

VIRAL HEMORRHAGIC DISEASE OF RABBITS

(Necrotic hepatitis of rabbits, rabbit hemorrhagic disease syndrome, X disease)

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Definition [top](#)

Viral hemorrhagic disease of rabbits (VHD) is a peracute viral disease of rabbits (*Oryctolagus cuniculus*) causing hepatic, intestinal, and lymphoid necrosis and massive terminal intravascular coagulation.

Etiology [top](#)

The causative agent has not yet been fully characterized. Following initial reports from the People's Republic of China (13) that the agent was a picornavirus (22), later studies identified a parvovirus (27). Though a caliciviral etiology has been suggested by various European workers (18,19,20), studies comparing isolates from Mexico, Korea, Spain, and Italy indicate that there is little or no serologic

difference between isolates (M. Beringer, personal communication).

The virus is very resistant to physical and chemical agents. It can persist in blood from an infected rabbit for more than 9 months at 4° C (39° F.). Organ homogenates are stable for more than 3 months at 20° C (68° F.) when dried on cloth (24). Virus can be shed in urine or feces of infected and recovered rabbits for up to 4 weeks (9,10). The virus is ether and chloroform resistant but is inactivated in 1 hour in 1 percent NaOH or 1 percent formalin at 37° C (98.6° F.) (26). Solutions of 2 percent One-stroke Environ (Vestal Lab Inc., St. Louis, MO) and 0.5 percent sodium hypochlorite (10 percent household bleach) have also been recommended (9).

Host Range [top](#)

Only the domestic rabbit and the European rabbit (both *Oryctolagus cuniculus*) appear to be susceptible to VHD. Other lagomorphs that have been experimentally exposed but did not show clinical signs of disease include the Eastern cottontail (*Sylvilagus floridanus*), black-tailed jackrabbit (*Lepus californicus*), and volcano rabbit (*Romerolagus diazi*). The European brown hare (*Lepus europaeus*) and the varying hare (*Lepus timidus*) appear not to be natural hosts for VHD but are susceptible to a very closely related virus that causes European brown hare syndrome. No other laboratory animal is susceptible to VHD.

Geographic Distribution [top](#)

The disease is enzootic in the People's Republic of China, Korea (1), most of continental Europe, Morocco, Cuba, Australia, and New Zealand. In Europe, the disease is also epizootic in the wild rabbit population with more cases occurring in the fall. An outbreak occurred in the Mexico City area in December 1988 (15,16). In February 1989, the Mexican government began a control and eradication program to eliminate the disease using test and slaughter methods. The campaign was successful; there were few reported cases in 1990 and none in 1992. Mexico is the first country to succeed in eradicating this disease.

A disease similar to VHD called European brown hare syndrome (6,7) has been reported from Sweden. European brown hare syndrome was first suspected to be caused by a severe hepatotoxin but has since been demonstrated to be caused by a virus closely related to VHD that seems to affect only hares (3,7). Both of these viruses are now widespread in continental Europe in its wild populations of rabbits and hares respectively.

Transmission [top](#)

Transmission of the virus is by direct contact with infected animals or, indirectly, by contact with objects contaminated with virus. Aerosol is generally not an important means of transmission. Natural infection is more likely through oral exposure. Experimental transmission can be accomplished through inoculation by oral, nasal, subcutaneous, intramuscular, or intravenous routes.

Incubation Period [top](#)

Experimentally, following oral exposure, the incubation period is about 24 hours to the onset of fever. This may vary up to 48 hours under field conditions.

Clinical Signs [top](#)

The most prominent sign is that young adult and adult rabbits die suddenly after 6 to 24 hours of fever with few clinical signs. Fever may be high (up to 105° F or 40.5° C) but often is not detected until rabbits show terminal clinical signs. Most rabbits appear depressed in the final hours and may have a variety of neurologic signs including excitement, incoordination, opisthotonos, and paddling. They sometimes emit a terminal squeal. A few rabbits may have a terminal serosanguineous, foamy, nasal discharge (Fig. 126).

Gross Lesions [top](#)

Many gross and histopathologic lesions have been attributed to VHD, including hemorrhages and necrosis in many organs. The primary and most consistent lesion of VHD is hepatic necrosis of the portal zone of each lobule (Fig. 127), which causes the liver to appear pale. On close examination, the liver has a fine reticular pattern of necrosis outlining each liver lobule. In some cases, necrosis is so extensive that the liver is diffusely pale. Hemorrhages are the most obvious postmortem lesion but are often variable or absent — especially in rabbits that are euthanized. Hemorrhages are the result of massive terminal intravascular coagulation in many organs and are likely the cause of death in most cases of VHD. Hemorrhages are common in the lung, (Fig. 128) trachea, and thymus whereas infarction is common in the kidneys and spleen. The spleen is usually thickened and black and has distinctly rounded edges. Infarcted kidneys may appear black. A more subtle lesion is a catarrhal enteritis due to small intestine crypt necrosis, but diarrhea usually is not present because rabbits commonly die peracutely before digestive alterations develop.

Morbidity and Mortality [top](#)

Morbidity with VHD is very high. Mortality is usually 90 percent in conventionally raised rabbits, and often only suckling rabbits are spared. Suckling rabbits may be spared because of maternal immunity to a closely related virus or owing to reduced susceptibility of the immature liver. In isolated and well-managed research colonies, mortality may be 50 percent or less. The reason for this difference is not well understood, but immunologic priming seems to predispose rabbits to the massive terminal intravascular coagulation (massive coagulopathy) that is responsible for the sudden death. Experimental priming has raised the mortality rate in research rabbits from 50 percent to 100 percent. Both minute virus of mice and porcine parvovirus have produced this priming effect.

Diagnosis [top](#)

Field Diagnosis [top](#)

A presumptive diagnosis can be made in a rabbitry when there are multiple cases of sudden death following a short period of lethargy and fever, and characteristic hepatic necrosis and hemorrhages occur. A field diagnosis is more difficult when there are few rabbits on the premise or rabbits are relatively isolated, as in research colonies.

Specimens for the Laboratory [top](#)

Unfixed liver, heparinized blood and serum, and fixed liver, spleen, kidney, lung, small intestine, and brain should be sent to the laboratory to confirm suspected cases.

Laboratory Diagnosis [top](#)

Ideally, several tests should be used in the laboratory. Virus can easily be concentrated from liver homogenate and visualized by electron microscopy using negative stains. Liver homogenate can also be used in a hemagglutination test (21). This virus agglutinates human type O and guinea pig erythrocytes at pH 6.3 to 7.4 at 4 to 25° C. Antibody from recovered rabbits can also be detected with this test by its inhibition of erythrocyte agglutination. Tissue sections can be immunostained using the avidin-biotin alkaline phosphatase staining system on either fresh or freshly fixed liver and spleen (8). Where VHD has become endemic, several different enzyme-linked immunosorbent assay (ELISA) systems have been developed (3).

Rabbits can be inoculated to confirm the first diagnosis of this disease in a new

region. No other laboratory animals are susceptible. The virus cannot easily be propagated in cell culture.

Histologically, diffuse hepatic necrosis with a periportal pattern accompanied by microthrombi in multiple organs is characteristic of this disease in rabbits.

Differential Diagnosis [top](#)

There are few diseases of rabbits that would be confused with this disease. Pulmonary pasteurellosis (snuffles) causes a severe pneumonia in rabbits and is one of the most common diseases of rabbits (4). However, this disease causes an obvious pneumonia, consolidation of the lungs, and abscesses, which are not features of VHD. A severe bacteremia or septicemia with secondary disseminated intravascular coagulation (DIC) is more likely to be confused with VHD. This may cause hemorrhages in multiple organs and multifocal liver necrosis (rather than diffuse). Enterotoxemia due to *E. coli* or *Clostridium perfringens* Type E can cause such a hemorrhagic syndrome (23,25). This is often associated with oral administration of antibiotics to rabbits.

Treatment [top](#)

There is no treatment for this disease. Most rabbits have a peracute disease course and are found dead.

Vaccination [top](#)

Several vaccines have been developed and are used where VHD is endemic (2,11,24). All of these vaccines are made from inactivated virus prepared from infected rabbit liver extracts. Vaccinated rabbits develop protective antibody in 5-10 days and must be revaccinated after 6 months. Owing to the short incubation time and rapid death, vaccination in the face of an outbreak is problematic. Many rabbits are likely to be exposed before they are fully protected by the vaccine. Many may survive, but it is uncertain whether some will shed virus as recovered rabbits have been shown to do experimentally.

Control and Eradication [top](#)

Countries free of this disease should restrict the importation of rabbits, frozen rabbit carcasses, raw rabbit pelts, and angora wool from countries where VHD is endemic. Vaccination should be considered only if eradication is not possible or if the disease becomes endemic in susceptible wild populations.

Blood and liver of infected rabbits may contain more than a million viral particles per gram. The virus is stable in blood for at least 9 months at 4° C and much longer frozen. Therefore, frozen rabbit meat imported from countries where the disease is endemic is a particularly likely source of virus introduction. Rabbit producers are often consumers of rabbit meat, thus raising the likelihood of contact with contaminated meat and transmission to susceptible rabbits. The disease could also inadvertently be introduced by purchasing breeding stock or raw angora wool from an endemic area. Rabbits are known to shed virus for at least 4 weeks after clinical recovery from this disease. Because clinically normal rabbits may be imported from any country into the United States without restriction, testing or quarantine, imported rabbits could easily be a source of an outbreak.

In Europe, where VHD has become endemic in both the domestic and wild populations of rabbits, control is based on strict sanitation, maintenance of closed rabbit colonies, and vaccination of breeding stock. Fecal contamination of forage by wild rabbits before it is harvested and used as feed for domestic rabbits remains a continuing source of viral exposure (17).

In countries where wild rabbits are not susceptible, eradication is feasible and should be attempted. Mexico chose to eradicate VHD because rabbits were recognized as an important source of animal protein that was produced with limited amounts of forage. The epizootic was controlled by depopulating the rabbits from affected areas, disinfection, inspection of facilities, introduction of sentinel rabbits after 30 days, and repopulation with government-raised rabbits. Continued serologic surveillance aided in the elimination of new outbreaks and possible carrier rabbits. A vaccine was not used in Mexico because it would have masked the disease and made serologic surveillance impossible.

GUIDE TO THE LITERATURE [top](#)

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