

RABBIT HAEMORRHAGIC DISEASE

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AETIOLOGY

Classification of the causative agent

Family Caliciviridae, Genus *Lagovirus*, Rabbit haemorrhagic disease virus (RHDV)

RHDV was identified in 1984 as the agent of a highly contagious, acute and fatal disease of rabbits (RHD). Rabbit lagoviruses consist of pathogenic viruses (RHDVs) and non-pathogenic viruses (RCVs), related but genetically divergent. Phylogenetic analyses of pathogenic RHDV strains indicate the existence of three distinct groups: the “classic RHDV” with the genogroups G1–G5 isolated from 1984 onwards, the antigenic variant RHDVa/G6 identified in 1996, and RHDV2 identified in 2010. The RHDV and RHDVa are phylogenetically related and their capsid protein (VP60) differs in nucleotide diversity from RHDV2 by more than 15%. RHDV2 was first identified in France on 2010, and since then has spread throughout Europe, replacing the circulating RHDV/RHDVa strains in most European countries. The available data (see below) suggest that RHDV2 is a newly emerged virus of unknown origin. Its antigenic profile is quite different from that of RHDV, to such an extent that it could be considered a distinct serotype. The provisional name RHDV2 therefore seems more appropriate than RHDVb, which is used by some authors. In addition to RHDV, RCVs have been identified, both in commercial and wild rabbits, that are genetically related to RHDV to varying degrees. Among these RCVs, those most closely genetically related to RHDV (identified in several European rabbit farms) induce a good level of cross-protection towards RHD. Other RCVs genetically less related to RHDV have been identified in Australian wild rabbit populations, and infected rabbits showed a very limited degree of protection, if any, when challenged with RHDV.

A similar disease termed European brown hare syndrome (EBHS) has been described mainly in the brown hare (*Lepus europaeus*) since 1970–80. The aetiological agent (EBHSV) is a lagovirus genetically and antigenically related to the RHDV. However, RHDV and EBHSV, in spite of their almost contemporaneous identification but in different geographical areas, represent two viral species with non-overlapping host ranges.

Resistance to physical and chemical action

The following characteristics were ascertained for RHDV/RHDVa, but have yet to be formally confirmed for RHDV2.

- Temperature: Survives heat of 50°C for 1 hour, and freeze–thaw cycles.
- pH: Stable at pH 4.5–10.5. Survives pH 3.0 but inactivated at pH >12.
- Chemicals: Inactivated with sodium hydroxide (1%) or formalin (1–2%). OIE *Terrestrial Animal Health Code* recommends formalin (3%) for disinfecting pelts. Treatment with 1.0–1.4% formaldehyde or 0.2–0.5% beta-propiolactone at 4°C inactivates the virus but does not reduce its immunogenicity and is therefore indicated for the production of vaccines.
- Disinfectants: Other suggested disinfectants include substituted phenolics (e.g. 2% One-stroke Environ®) and 0.5% sodium hypochlorite. Viral infectivity is not reduced by ether or chloroform and trypsin.
- Survival: RHDV and EBHSV are very resistant to inactivation, particularly when protected by organic material. Virus may persist in chilled or frozen rabbit meat, as well as in decomposing carcasses in the environment, for months. It is protected within tissues, and can survive >7 months in organ suspensions stored at 4°C, at least 3 months in the dried state on cloth at room temperature, for up to 20 days at 22°C in decomposing rabbit carcasses and at least 2 days at 60°C in an organ suspension and the dried state.

EPIDEMIOLOGY

RHD is an extremely contagious and fatal viral hepatitis of adult domesticated and wild rabbits belonging to the *Oryctolagus cuniculus* species. Young rabbits (less than 6–8 weeks old) are subclinically infected, developing a specific humoral response. Severe losses are common in unvaccinated animals, and in intensive farms a variable proportion of rabbits may die according to the type of virus. In fact, the virulent

RHDV/RHDVa may cause death of most or all the rabbits (80–90% lethality) whereas a variable rate of mortality is observed in rabbits infected by RHDV2 (from 5 to 70%). This disease, independently from the causative strain, has also caused dramatic declines in some wild rabbit populations, particularly when it is first introduced. RHD spreads very readily.

Hosts

- RHD affects wild and domesticated members of the species *Oryctolagus cuniculus*, the European rabbit.
- Other rabbit species including cottontails (*Sylvilagus floridanus*), black-tailed jackrabbits (*Lepus californicus*) and volcano rabbits (*Romerolagus diazzi*) are not susceptible.
- Among hare species, European brown hares (*Lepus europaeus*) and other hare species (*L. timidus*, *L. corsicanus*, *L. capensis*) are not affected by RHDV/RHDVa classical strains. However, the recently emerged RHDV2 was shown to be able to infect and cause a RHDV-like disease in at least two species of hares, i.e. the Sardinian cape hare (*L. capensis* var *mediterraneus*) and the Italian hare (*L. corsicanus*).
- Among hare species, *Lepus europaeus*, *L. timidus* and *L. corsicanus*, but apparently not *L. granatensis*, *L. castroviejo* and *L. capensis*, are affected by a disease caused by a different lagovirus (European brown hare syndrome – EBHS).
- EBHSV was also shown to occasionally infect and cause an EBHS-like disease in cottontails (*Sylvilagus floridanus*).
- Although rabbits of all ages can be infected, the infection is subclinical in animals younger than 6–8 weeks old if the causative agents are the classical RHDV/RHDVa. Conversely, RHDV2 causes disease and mortality even in young animals from 15–20 days old onwards.
- Virus replication has not been reported in other mammals, including rabbit predators, although seroconversion can occur. Inoculation of tissue suspensions from infected rabbits into 28 different vertebrate species other than rabbits failed to produce disease, and no replication of the virus was detected by reverse-transcription polymerase chain reaction (RT-PCR).

Transmission

- Direct contact with infected animals through the oral, nasal or conjunctival routes.
- Exposure to an infected carcass or hair from an infected animal.
- By means of fomites, including contaminated food, bedding and water.
- Experimental transmission by oral, nasal, subcutaneous, intramuscular, or intravenous routes.
- Importation of infected rabbit meat. This could be one of the main means of transmission of RHD to a new area. Meat contains high levels of virus-infected blood, which survives freezing well.
- Mechanical transmission. Flies and other insects are very efficient mechanical vectors; only a few virions are needed to infect a rabbit by the conjunctival route. Wild animals can transmit the virus mechanically. Although virus replication does not seem to occur in predators or scavengers, these animals (dogs, foxes, etc.) can excrete RHDV in faeces after eating infected rabbits.
- How long rabbits that have recovered from RHD may remain infectious remains unknown. A low level of serum antibodies is sufficient to protect rabbits from the disease, but infection at the intestinal level could occur with shedding of the virus in the faeces. High sensitivity PCR demonstrated a long-term persistence (up to 2 months) of the viral RNA in recovered or in vaccinated and then infected rabbits. Whether this is due to real and active persistent or latent RHDV infections is still to be demonstrated.

Sources of virus

- The liver has the highest virus titre, followed by the spleen and serum.
- Most or all excretions, including urine, faeces and respiratory secretions, are thought to contain virus.
- Rabbit meat contains virus by virtue of its high blood supply.

Occurrence

RHD was first reported in 1984 in China (People's Rep. of) and 2 years later in Europe. To date, RHD has been reported in over 40 countries in Africa, the Americas, Asia, Europe and Oceania and is endemic in most parts of the world. The RHDVa subtype has been identified in Europe since 1996–97 and is also reported in other continents (Asia, Australia and the Americas). RHDV2 was firstly detected on 2010 in France in wild and farmed rabbits and then it rapidly spread to Europe and Mediterranean basin causing significant losses in farmed and wild rabbits in many countries (to date [mid-2015] France, Germany, Italy, Malta, Norway, Portugal, Spain, Sweden, Tunisia and the United Kingdom).

For more recent, detailed information on the occurrence of this disease worldwide, see the OIE World Animal Health Information Database (WAHID) Interface [<http://www.oie.int/wahis/public.php?page=home>] or refer to the latest issues of the World Animal Health and the OIE *Bulletin*.

DIAGNOSIS

- A presumptive diagnosis can be made in an unvaccinated rabbitry when there are multiple cases of sudden death following a short period of lethargy and fever, and characteristic hepatic necrosis and haemorrhages are visible at necropsy
- A field diagnosis is more difficult when there are few rabbits on the premises, rabbits are relatively isolated, as in research colonies, or the rabbitries are partially vaccinated or vaccination is only partially protective, such as in the case of infection with RHDV2 of premises vaccinated against RHDV/RHDVa. The clinical manifestations have been described mainly in the acute infection (nervous and respiratory signs, apathy and anorexia). Clear and specific lesions, both gross and microscopic, are present. There is primary liver necrosis and a massive disseminated intravascular coagulopathy in all organs and tissues. The most severe lesions are in the liver, trachea and lungs. Petechiae are evident in almost all organs and are accompanied by poor blood coagulation. The incubation period of classical RHDV/RHDVa infection is 1–3 days, and death usually occurs 12–36 hours after the onset of fever. The disease is characterised by a high morbidity (almost 100%) and a mortality rate that usually ranges between 70 and 90%. The highest morbidity and mortality rates are seen in adult rabbits from naïve populations. Young rabbits less than 6–8 weeks old are less likely to become ill or die. Rabbits 4 weeks old and younger are unaffected. The age-related resistance in very young rabbits is still poorly understood. Surviving rabbits develop immunity and become fully resistant to related strains of RHDV but not to RHDV2, for which immunity is only partially protective. The disease caused by RHDV2 has typical features different from those of “classical” RHD. The mortality rate is lower but highly variable (5–70%) with an average mortality of 20% in experimentally infected rabbits; death could occur in non-vaccinated fattening rabbits and in lactating rabbits from 15 days of age onwards and the course of the diseases is usually longer (3–5 days), with more rabbits showing subacute-chronic signs and lesions.
- In wild rabbits, outbreaks can be seasonal. In some populations, they have been associated with the breeding season.
- The morbidity and mortality rates vary among populations. In Europe, RHD has caused dramatic declines in wild rabbit populations in France, Portugal and Spain, but wild rabbits in the United Kingdom and some other Northern European countries have been less severely affected. Such different evolution is most probably related to the circulation and presence in wild rabbits of non-virulent RHDV-like strains, which may induce variable levels of cross protection within each population.

Clinical diagnosis

While the clinical evolution of the disease can be peracute, acute, subacute or chronic, clinical manifestations have been described mainly in the acute infection, as there are usually no clinical signs of disease in the peracute form, and the subacute form is characterised by similar but milder signs. The incubation period varies between 1 and 5 days depending on the type of causative agent, and death may occur 12–36 hours after the onset of fever (>40°C). During this phase, various signs can be observed, such as anorexia, apathy, dullness, prostration, nervous signs (convulsion, ataxia, paralysis, opisthotonos, paddling), groans and cries, respiratory signs (dyspnoea, frothy and bloody nasal discharge), and cyanosis of mucous membranes. During an outbreak, a certain number of rabbits (5–10% in the case of RHDV/RHDVa and significantly more if the infection is caused by RHDV2) may show a chronic or subclinical evolution of the disease, which is characterised by severe and generalised jaundice, loss of

weight and lethargy. These animals often die 1–2 weeks later, probably due to liver dysfunction, but some rabbits survive showing very high seroconversion.

Lesions

Due to the rapid course of this disease, the animals are usually found in good condition after death. Gross pathological lesions are variable and may be subtle and include circulatory and degenerative disorders. Liver necrosis and splenomegaly are the primary lesions. The liver appears yellowish-brown in colour, brittle and degenerated, with a marked lobular pattern. The tracheal mucosa is hyperaemic, containing abundant frothy fluid, and the lungs are oedematous and congested. The spleen is engorged, with rounded edges and enlarged (splenomegaly). The presence of clotted blood in blood vessels is due to disseminated intravascular coagulation (DIC). Such massive coagulopathy is usually the cause of haemorrhages in a variety of organs and sudden death. In subacute and chronic disease, an icteric discoloration of the ears, conjunctiva and subcutis is clearly evident.

Differential diagnosis

- septicaemic pasteurellosis
- poisoning
- heat exhaustion
- other causes of severe septicaemia with secondary DIC

Laboratory diagnosis

Samples

- Fresh liver, spleen, and blood
- Formalin-fixed samples of liver, spleen, lung, kidney and other organs

The liver contains the highest viral titre (from 10_3 LD₅₀ [50% lethal dose] to $10_{6.5}$ LD₅₀/ml of 10% homogenate) in acute or peracute disease, and is the organ of choice for viral identification of both RHDV and EBHSV. Serum and spleen may also contain high levels of virus. In rabbits with chronic or subacute disease, RHDV may be easier to find in the spleen than the liver. RT-PCR can detect viral RNA in a many organs, urine, faeces or serum. Serum should be collected for serology.

Procedures

Identification of the agent

- Haemagglutination (HA) test: first test used for routine laboratory diagnosis of RHD, but it is less sensitive and specific than other assays and requires human type O red blood cells – now replaced by virus detection enzyme-linked immunosorbent assay (ELISA). The HA test is performed on 10% tissue homogenate of liver or spleen. HA may give false negative results: a) in the chronic form of RHD, i.e. in rabbits that die from 4 to 7 days post-infection onwards; b) with some isolates that have lost the ability to haemagglutinate.
- Electron microscopy: negative-staining EM, immuno-EM, and immunogold EM. For diagnostic purposes and when other methods give doubtful results, the best EM method is an immuno-EM technique (IEM) using monoclonal antibodies (MAbs) or specific hyperimmune sera. This induces clumping of viral particles into aggregates that are quickly and easily identified by EM.
- Virus detection ELISA: performed on 10% liver homogenate. An MAb-based ELISA developed at the OIE Reference Laboratory for RHD enables the subtyping of RHDV isolates. The MAb panel has been improved by including specific MAbs produced towards RHDV2.
- Immunostaining: tissues fixed in 10% buffered formalin and embedded in paraffin can be immunostained using an avidin–biotin complex (ABC) peroxidase method with intense staining mainly in periportal areas of the liver, macrophages of the lungs, spleen and lymph nodes, and mesangial cells of the kidney. Tissue cryosections of liver, spleen and kidney fixed in methanol can also be directly immunostained for specific fluorescence.
- Western blotting: used when HA or ELISA are inconclusive.
- RT-PCR: ideal rapid diagnostic test for RHD because of its high sensitivity. This method is performed on organ specimens (optimally liver), urine, faeces and sera. Different sets of

primers may be used for RT-PCR, of which some allow the identification of all RHDV viruses. Other protocols were set up employing specific primers for the diagnosis of RHDV2. Similar RT-PCR methods have been used to identify the nonpathogenic RCV and EBHSV. RT-PCR is not strictly necessary for routine diagnosis, but it is more sensitive (10^5 -fold more sensitive than ELISA), convenient and rapid than other tests. Considering its high sensitivity and the complicated epidemiological picture of rabbit caliciviruses, PCR results require a careful interpretation. A best choice is real-time PCR that, allowing a viral quantification (in a 10% liver homogenate there are between 10^6 and 10^9 copies of genome per ml), permits an easy diagnosis and the identification of acute cases.

- *In-situ* hybridisation. highly sensitive and can detect RHDV as early as 6–8 hours after infection, but this technique is mainly used in research.
- Never grown in cell cultures. Rabbit inoculation remains the only way of isolating, propagating and titrating the infectivity of RHDV. Not a practical method for the routine diagnosis of RHD, and should be considered only when all other methods give inconclusive results. When this occurs, the rabbits involved must be fully susceptible to the virus, i.e. they should be over 2 months old and have no RHDV antibodies (see serological methods).

Serological tests

Characterisation and titration of specific antibodies arising from natural infection or from immunisation are performed using the haemagglutination inhibition test or indirect or competitive ELISAs. Antibodies may be detected experimentally 4–6 days post-inoculation. Humoral response has great importance in protecting animals from RHD.

At least three basic techniques are applied for the serological diagnosis of RHDV:

- Haemagglutination inhibition (HI).
- Indirect ELISA (I-ELISA)
- Competitive ELISA (C-ELISA)

Each of these methods has advantages and disadvantages. With respect to the availability of reagents HI is the most convenient method, followed by the I-ELISA and C-ELISA, respectively. However, both ELISAs are quicker and easier than HI, particularly when a large number of samples are tested. The specificity of the C-ELISA is markedly higher than the other two methods. However, considering the antigenic difference existing between the “classical” RHDV/RHDVa strains and RHDV2, two different antibody responses following homologous vaccination or infection could be qualitatively and quantitatively detected using protocols employing specific sets of MAbs recognising the respective viruses. Indirect ELISA (RHDV directly adsorbed onto the solid phase of the plate) is the test of choice for detecting cross-reactive lagovirus antibodies induced in rabbit by non-pathogenic calicivirus and as well in hares by EBHSV.

The isotype-specific ELISAs (detecting IgM, IgA and IgG) have been very useful for epidemiological studies both in commercial rabbits and wild populations. Similarly to C-ELISA, two sets of anti-isotype-specific ELISAs were developed and can be used to determine specific Ig response to RHDV/RHDVa and RHDV2, respectively.

For more detailed information regarding laboratory diagnostic methodologies please refer to Chapter 2.6.2 Rabbit haemorrhagic disease in the latest edition of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading “Diagnostic Techniques”.

PREVENTION AND CONTROL

Sanitary prophylaxis

- In uninfected countries prevention of introduction is the optimal control method. Restrictions are placed on the importation of rabbits, meat and angora wool from endemic areas.
- In an outbreak, strict quarantine is necessary.
- In those regions where wild rabbits belong to non-susceptible species (i.e. *Sylvilagus* spp. and *Romerolagus* spp.), control through stamping out is possible.
- RHDV is extremely contagious; it can be transmitted on fomites and by insects, birds and scavenging mammals. Eradication can therefore be accomplished by depopulation, disinfection, surveillance and quarantines.
- Sentinel seronegative rabbits can be used on treated premises to monitor for persistence of viral circulation.

- In regions where RHDV circulates in wild rabbits (*Oryctolagus cuniculus*), eradication is not feasible. Instead, this disease is controlled in domesticated rabbits with biosecurity measures including sanitation and disinfection, the maintenance of closed colonies, and vaccination.
- Vaccination may be limited to breeding animals if RHD has not been reported on a farm, but all animals should be vaccinated if an outbreak has occurred. Even with strict sanitation and other control measures, the likelihood of reinfection is high after an outbreak, due to the possible persistence of the virus in the environment.
- The level of cross protection induced by vaccination with RHDV/RHDVa vaccines against RHDV2 is poor and does not prevent infection and losses due to clinical disease. Therefore combined vaccination with both antigenic types or the use of a vaccine homologous to the RHDV strain identified during the epizootics or the outbreak are highly advisable.

Medical prophylaxis

- Immunity is solid following natural infection. However, because the virus is hardy in the environment and the disease becomes endemic in populations, it is probable that recovered animals are repeatedly exposed to the virus to re-boost immunity.
- In endemic areas where control is desirable, a vaccine consisting of clarified liver suspension that has been inactivated and adjuvanted is used. This inactivated vaccine is administered initially twice at a 2-week interval, and then annually. In many countries, different types of vaccines, including either RHDV or RHDVa, are commercially available and commonly used. Vaccines specific for the “new” RHDV2 have been registered in two countries (France and Spain) but they are also prepared and employed as autovaccines.
- Vaccinated animals quickly produce strong systemic immunity but a low, if any, mucosal immunity (no IgA production). As a consequence, animals are fully protected from the disease but not from infection that primarily occurs at the intestinal level.
- It is advisable to vaccinate only breeding stock; vaccination of meat animals is not necessary if disease has not recently occurred on the farm.
- A recombinant vaccine (a modified myxomavirus expressing the main RHDV protein) administered by the parenteral route has been developed and registered and is commercially available.

For more detailed information regarding vaccines, please refer to Chapter 2.6.2 Rabbit haemorrhagic disease in the latest edition of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading “Requirements for Vaccines”.

For more detailed information regarding safe international trade in terrestrial animals and their products, please refer to the latest edition of the OIE *Terrestrial Animal Health Code*.

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The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Scientific and Technical Department (scientific.dept@oie.int). Last updated July 2015.