

# Rabbit Hemorrhagic Disease

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**Rabbit Hemorrhagic Disease (RHD) is a rapidly lethal infectious viral disease of the European Rabbit (*Oryctolagus cuniculus*) characterized by high mortality rates, acute hepatic necrosis, and disseminated intravascular coagulation. Although this disease is considered enzootic in Europe and parts of Asia, it is rarely seen in the Western Hemisphere since its eradication from Mexico in 1992. In recent years, three cases of RHD have been identified in the United States. Due to the quick action of veterinarians these cases were confined and controlled before the disease could spread. © 2004 Elsevier Inc. All rights reserved.**

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Rabbits are raised for food, for pets, and as show animals worldwide. Rabbits are particularly important in Asia and central Europe, where small-scale rabbitries are common and an integrated part of the culture. In this article an emerging disease, Rabbit Hemorrhagic Disease (RHD), is described. RHD already has had a major global impact and is a real threat to the rabbit industry and pet rabbits in the Americas.

## History

Rabbit Hemorrhagic Disease was first recognized in China in 1984. The epicenter of the outbreak occurred in a group of commercially bred Angora rabbits recently imported from Germany to Jiangsu Province, China. These rabbits soon exhibited a contagious rapidly fatal disease that spread over 50,000 square kilometers in 9 months killing 470,000 rabbits. This disease was variously called "X-Disease of Rabbits," "rabbit viral sudden death," "picornavirus hemorrhagic fever in rabbits," "hemorrhagic septicemia syndrome in rabbits," and "infectious necrotic hepatitis of leporidae." Today, this disease is known as Rabbit Hemorrhagic Disease (RHD), Viral Hemorrhagic Disease of rabbits, or Rabbit Calicivirus Disease (RCD). Since 1984, RHD has disseminated widely

and has been reported in over 40 countries from Asia, Africa, Europe, and the Americas.<sup>1-4</sup>

## Disease

RHD is caused by the Rabbit Hemorrhagic Disease Virus (RHDV). RHDV is a member of the family Caliciviridae, genus Lagovirus, and is closely related but distinct from the European Brown Hare syndrome virus, which causes similar symptoms and disease as RHDV in hares.<sup>4</sup> RHDV is readily disseminated. Virus is shed in the feces and nasal secretions of infected rabbits. Both ingested and inhaled virus can result in infection. The virus is stable in the environment. This allows RHDV to be spread by contact with contaminated caging, shavings, bowls, feedstuffs, and other fomites. The virus can also be passively transported by flies over short distances and can also travel by movement of people, equipment, wild or domestic animals, pelts, and rabbit carcasses.<sup>3</sup>

The incubation period for RHDV is short, only 16 to 48 hours. RHDV is highly infectious and highly virulent. As a result, morbidity and mortality rates may reach 90% to 100%. Death usually occurs between 2 and 3 days postinfection, although some rabbits may live for several days before they die. The disease is confined to rabbits over 2 months of age. It is believed maternal immunity protects the infant rabbits from this disease. As the maternal immunity declines at 2 months of age, the rabbits become susceptible to RHDV.<sup>1-3</sup>

Three forms of the disease are recognized depending on past history of the disease in the affected rabbit population. A peracute form of the disease occurs in naïve rabbit populations. In this form of the disease, rabbits die suddenly,

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**Figure 1.** Rabbit with Rabbit Hemorrhagic Disease. This animal is severely depressed and poorly responsive. In a sudden outbreak of rabbit hemorrhagic disease, the duration of signs in rabbits before death is usually less than a day (Photograph kindly provided by Elizabeth Morales Salinas).



**Figure 2.** Carcass of a rabbit with Rabbit Hemorrhagic Disease. Bleeding from the nostrils and the vagina is a characteristic finding in rabbits with Rabbit Hemorrhagic Disease (Photograph kindly provided by Elizabeth Morales Salinas).

exhibiting no or very few signs. The acute form of the RHD is seen in rabbit populations where the disease is enzootic. These rabbits typically show some signs of disease before death. A subacute form of the disease is uncommon and occurs in the later stages of an epizootic. In this form of the disease, affected rabbits are clinically ill, but many survive.<sup>1-3</sup>

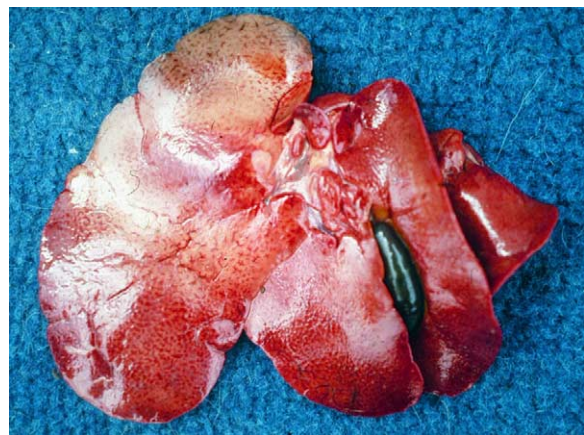
Several clinical signs have been observed in rabbits both experimentally infected with RHDV and those that were naturally infected (Fig 1). Not all clinical signs were present in every animal. Animals may have a temperature above 104°F (41°C), show rapid respiration, cyanosis, and become anorexic and recumbent. Severe diarrhea is common. In the late stages of the disease, various neurological signs are apparent, including lateral recumbency, paddling, ataxia, and terminally frenetic behavior sometimes accompanied by squealing. Opisthotonos has been observed in many animals, and 20% of infected rabbits have a bloody foamy discharge from their nose and, less frequently, from the vagina (Fig 2).

Hematological findings in rabbits with the acute form of the disease include lymphopenia, thrombocytopenia, and alterations in the coagulation panel. Liver enzymes also are expected to be elevated.<sup>2,3</sup>

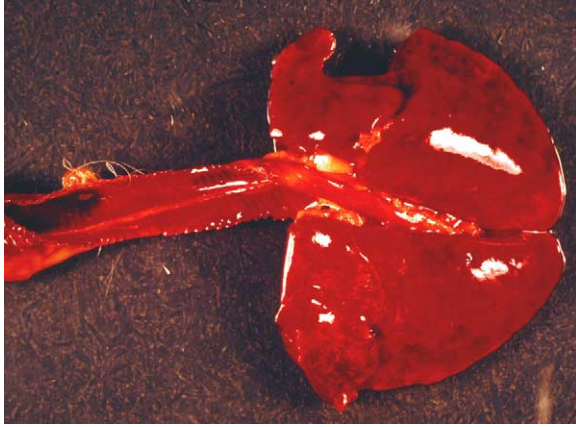
Typically, rabbits dying with RHD are in good body condition and have recently ingested food. RHD causes a severe diffuse necrotic hepatitis and disseminated intravascular coagulation. The liver may be pale, yellow, gray, friable, or congested and have a distinct lobular pattern. Multifocal petechial hemorrhages occur in the liver, lungs, kidneys and heart (Figs 3 and 4). The spleen is often dark and engorged. Pneumotracheitis and

tracheal hemorrhage are common, and jaundice has been occasionally noted. Lesions of the digestive tract are usually absent, although in some outbreaks, a catarrhal enteritis is a feature of RHD. In cases of acute RHD the characteristic hemorrhages might not be present.<sup>1-3</sup>

Microscopic lesions of the liver are characterized by an acute diffuse hepatic necrosis and hemorrhage with minimal inflammation. Round eosinophilic inclusion bodies are seen in hepatocytes. Lymphoid necrosis in the spleen and lymph nodes is another characteristic lesion of RHD. Glomeronephritis, encephalomyelitis, and enteritis also may be seen histologically.<sup>1-3</sup>



**Figure 3.** Liver from a rabbit with rabbit hemorrhagic disease. Note the diffuse reticular pattern that results from zonal hepatic necrosis (Photograph kindly provided by Elizabeth Morales Salinas).



**Figure 4.** The lungs and trachea from a rabbit with rabbit hemorrhagic disease. The lungs are hemorrhagic and the trachea is filled with blood (Photograph kindly provided by Elizabeth Morales Salinas).

## Diagnosis

A presumptive diagnosis can be made on client history, clinical signs, and postmortem findings (Table 1). In North America and Mexico, if this disease is suspected, a regulatory veterinarian should be immediately contacted. At specialized facilities, a diagnosis can be confirmed by electron microscopy of fixed tissues or homogenates of fresh tissue, immunofluorescence, a hemagglutination assay, or a viral antigen detection ELISA. A complete set of tissues should be formalin-fixed for histopathology. Small intestine, lung, liver, spleen, and kidney samples should be saved fresh for virus detection.<sup>5</sup>

## Eradication

Eradication is currently considered the best response to this disease when it is introduced to a country that does not have RHD. When infected rabbits are identified, all in contact rabbits are destroyed. The carcasses, all wooden caging and housing, and all organic material is buried. Metal cages and food bowls and glass water bottles are cleaned and then disinfected with 2% sodium hypochlorite solution. Buildings that housed rabbits are power washed and then disinfected with sodium hypochlorite solution. Soil that may have been in contact with rabbits, rabbit feces or urine is treated with the sodium hypochlorite solution and then calcium hypochlorite (lime). In the United States, sentinel rabbits were housed on the

facilities and monitored for disease for 1 month before the facility was allowed to be repopulated.<sup>1</sup>

## Treatment

Treatment is only an option in countries where this disease is enzootic. Because of the vigor and speed with which this disease kills rabbits, most rabbits are dead before any care can be administered. If rabbits are exhibiting clinical signs, isolation, supportive care, and symptomatic treatment is all that can be done.

## Prophylactic Measures

### Quarantine and Sanitation

In areas where RHD is enzootic, cleanliness is vital. The virus is inactivated with a 1% sodium hypochlorite solution. Rabbits should be housed indoors if possible. Stray animals should be kept away from rabbit housing and flying insects kept to a minimum. Access to the rabbitry should be limited, and caretakers should not have contact with other rabbits from other facilities. Maximizing sanitation within the rabbitry, especially cleaning and disinfecting cages between rabbits, may reduce the chance of disease transmission. New stock should be quarantined in a separate facility for 4 months, as rabbits that have survived RHD shed virus in their feces for up to 4 months.<sup>2,3</sup>

### Immunization

Vaccines against RHD are available in countries with enzootic RHD. There is a 6-month and a 1-year vaccine available. The vaccines are relatively safe, although illness, infections at injection sites, and death have been documented. RHD vaccines are not available in the United States and Canada at this time. The vaccine currently being used in Australia is Cylap HVD (Cyanamid, Spain) and is a killed vaccine. It is safe to consume a rabbit vaccinated against RHD. Rabbits can be immunized at 6 weeks of age or older. If the rabbit is less than 10 weeks old at first vaccine, a second immunization should be given in 4 weeks. Animals demonstrating any signs of ill health should not be immunized.<sup>6</sup>

## RHD in Selected Countries

### RHD in Mexico

The Americas were free of RHD until December of 1988 when it is thought that a shipment of

**Table 1. Differential Diagnoses for Rabbit Hemorrhagic Disease\***

Condition	Signs	Diagnostics
Rabbit enteropathogenic <i>E. coli</i>	<ul style="list-style-type: none"> <li>-Neonatal rabbits 1-14 days old.</li> <li>Watery Diarrhea typically staining peritoneum yellow. Morbidity and mortality can reach 100%.</li> <li>-In postweaning rabbits. Mild diarrhea and weight loss.</li> <li>Morbidity and mortality can exceed 50%. Retarded growth has been noted in rabbits who recover from <i>E. Coli</i></li> </ul>	<ul style="list-style-type: none"> <li>-Presumptive diagnosis can be made by isolation of <i>E.coli</i> from stool or tissue samples.</li> <li>-Definitive diagnosis requires histological examination and visualization of <i>E. coli</i> attachment to intestinal cells.</li> </ul>
Tyzzer's Disease (caused by <i>Clostridium piliforme</i> )	<ul style="list-style-type: none"> <li>-Watery diarrhea, depression, and death. Morbidity and mortality are highest in weanling rabbits.</li> <li>-Older rabbits may experience chronic weight loss.</li> </ul>	<ul style="list-style-type: none"> <li>-Characteristic foci of necrosis in the liver and degenerative lesions of the myocardium are evident on post mortem analysis.</li> </ul>
Rabbit enteric Coronavirus	<ul style="list-style-type: none"> <li>-Lethargy, diarrhea, abdominal swelling, and death are the signs seen in rabbits 3-10 weeks old.</li> <li>-Coronavirus is associated with high morbidity and mortality approaching 100% in 24 hours of showing symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>-The virus agglutinates red blood cells. A positive hemagglutination test in feces supports a tentative diagnosis.</li> <li>-Fluid cecal contents are evident on post mortem examination.</li> <li>-Atrophy of intestinal villi is evident on histopathologic examination.</li> <li>-Detection of virus in feces or cecal contents.</li> </ul>
Rotavirus	<ul style="list-style-type: none"> <li>-Rabbits 30-80 days old are most affected.</li> <li>-Infections caused by rotavirus alone may be only result in a mild disease. However, a synergistic infection with pathogenic bacteria can result in a severe diarrheal disease.</li> <li>-Severe anorexia, dehydration, mucoid or greenish-yellow watery diarrhea.</li> </ul>	<ul style="list-style-type: none"> <li>-On postmortem examination congestion and distention of the intestine and cecum, and petechial hemorrhages in the small intestine and colon have been reported.</li> <li>-Histopathologic examination of the intestine, isolation of the virus, or demonstration of antibodies are needed for definite diagnosis.</li> </ul>
Enteritis Complex (enterotoxemia caused by <i>Clostridium. spiroforme</i> )	<ul style="list-style-type: none"> <li>-This is the most common disease seen in clinical practice.</li> <li>-Signs can range from soft stool and brown watery diarrhea with or without mucous or blood, to enterotoxemia, sepsis. Severely affected rabbits will become anorectic and depressed, and die.</li> <li>-Rabbits become hypothermic and moribund and die after 24-48 hours. Occasionally a chronic form of the disease is seen with rabbits intermittently having diarrhea, anorexia, and weight loss.</li> </ul>	<ul style="list-style-type: none"> <li>-Post mortem findings include petechial and ecchymotic hemorrhages on the serosal surface of the cecum, sometimes including the appendix and colon.</li> <li>-Gas may also be present in the small intestines, cecum, and colon.</li> <li>-A definitive diagnosis is made by histopathology.</li> </ul>
Mucoid Enteritis	<ul style="list-style-type: none"> <li>-Major cause of morbidity and mortality of rabbits 7-14 weeks of age.</li> <li>-Anorexia, lethargy, weight loss, and diarrhea.</li> </ul>	<ul style="list-style-type: none"> <li>-Cecal impactation and excessive production of mucus are commonly seen on <i>postmortem</i> examination.</li> </ul>
Dysbiosis Secondary to Treatment with Antibiotics	<ul style="list-style-type: none"> <li>Clinical signs are the same as enteritis.</li> <li>Clinical signs</li> </ul>	<ul style="list-style-type: none"> <li>-Recent treatment with Clindamycin, lincomycin, penicillin, ampicillin, amoxicillin, amoxicillian-clavulanic acid, cephalosporins, or erythromycin.</li> </ul>

\*Data adapted from Jenkins [9]

18,000 kg of rabbit meat tainted with the RHDV introduced RHD to Mexico. This tainted meat was delivered to a supermarket chain outside of Mexico City, where it is speculated one of the workers handling the meat may have transmitted the virus to his own rabbitry. By the end of February 1989, the disease had spread to 159 separate rabbitries in six Mexican States (one infected premise was located just 400 miles from the Texas border). Realizing the drastic affects of RHD, and to prevent it from spreading, the Mexican Government conducted extensive serological surveys from 1989 to 1992, depopulating all seropositive animals and their contacts. During the course of the eradication campaign, 120,579 rabbits were destroyed, and in 1992, Mexico became the first country to successfully eradicate RHD.<sup>1,3</sup>

### Australia

While the rest of the world tried to contain the spread of RHD, Australia has used this disease in an attempt to mitigate the impact of the introduced European rabbit to its agriculture and wildlife. In 1991, Rabbit Hemorrhagic Disease Virus was imported into the Australian Animal Health Laboratory (AAHL) to conduct studies on its efficacy at killing rabbits and its species specificity. The AAHL confirmed that RHD was species-specific to the European Rabbit (*Oryctolagus cuniculus*). Based on this information, field trials were started on Wardang Island, South Australia in March of 1995. Despite many precautions, RHD escaped quarantine in September 1995. The disease rapidly spread throughout South Australia. By December 1995 the virus had crossed state lines. In a 2-month period, RHD killed 10 million rabbits.<sup>7,8</sup>

### United States

There have been three outbreaks of RHD in the United States. The first was an isolated rabbitry in Iowa in 2000. This premise was depopulated and additional cases were not found. The source of this outbreak was never determined. The second outbreak originated in Utah in 2001, but was first recognized in an Illinois facility that had received rabbits from the Utah source. Both facilities were depopulated and the disease eradicated. The source of this disease was not confirmed; however, individuals on the Utah facility had a history of

traveling to countries where this disease was enzootic and may have brought the virus back on their clothing. The third outbreak occurred in a zoo in New York State. The veterinarian for the zoo suspected RHD and immediate action kept the disease from spreading from the zoo. The source of this outbreak is thought to be imported rabbit meat.<sup>1</sup>

### Conclusion

RHD is a disease with a potentially devastating impact on the rabbit industry in countries where this disease has previously been excluded. As the economy becomes increasingly global and rabbit products from RHD-infected countries are imported into RHD-free countries, the chance for outbreaks increases. Veterinarians are the first line of defense against RHD and are vital to its control. If RHD is suspected at your clinic, you should immediately contact local or national regulatory authorities.<sup>9</sup>

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