Rabbit Hemorrhagic Disease: A Brief Summary

Rabbit hemorrhagic Disease (RHD) is a usually fatal disease affecting almost exclusively lagomorphs caused by the Rabbit Hemorrhagic Disease Viruses (RHDV). While initial outbreaks of RHDV-1 occurred in Europe and Asia, RHDV-2 has emerged and spread across the globe within the span of the last 10 years.[3,7] RHDV-2 has resulted in major outbreaks of RHD in wild and domestic rabbits in Washington State and the North American Southwest (USA and Mexico) since 2020 and is a reportable Foreign Animal Disease (FAD) in the US.

Epidemiology and Outbreak Spread

RDHV viruses are lagoviruses in the Family Calciciviridae.[4] These viruses are a single stranded positive sense RNA virus with a non-enveloped capsid consisting of major capsid protein VP-60.[4] The main pathogenic lagoviruses are RHDV-1/RHDV-1a, RHDV-2, and European Brown Hare Virus.[4] While RHDV-1/RHDV-1a are very species specific restricted to infecting European Cottontails and their domesticated versions (Oryctolagus cuniculus), RHDV-2 has been documented to cause disease in a wider range of species including the Genera Lepus and Sylviagus.[3,4,7] One recent study documented that RHDV-2 had resulted in morbidity and mortality of Eurasian badgers.[1] Several non-pathogenic and moderately pathogenic rabbit caliciviruses have been reported in Europe, Australia, Asia and Michigan.[3,10]

The first known outbreak of RHD occurred in China in 1984 with RHDV-1.[3] From this initial outbreak, RHDV-1 spread rapidly through Asia and Europe, becoming endemic.[3] RHDV-1 was purposefully introduced to Australia to control rabbit overpopulation, but largely remained out of the Americas except for sporadic outbreaks.[6]

RHDV-2 was first reported in France in 2010 and has spread to Europe, Asia, Cuba, Africa, Canada, Uruguay, US, Mexico, Australia, Middle East.[7,9] RHDV-2 may be replacing RHDV-1 in endemic regions.[9] Unlike RHDV-1, RHDV-2 causes disease and high viremia in kits under 11 weeks.[3,7] RHDV-2 has had variable mortalities reported in the field (20-90%) and in laboratory settings (0-100%).[7] This variance may be due the emergence of numerous strains.7 The genetic variability of RHDV-2 might be due to recombination events occurring with the non-pathogenic caliciviruses.[7,10]

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Clinical Presentation

RHDV is a non-enveloped virus that is transmitted via the oral-fecal route is extremely stable in the environment.[3,8] RHDV remains infective for a period up to 12 weeks, especially in decomposing carcasses.[8] RHDV-2 has proven stable and infective from 4-60 degrees Celsius, albeit for varying lengths of time.[8] Transmission can occur from direct contact, contaminated fomites, and vectors (blood-feeding insects).[3,8]

RHDV replicates mainly in the liver, with viral replication also documented in the spleen, lung, and blood mononuclear cells.[3,7] The disease is characterized by a necrotizing hepatitis that leads to Disseminated Intravascular Coagulation (DIC) and death.[3,7]

Both RHDV-1 and RHDV-2 present with similar signs, with peracute death the most reported symptom.[3,5] Other include conjunctivitis, dyspnea, anorexia, ataxia, paralysis, ocular hemorrhage, epistaxis, pyrexia progressing to hypothermia, weight loss (common in RHDV-2), and terminal seizures.[3,7] While epistaxis secondary to DIC has been noted with both diseases, it is not a reliable predictor whether a peracute death is caused by RHD.

A chronic form of RHDV-1 has been occasionally reported with disease progression averaging 1-2 weeks and milder clinical signs before death occurs.[3] Viral incubation ranges from 1-3 days with death within 12-36 hours after onset of symptoms.[3,7] Death may be swifter with RHDV-2 infected kits.[7]

Diagnostics

At the current time, all diagnostics are performed post-mortem. This is largely due to the peracute nature of the disease progression. The gold standard of diagnosis is RT-qPCR from liver tissue designed to target conserved sections of the VP-60 gene.[5]

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Disease Prevention

Vaccination is the mainstay of disease prevention.[3] Two killed virus vaccines approved for use in Europe, Eravac and Filivac, but are not USDA approved.[3] US veterinarians in affected states have received special importation privileges for these vaccines for emergency use only. Importation of the European vaccines will cease when the US RHDV-2 vaccine receives USDA approval.

Medgene Labs, based in South Dakota, have recently received emergency use approval for their recombinant subunit protein RHDV-2 vaccine. This is a recombinant vaccine that uses a subunit protein of RHDV2 produced in a proprietary Baculovirus expression system, by-passing the difficulties of in vitro cultivation associated with RHDV-2. A summary of the efficacy of their challenge study is summarized in **Table 1.1**. The vaccine is a two-vaccine series for all naïve rabbits and with annual revaccination thereafter.

Challenge Study Results
Table 1.1

	Mortality
Naïve	69%
Vaccinated	0%

*P=0.0017

Conclusion

RHD is emerging infectious rabbit disease that is rapidly spreading across the globe. Due to the peracute nature of clinical disease progression, identifying and managing disease outbreaks will continue to be a challenge. Continued study of this rapidly evolving deadly disease is warranted, with focus on efficacious vaccine development. Due to the high rate of mutation RHDV-2 exhibits, an easily adaptable vaccine is required. Killed virus vaccines require new vaccine development for vaccine resistant strains of RHDV-2. The recombinant subunit protein Medgene vaccine is the most advantageous of the currently available vaccines due to the ease in modifying target proteins.

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