV2 had no clinical signs other than epistaxis before death. Wild cape hares and European brown hares infected with this virus were found dead.

European brown hare syndrome

European brown hare syndrome resembles rabbit hemorrhagic disease, with peracute, acute and subacute cases. In addition to frank neurological signs (e.g., running in circles, opisthotonos, ataxia, paralysis of the hind legs), some hares display abnormal behavior, such as loss of normal fear responses toward humans or dogs. Catarrhal to necrotizing conjunctivitis, with an opaque and occasionally ulcerated cornea, has also been reported in hares. Pregnant hares may abort, and some of these does survived. Histological lesions suggestive of chronic hepatitis with mild focal lesions were seen in some wild hares with nucleic acids in the liver.

The clinical signs were similar in eastern cottontails inoculated with EBHSV.

Michigan rabbit calicivirus

An outbreak caused by Michigan rabbit calicivirus was characterized by acute fatalities over a 3-week period, and appeared very similar to rabbit hemorrhagic disease. The first signs of illness on the farm were inappetence in some animals and vulvar hemorrhages in pregnant does. Some rabbits also developed epistaxis, neurological signs, diarrhea and/or ocular discharge. Clinical signs were rare and mild (transient decreases in activity, inappetence) in rabbits experimentally infected with this virus.

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

The carcasses of rabbits with rabbit hemorrhagic disease are usually in good condition. Serohemorrhagic fluid may sometimes be noted at the nostrils. The primary lesion is hepatic necrosis, and gross lesions are most consistently seen in the liver and spleen. The liver is often pale yellow or has a grayish tinge and may be friable or congested. It often has a lobular pattern; however, the livers of some animals have a finely granular surface or are diffusely pale. The spleen is usually black and engorged, with rounded edges, and the trachea is often hyperemic and contains frothy, bloodstained mucus. Congestion, edema and multifocal hemorrhages may be observed in the lungs. Congestion is also common in other internal organs.

Disseminated intravascular coagulation (DIC) is common in the terminal stages and results in petechiae and other hemorrhagic signs in various organs and tissues. Infarcts may also be noted. Hemorrhages are not necessarily

present in rabbits euthanized earlier in the disease. Icterus, sometimes with yellowish serous transudates in body cavities, may be evident in subacute cases. Catarrhal enteritis of the small intestine or catarrhal gastritis with mucosal erosions were noted in some outbreaks.

European brown hare syndrome is similar to rabbit hemorrhagic disease, and many of the same gross lesions may be seen. However, some wild hares can be in poor condition due to factors such as concurrent diseases or food shortages. The primary lesion is hepatic necrosis, but descriptions of gross liver lesions from outbreaks in wild or farmed hares are variable. Friable and discolored livers with a pronounced lobular pattern were seen in some outbreaks, but other authors mainly reported congestion and hemorrhages in the liver, or only subtle gross lesions despite histological evidence of hepatic necrosis. Reports of hemorrhagic lesions are also inconsistent. The original descriptions indicated that the internal organs are sometimes congested but do not usually have hemorrhages (other than blood-tinged urine in the bladder); however, other sources found petechiae on the serosal and mucosal surfaces of internal organs, or even uncoagulated blood in the thoracic and abdominal cavities. The lesions of RHDV2 infections in hares are indistinguishable from European brown hare syndrome.

Michigan rabbit calicivirus infections resembled rabbit hemorrhagic disease in naturally infected rabbits, but there were no gross lesions in experimentally infected rabbits. Histopathological evidence of rare hepatocellular necrosis was sometimes noted in the liver of the latter animals. No gross lesions were apparent in the carcasses of an infected Mediterranean pine vole or two white-toothed shrews found dead in the vicinity of RHDV2-infected rabbits.

Diagnostic Tests

RHDV, RHDV2 and EBHSV have never been recovered in cell cultures; however, these diseases can be diagnosed by identifying viral nucleic acids and/or antigens in tissues, secretions/excretions and blood. The liver contains the highest viral titers in peracute or acute cases, but viruses can be abundant in the blood and spleen as well. When the course of the disease has been prolonged, RHDV (in the form of a virus-like particle) may be easier to find in the spleen than the liver. Viral RNA can also be found in many other organs, and in urine and feces. It may be detectable in some convalescent animals for a prolonged period.

RT-PCR tests are often used for diagnosis. Assays have been developed for RHDV, RHDV2, and EBHSV, but test availability can vary. Some tests are specific for certain viruses, while others do not distinguish RHDV, RHDVa and RHDV2. A RT-PCR assay that can amplify both RHDV2 and EBHSV has been developed for hares. Reverse-transcription loop-mediated isothermal amplification (RT-LAMP) assays have been described in the literature.

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Tests to detect viral antigens are available for RHDV and EBHSV. Tests for RHDV may identify all of the viruses or be specific for either classical RHDV/RHDVa or RHDV2. ELISAs are often used, but other assays including immunostaining, immunoblotting (Western blotting) and negative-staining immunoelectron microscopy may be available. The hemagglutination test for classical RHDV is less sensitive and specific than other assays, and has generally been replaced by ELISAs. A rapid penicillin lateral flow immunochromatographic assay specifically for RHDV2 has been published. Cross-reactions with nonpathogenic rabbit caliciviruses may be an issue in some tests.

Antibodies to RHDV can be detected with ELISAs or hemagglutination inhibition assays. Histopathology helps support the diagnosis, and electron microscopy may be helpful in some circumstances. Animal inoculation into lagomorphs has been used occasionally, for instance to help identify cases that could not be definitively diagnosed by other means.

Treatment

Treatment is currently limited to supportive care. Hyperimmune antiserum can protect rabbits that have not yet developed clinical signs, but it is reported to be ineffective in symptomatic rabbits.

Control

Disease reporting

A quick response is vital for containing outbreaks in disease-free regions. Veterinarians who encounter or suspect rabbit hemorrhagic disease or European brown hare syndrome 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

Uninfected countries may place restrictions on the importation of live lagomorphs, meat and other animal products (e.g., Angora wool) from endemic areas. Rabbit hemorrhagic disease can sometimes be eradicated by depopulation, disinfection of infected premises, surveillance and strict quarantines; however, eradication is generally impossible if a virus becomes established in wild lagomorphs. Infected farms should not be restocked immediately, as the viruses can persist for a time in the environment. Sentinel rabbits can be used to monitor the premises for persistent RHD viruses.

In regions where RHD viruses circulate in wild rabbits, domestic rabbits are protected with biosecurity measures including separation from wild rabbits, sanitation and disinfection, and vaccination. Maintaining closed colonies can help prevent the virus from entering the premises. If new stock is introduced, quarantining them initially is prudent. Similar measures can be used on farms that raise hares in areas endemic for EBHSV or RHDV2. If sick lagomorphs are treated during an outbreak, they should be

isolated and stringent precautions should be used to keep the viruses from spreading. Surviving animals, as well as any animals introduced later to the farm, should be vaccinated.

Vaccines are manufactured for RHDV2, RHDV or both serotypes (bivalent vaccines); there is limited or no cross-protection between classical RHDV/ RHDVa and RHDV2. There is at least one report of an inactivated EBHS vaccine being used in an outbreak in farmed hares. Because the production cycle is short, commercial rabbit farms may only vaccinate breeding animals if rabbit hemorrhagic disease has not been reported in the area. However, all animals should be vaccinated when outbreaks are occurring, as the likelihood of infection is high even with strict sanitation and other control measures. Vaccination may also be useful as post-exposure prophylaxis, as immunity to RHDV usually develops in approximately 7-10 days. Sentinel animals can be used to monitor vaccinated farms for RHDV.

Morbidity and Mortality

RHDV

Reported morbidity and mortality rates in outbreaks caused by RHDV are in the range of 30-100% and 40-100%, respectively, with the highest fatalities among adult rabbits from naïve populations. Clinical cases may be sporadic in some situations where rabbits are well separated from each other (e.g., some research environments). Deaths caused by RHDV are rare in animals < 4 weeks of age, which are inherently resistant to the illness regardless of maternal antibody status. However, they can still become infected and seroconvert. Rabbits lose their resistance between 4 and 12 weeks of age. Animals that survive rabbit hemorrhagic disease develop immunity to related strains. Exposure to nonpathogenic rabbit caliciviruses may also provide some degree of protection, although this seems to vary with the virus.

RHDV2

Mortality rates from 5% to 70% have been reported in rabbits infected with RHDV2. Studies with early isolates of this virus suggested that it is less virulent than RHDV, with an average mortality rate of 20-30% in experimentally infected rabbits. However, some recent RHDV2 isolates were more pathogenic, with mortality rates up to 80%, and severe outbreaks have also been seen sometimes in naturally infected animals. Young rabbits and hares do not seem to be resistant to RHDV2.

Effects of RHDV and RHDV2 on wild rabbits and hares

In Europe, the introductions of both RHDV and RHDV2 resulted in severe epidemics in wild European rabbits. RHDV caused dramatic declines in some wild rabbit populations, while other areas were less severely affected. Initial high morbidity and mortality rates were

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sometimes be followed by sporadic, less severe outbreaks and recovery of the population. Epidemics in wild rabbits can lead to outbreaks in domestic rabbits. RHDV2 can also cause outbreaks of fatal illness in hares. Most of these events seem to be associated with virus spillover from rabbits; however, RHDV2 was reported to circulate in one isolated population of hares for at least 4-6 months after its introduction. Deaths caused by this virus in wild hares have been sporadic in some areas, but epidemics and widespread infections have also been reported.

European brown hare syndrome

In wild hares, European brown hare syndrome is a seasonal disease that is uncommon in the warmer months. It is usually seen between October and December in Scandinavian countries, and to a lesser extent during the rest of winter, but typically occurs between December and May in Greece. Epidemiological observations suggest that European brown hares are probably more susceptible to EBHSV than mountain (varying) hares. The mortality rate is variable, and ranges from 0% to 50% in experimentally infected animals. Young hares < 2-3 months of age appear to be resistant or relatively resistant to disease. Mortality is usually high when the virus is introduced to naive populations. It can approach 100% on small farms, with sporadic mortality often seen in later years. Eastern cottontails are also susceptible to EBHSV, but appear less likely to succumb to the illness. In one study, only one of 4 experimentally infected cottontails died, though all four animals seroconverted.

Rabbit and hare caliciviruses, and the emergence of pathogenic viruses

Most rabbit and hare caliciviruses are thought to infect lagomorphs subclinically. Infrequent outbreaks caused by rabbit caliciviruses (e.g., Michigan rabbit calicivirus) might be related to a more virulent strain, or to unusual susceptibility of a group of animals. How pathogenic lagoviruses emerge is unclear, but the suspicion is that they either 1) come from nonpathogenic viruses already circulating in that host or 2) result from virus jumps between different species of lagomorphs. Proponents of the latter hypothesis note that the Eastern cottontail rabbit was introduced to Europe around the time both EBHSV and RHDV emerged.

Internet Resources

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

United States Animal Health Association. Foreign Animal Diseases
http://www.aphis.usda.gov/emergency_response/downloads/nahems/fad.pdf

World Organization for Animal Health (OIE)
<https://www.oie.int/>

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

<http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/>

OIE Terrestrial Animal Health Code

<http://www.oie.int/international-standard-setting/terrestrial-code/access-online/>

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