RABBIT HEMORRHAGIC DISEASE STANDARD OPERATING PROCEDURES: 1. OVERVIEW OF ETIOLOGY AND ECOLOGY

FAD PReP

Foreign Animal Disease Preparedness & Response Plan

USDA

United States Department of Agriculture

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The Foreign Animal Disease Preparedness and Response Plan (FAD PReP) Standard Operating Procedures (SOPs) provide operational guidance for responding to an animal health emergency in the United States.

These draft SOPs are under ongoing review. This document was last updated in **October 2013.** Please send questions or comments to:

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Rabbit Hemorrhagic Disease (RHD)

Etiology & Ecology Quick Summary

Disease

Rabbit hemorrhagic disease, rabbit viral sudden death, X-disease of rabbits, hemorrhagic septicemia syndrome in rabbits, viral hemorrhagic pneumonia in rabbits, rabbit viral hemorrhagic disease.

Mortality & Morbidity

High, morbidity and mortality rates can be over 90 percent.

Susceptible Species

Domestic and wild European rabbits (*Oryctolagus cuniculus*), also called common rabbits.

Zoonotic Potential?

Not a threat to public health.

Transmission

Infected rabbits shed the virus in excretions and secretions. RHD is readily spread by direct contact, fomites, mechanical vectors, pelts, and infected rabbit meat and carcasses.

Persistence in the Environment

Highly stable, especially when ensconced in organic material.

Animal Products and By-Products

RHD is extremely hardy in rabbit meat; it may survive in chilled, frozen, or decomposing meat for months.

1.1 Introduction

Rabbit hemorrhagic disease (RHD) is a highly contagious viral disease that affects European rabbits (*Oryctolagus cuciculus*). It is caused by the rabbit hemorrhagic disease virus (RHDV), a Calicivirus. Acute infection is characterized by nervous and respiratory signs, lethargy, and anorexia, with the presence of gross and microscopic lesions. The disease tends to progress rapidly, and death is a frequent outcome.

Since its discovery in China in 1984, the spread of RHD has caused hundreds of millions of fatalities in domestic and wild European rabbits (also called the common rabbit). This species is widely raised for commercial purposes and is a commonly known lagomorph in the wild throughout its native and introduced range (extending over Europe, much of Australia, and, to a limited extent, northern Africa and South America). Wild European rabbits are invasive to Australia and New Zealand, and RHD was inadvertently introduced there while the virus was being tested as a tool to control their overpopulation.[1]

1.1.1 Goals

As a preparedness goal, the Animal and Plant Health Inspection Service (APHIS) will provide etiology and ecology summaries for RHD and update these summaries at regular intervals.

As a response goal, the Unified Command and stakeholders will have a common set of etiology and ecology definitions and descriptions, to ensure proper understanding of RHD when establishing or revising goals, objectives, strategies, and procedures.

1.1.2 Further Information

This document is intended to be an overview of RHD. Additional resources, as well as references cited in this SOP, are listed in Attachment 1.A.

Foreign Animal Disease Preparedness and Response Plan (FAD PReP) documents are on the Animal and Plant Health Inspection Service (APHIS) Intranet (http://inside.aphis.usda.gov/vs/em/fadprep.shtml, for APHIS employees), and on a public website (http://www.aphis.usda.gov/animal_health/emergency_management/).

1.2 Purpose

This document provides responders and stakeholders with a common understanding of the disease agent.

1.3 Etiology

1.3.1 Name

This disease is most commonly called rabbit hemorrhagic disease. Other names include rabbit viral sudden death, X-Disease of Rabbits, hemorrhagic septicemia syndrome in rabbits, viral

[1] Kovaliski J. 1998. Monitoring the spread of rabbit hemorrhagic disease virus as a new biological agent for control of wild European rabbits in Australia. *Journal of Wildlife Diseases*. 34(8): 421-428.

hemorrhagic pneumonia in rabbits, or rabbit viral hemorrhagic disease.[2]

1.3.2 Virus Characteristics

According to the International Committee on Taxonomy of Viruses, this disease has the following characteristics:[3]

- Family: Caliciviridae
- Genera: *Lagovirus*
- Baltimore Classification: Group IV (+) ssRNA.

1.3.3 Morphology

RHD is caused by a non-enveloped, single-stranded ribonucleic acid (RNA) virus approximately 32-44 nm in diameter. The virus particle's capsid has icosahedral symmetry and is comprised of one capsid protein, VP60, whose P domain controls binding to host tissue. [4] The P2 subdomian exhibits the most genetic variation. In addition to its genomic RNA, the virus also expresses subgenomic RNA in the form of extra structural proteins that are needed in the later stages of infection.[5]

1.3.4 RHD Serotypes and Strains

There is only one known serotype of RHD with two main subtypes: RHDV and its antigenic variant, RHDVa.[6] Experimental evidence suggests that vaccines against RHDV are effective against RHDVa; it is unknown whether this is true for farmed and wild rabbits, as levels of immunological protection are highly variable.[7] This variability is likely due to avirulent strains of viruses that are similar to RHDV and have been found to circulate in some regions, such as Northern Europe, leading to cross protection in wild rabbits.[8]

1.4 Ecology

1.4.1 General Overview

As seen in Figure 1-1, RHD is endemic in Australia, New Zealand, Cuba, parts of Asia and

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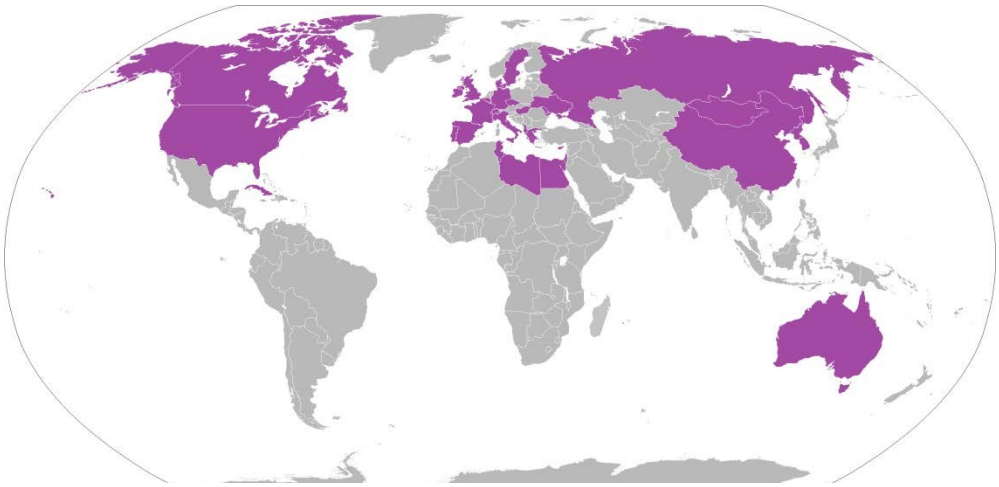
[2] Mitro S, Krauss H. 1993. Rabbit hemorrhagic disease: a review with reference to its epizooitology. *European Journal of Epidemiology*.9(1): 70-78.
[3] International Committee on Taxonomy of Viruses. 2012. ICTV Taxonomy History for Rabbit hemorrhagic disease virus. Available at http://ictvonline.org (accessed July 2013).
[4] Wang X, Xu F, Liu J, Gao B, Liu Y, Zhai Y, Ma J, Zhang K, Baker TS, Schulten K, Zheng D, Pang H, Sun F. 2013." Atomic model of rabbit hemorrhagic disease virus by cryo-electron microscopy and crystallography". *PLoS Pathogens.* 9(1): e1003132.
[5] Abrantes J, van der Loo W, Le Pendu J, Esteves PJ. 2012. Rabbit haemorrhagic disease (RHD) and rabbit haemorrhagic disease virus (RHDV): a review. *Veterinary Research*. 43:12.
[6] Center for Food Security and Public Health, Iowa State University (CFSPH). 2006. "Rabbit Hemorrhagic Disease" *Technical Factsheet.* www.cfsph.iastate.edu.
[7] Capucci L, Fallacara F, Grazioli S, Lavazza A, Paciiarini ML, Brocchi E. 1998. A further step in the evolution of rabbit hemorrhagic disease virus: the appearance of the first consistent antigenic variant. *Virus Research*. 58:115-126.
[8] World Organization for Animal Health (OIE). 2009. Rabbit Haemorrhagic Disease. *OIE Technical Disease Card*. http://www.oie.int.

Africa, and much of Europe. Outbreaks have also occurred in the Middle East, affecting only domestic rabbits. While present in North America, RHD was eradicated in Mexico since a large outbreak from 1980 to 1991; cases appear intermittently in the United States (Iowa, 2000; Utah, Illinois, and New York, 2001; Indiana, 2005; Maryland, 2008; Minnesota, 2010) and, most recently, in Canada (2011).[9,10]

Figure 1-1. Distribution of RHD, 2007-2012



Source: World Animal Health Information Database (WAHID), RHD Disease Timeline, 2013

1.4.2 Susceptible Species

Both wild and domesticated European rabbits, of the species *Oryctolagus cuniculus*, are susceptible to RHD. This species is the only rabbit to have been widely domesticated, and all types of commercially bred or farmed rabbits in the United States are genetically linked to it. Other rabbits and hares are not affected by RHD, including the common American wildlife species known as the cottontail, the snowshoe hare, and the black-tail jackrabbit.[11] However, there are several species of hares that are susceptible to a similar Calicivirus disease known as European brown hare syndrome (EBHS).[12]

1.4.3 Introduction and Transmission of RHDV

RHD is highly contagious. Transmission can occur through direct contact, exposure to infected carcasses or animal product, fomites, and mechanical vectors. World-wide spread of RHDV can

[9] CFSPH. 2006. "Rabbit Hemorrhagic Disease" *Technical Factsheet.* www.cfsph.iastate.edu.
[10] Embury-Hyatt C, Postey R, Hisanaga T, Burton L, Hooper-McGrevy K, McIntyre L, Millar K, Pasick J. 2012. The first reported case of rabbit hemorrhagic disease in Canada. *Canadian Veterinary Journal*. 53: 998-1002.
[11] Campagnolo ER, Ernst MJ, Berninger ML, Gregg DA, Shumaker TJ, Boghossian AM. 2003. Outbreak of rabbit hemorrhagic disease in domestic lagomorphs. *Journal of the American Veterinary Medical Association*. 223: 1151-1155.
[12] OIE, 2009

be partially attributed to international trade of rabbits and rabbit meat.[13]

1.4.3.1 Live Animals and Virus Shedding

RHDV may be transmitted through oral, nasal, parenteral, or conjunctival routes. The virus is shed in feces and other excretions; contact with excreted virus is the main method of RHD transmission.[14] Aerosolized virus may also spread infection, particularly among animals in kept in close proximity.[15]

1.4.3.2 Fomite Transmission

RHDV is easily spread through contaminated food, bedding, water, clothing, cages, and equipment. Transmission via fomites and surroundings are of special concern due to the stability of the virus on organic materials and the low infectious dose.[16]

1.4.3.3 Mechanical Vectors

Insects readily transmit virus over short distances and, along with other non-lagomorph wildlife, can serve as mechanical vectors; particularly, predators or scavengers that consume infected rabbits do not replicate the virus but will excrete it in feces. Personnel in contact with infected rabbits and/or excretions can also be mechanical vectors. [17]

1.4.3.4 Wildlife

Wild European rabbits are highly susceptible to RHD, and concurrent observations of RHD infections at rabbit farms along with a decline in wild rabbit populations have been made.[18] Transmission from wild to domesticated rabbits has been suggested in several past incidents, and the movement of wild rabbits carries a great risk of disease spread. Predatory wildlife can also introduce the virus to wild colonies. RHD outbreaks may follow a seasonal pattern and/or be associated with the breeding season in wild populations. [19]

1.4.4 Incubation Period

The incubation period for RHD ranges from 16 to 48 hours. Fatalities usually occur 2 to 3 days after infection. The infectious period may last up to one month.[20]

1.4.4.1 Infectious Dose

Susceptibility to RHDV varies among animals, populations, and geography, and the minimum infectious dose also varies by route of transmission. It is generally thought that a very low dose is

[13] Chasey D. 1997. Rabbit haemorrhagic disease: the new scourge of *Oryctolagus cuniculus*. *Laboratory Animals.*31: 33-44.
[14] Abrantes et al., 2012.
[15] Campagnolo et al., 2003.
[16] Chasey, 1997.
[17] CFSPH, 2006.
[18] Mitro and Krauss, 1993.
[19] Chasey, 1997.
[20] CFSPH, 2006.

able to cause infection in many situations– for example, conjunctival transmission of RHDV is possible by only a few virus particles.[21]

1.4.5 Morbidity and Mortality

The morbidity and mortality of RHD is often very high, in part due to the rapid progression of disease. Rates of morbidity vary from 30 to 80 percent, and mortality can range from 40 to 100 percent.[22] Morbidity rates in domesticated animals are likely to be higher if rabbits are housed in groups.[23]

1.4.5.1 Clinical Signs

Infection with RHDV takes one of four forms:

- Peracute disease–Death often occurs quickly, and clinical signs will be absent or rare.[24]
- Acute disease– Rabbits may present with a variety of symptoms, which commonly include shortness of breath, epistaxis, loss of coordination, depression, anorexia, and apathy. There also may be observable hemorrhages in the eye, blood in feces, icteric skin coloration, and internal signs such as anemia, leukocytosis, and coagulation disorders. With this disease form, death typically occurs in 1 to 3 days.
- Subacute–Generally mild and may cause affected rabbits to survive minor clinical symptoms and develop antibodies.[25]

Domestic rabbits typically experience peracute or acute disease, but chronic illness, where jaundice, weight loss and lethargy give way to death after a few weeks, is also possible in a small percentage of infected animals.[26] After presenting with fever, nervous signs, such as convulsion, paddling, or paralysis, may occur along with groans and cries in the acute form. Infection with RHDV also causes lesions throughout internal organs and tissues, particularly on the liver, lungs and heart, resulting in the characteristic hemorrhaging and fatally rapid progression of the disease.[27, 28] Rabbits can become infected with RHD at any age, but young rabbits (less than 40 to 50 days old) experience only subclinical disease.

Signs of RHD may be similar to septicemic pasteurellosis, severe septicemia from other causes presenting with secondary disseminated intravascular coagulation, poisoning, and heat exhaustion. [29]

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[21] CFSPH, 2006.
[22] OIE, 2009.
[23] Mitro and Krauss, 1993.
[24] Belz K. 2004. Rabbit hemorrhagic disease. *Seminars in Avian and Exotic Pet Medicine.*13(2):100-104.
[25] Mitro and Krauss, 1993.
[26] CFSPH, 2006.
[27] Lavassa A, Capucci L. 2008. How many caliciviruses are there in rabbits? A review on RHDV and correlated viruses. In: *Lagomorph Biology: Evolution, Ecology and Conservation.* Springer-Verlag Berlin: 263-278.
[28] Abrantes et al., 2012.
[29] OIE, 2009.

1.5 Environmental Persistence of RHDV

RHDV is highly stable and resistant to inactivation, especially when it is within tissue. The virus can persist in conditions of low pH (under 3.0) and through freeze-thaw cycles.[30] Table 1-1 describes RHDV persistence under various conditions.

Table 1-1. Resistance of RHDV to Physical and Chemical Action

Action	Resistance
Temperature	Survives heat of 50ºC for an hour and freeze-thaw cycles.
pH	Stable at pH 4.5–10.5. Survives pH 3.0 but inactivated at pH >12.
Disinfectants	Inactivated by sodium hydroxide (1%) or formalin (1-2%). Treatment with 1.0–1.4% formaldehyde or 0.2–0.5% beta-propiolactone at 4ºC inactivates the virus but does not reduce immunogenicity and is therefore indicated for the production of vaccines. 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 4ºC, at least 3 months in the dried state on cloth at room temperature, for up to 20 days at 22ºC in decomposing rabbit carcasses, and at least 2 days at 60ºC in an organ suspension and in the dried state.

Source: OIE Technical Disease Card for RHD, 2009.

1.5.1 Environmental Persistence of RHDV in Excretions and Surroundings

The virus can remain stable for 3 months when dried, but, exposed RHDV typically does not persist in excretions on surroundings longer than a few weeks and grows less viable over that time. It can be spread via contact with articles of infected rabbits' surroundings, such as food and bedding. [31]

1.5.2 Environmental Persistence of RHDV in Meat and Meat Products

Chilled, frozen, and decomposing rabbit meat can harbor RHDV for several months and presents a significant risk of introducing the disease during trade, as blood viral titers are particularly high.[32] There have been several cases of RHDV-contaminated rabbit meat spreading the disease, such as in Mexico where meat imported from China caused a widespread outbreak over several years.[33] Additionally, the lengthy persistence of infective RHDV in carcasses may provide a

[30] OIE, 2009.
[31] CFSPH, 2006.
[32] OIE, 2009.
[33] Belz, 2004.

reservoir of disease after outbreaks in the wild, as viable virus has been found in decaying tissue after 90 days outdoors.[34]

1.5.3 Environmental Persistence of FMDV in Fur and Pelts

The fur of an infected rabbit can be a source of RHDV transmission.[35] Pelt and hair trading among countries with an active fur industry may lead to further spread of the virus.[36]

1.6 RHD in the United States

RHD has been found in the United States as recently as 2010, and was detected in Canada in 2011.[37] Thus far, outbreaks have been controlled quickly through quarantine, depopulation, disease tracing, and cleaning and disinfection; however, rabbit losses have been in the thousands. An RHD vaccine exists, but it is not recommended for use where the disease is not widespread in wildlife, as it may hide signs of disease[38] and is not considered a practical response for such a rapidly spreading disease. After the Illinois outbreak of 2001, wild rabbit species native to the United States and found near outbreak sites were tested but did not harbor RHDV.[39] Strict biosecurity measures are recommended to prevent RHD from reaching susceptible animals. [40]

[34] Henning J, Meers J, Davies PR, Morris RS. 2004. Survival of rabbit hemorrhagic disease virus (RHDV) in the environment. *Epidemol. Infect.*133: 719-730.
[35] OIE, 2009.
[36] Mitro and Krauss, 1993.
[37] Embry-Hyatt et al., 2012.
[38] CFSPH, 2007.
[39] Campagnolo et al., 2003.
[40] OIE, 2009.

Attachment 1.A References and Selected Resources

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Mitro S, Krauss H. 1993. Rabbit hemorrhagic disease: a review with reference to its epizooitology. *European Journal of Epidemiology.*9(1): 70-78.

Wang X, Xu F, Liu J, Gao B, Liu Y, Zhai Y, Ma J, Zhang K, Baker TS, Schulten K, Zheng D, Pang H, Sun F. 2013. Atomic model of rabbit hemorrhagic disease virus by cryo-electron microscopy and crystallography. *PLoS Pathogens*. 9(1): e1003132.

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Attachment 1.B Abbreviations

APHIS	Animal and Plant Health Inspection Service
FAD PReP	Foreign Animal Disease Preparedness and Response Plan
RHD	rabbit hemorrhagic disease
RHDV	rabbit hemorrhagic disease virus
OIE	World Organization for Animal Health
NAHEMS	National Animal Health Emergency Management System
RNA	ribonucleic acid
SOP	standard operating procedure
TDD	telecommunications device for the deaf
USDA	United States Department of Agriculture