REVIEW ARTICLE

Rabbit haemorrhagic disease: the new scourge of *Oryctolagus cuniculus*

David Chasey
Department of Virology, Central Veterinary Laboratory, Addlestone, Surrey KT15 3NB, UK

Summary

A new, widespread and important disease of rabbits, rabbit haemorrhagic disease (RHD), is concisely reviewed and discussed. RHD is an acute, infectious condition of adult rabbits and morbidity and mortality, after a relatively short incubation period, can be very high. The disease appears typically as a necrotizing hepatitis with associated haemorrhaging, and death occurs as a result of generalized organ dysfunction. RHD is caused by a calicivirus, antigenically related to a similar virus found in brown hares but distinct from other known caliciviruses, and is spread to susceptible rabbits by a number of routes and vectors. The disease is easily identified and can be effectively controlled in commercial and domestic rabbit populations by slaughter and vaccination regimes. The occurrence of pre-existing cross-reacting antibody in a proportion of rabbits unchallenged by the disease implies the presence of non-pathogenic strains of the virus. This antibody protects against disease on subsequent exposure to RHD. Uniquely, pre-existing antibody does not occur in rabbits in Australia where, after accidental release, the virus is currently spreading rapidly.

Keywords Rabbit haemorrhagic disease; RHD calicivirus; lagomorph

Of the many known disease syndromes in wild and domestic mammals, myxomatosis in the European rabbit has been notorious for several decades. Within the last ten years or so, another infectious fatal rabbit disease has appeared in much of the northern hemisphere to rival myxomatosis in importance. This review aims to give a concise background to, and description of, the new disease with key references from the now extensive literature; further publications are listed in many of the papers quoted here, particularly the reviews by Kuttin *et al.* (1991), Mitro & Krauss (1993), Ohlinger *et al.* (1993) (in English) and Haas & Thiel (1993) (in German).

Rabbit haemorrhagic disease was unknown before 1984 when a group of commercially-bred Angoras was imported from Germany into the Jiangsu Province of the People's Republic of China (Liu *et al.* 1984). A contagious rapidly fatal disease appeared in these animals and initial descriptions were reported from China before the syndrome spread to, and became known in, Europe 2 years later. There is no account of the disease elsewhere prior to 1984, although it may have been observed previously in Germany (Patton 1989). The new disease was variously termed 'X-Disease of rabbits', 'rabbit viral sudden death', 'picornavirus haemorrhagic fever in rabbits', 'haemorrhagic septicaemia syndrome in rabbits', 'viral haemorrhagic pneumonia in rabbits' and 'infectious necrotic hepatitis of leporidae' but is now commonly referred to as 'RHD' or 'viral haemorrhagic disease of rabbits' (VHD). Exceptionally, Australia has termed the syndrome 'rabbit calicivirus disease' (RCD). This paper will refer to the disease as RHD.

Commercial rabbit production across the world is an important industry, particularly in Asia and central Europe where small scale rabbit husbandry is an integral part of the cultures. The highly contagious and fatal

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nature of RHD has had profound economic effects over a wide area which coupled with implications for conservational aspects has led to intensive international effort to understand and control the disease.

Geographical distribution

In addition to the original outbreak in China in 1984, RHD also occurred in Korea (Park *et al.* 1987). The disease then appeared in Italy in 1986 (Marcato *et al.* 1988) spreading to Russia and much of eastern, central and western Europe by 1991 (Arguello Villares *et al.* 1988, Morisse 1988, Anon 1989, Loliger *et al.* 1989, Allegranza *et al.* 1990, Nowotny *et al.* 1990, Peeters *et al.* 1990, Morisse *et al.* 1991, Rodak *et al.* 1991). RHD occurred on the Swedish island of Gotland in 1990 (Gavier-Widen 1993, Gavier-Widen & Morner 1993), and it reached the mainland in 1993 (Wiss 1993). The UK remained free of the disease until 1992 (Fuller *et al.* 1993), with outbreaks in the Channel Islands a year later (Chasey *et al.* 1994), and Ireland reported its first known cases in 1995 (Collery *et al.* 1995).

Several countries in north Africa and the Mediterranean have experienced RHD (Morisse *et al.* 1991), and although not confirmed it has probably been described in India (Sundaram *et al.* 1991). The disease has occurred on Reunion Island, in the Indian Ocean (Morisse *et al.* 1991), and there was an important outbreak in Mexico in 1988 (USDA 1989, Gregg *et al.* 1991, Juan Gay 1991). In 1995 RHD entered Australia in exceptional circumstances, discussed below.

Disease

RHD is an acute, highly infectious, and usually fatal condition that affects domestic, farmed and wild rabbits of the species *Oryctolagus cuniculus*. No other rabbits, such as the Central American Volcano (*Romerolagus diazzi*) and Cottontail (*Sylvilagus floridanus*) species, have been shown to be susceptible (Gregg *et al.* 1991). The incubation period following infection is between 16 and 48 h, and morbidity and mortality rates in a population can be as high as 90–100%. Death usually occurs between two and three days post-infection, but can occur several days later. The disease is confined to adult rabbits, over about two months of age, and, for reasons that are not clear, the young are in general unaffected (Xu & Chen 1989, Peeters *et al.* 1990, Mocsari *et al.* 1991, Smid *et al.* 1991, Salem & El-Ballal 1992, Mitro & Krauss 1993, Ohlinger *et al.* 1993). Original descriptions in China identified three categories of the disease (Xu & Chen 1989): the *peracute* form occurred when infection was newly introduced to a colony and rabbits usually died suddenly with few clinical signs; the *acute* form was characteristic in areas where RHD was established, and rabbits exhibited clinical signs before death and the *subacute* form was found in the later stages of an epidemic where there were clinical signs but most of the rabbits survived. The majority of subsequent descriptions of RHD in naturally and experimentally infected rabbits have been consistent with the first two of these categories.

Several clinical signs can be observed in both naturally and experimentally infected rabbits, although they are not all present in all cases. In particular, animals may have elevated temperatures, 41 °C or above, show rapid respiration and cyanosis, and become anorexic and recumbent. Nervous signs may be seen in the late stages with 'paddling' movements from the limbs, ataxia, or final frenetic behaviour with squealing before death. Opisthotonos may be observed in many animals (Mitro & Krauss 1993). Approximately 20% of affected rabbits have foamy bloody discharge from the nostrils, and more rarely from the vagina, and sometimes there may be diarrhoea or constipation (Lee & Park 1987, Xu & Chen 1989, Marcato *et al.* 1991, Sundaram *et al.* 1991, Plassiart *et al.* 1992, Salem & El-Ballal 1992, Fuller *et al.* 1993, Gavier-Widen 1993).

Pathology

Rabbits that die of RHD, after either natural or experimental infection, are commonly in good bodily condition with full stomachs. The gross pathology is typically characterized as a severe disseminated necrotic hepatitis,

with multifocal petechial haemorrhages in the liver, and also in other organs such as lungs, kidney and heart. The liver may be pale, yellow, grey, friable or congested with a distinct lobular pattern, and the spleen is often dark and engorged. Pneumo-tracheitis and tracheal haemorrhage are common features, and jaundice has occasionally been noted. The digestive tract is usually normal but there have been reports of enteritis (Lee & Park 1987, Xu & Chen 1989, Lee *et al.* 1990, Nowotny *et al.* 1990, Peeters *et al.* 1990, Glavits *et al.* 1991, Marcato *et al.* 1991, Mitro & Krauss 1993). Despite the characteristic description of haemorrhage in the disease this feature may not always be seen in cases of acute RHD (Gunning & Proud 1994, Collery *et al.* 1995, Patterson & Howie 1995).

Histological and ultrastructural alterations in the liver are consistent with acute hepatitis, and there is multifocal necrosis with intralobular foci of haemorrhage and formation of Councilman bodies. Various histological changes may be seen in other organs, and glomerulonephritis, encephalomyelitis and lymphoid tissue necrosis have been described (Lee & Park 1987, Marcato *et al.* 1988, Marcato *et al.* 1989, Marcato *et al.* 1991, Brander *et al.* 1992, Fuchs & Weissenboch 1992, Mitro & Krauss 1993, Park *et al.* 1995).

Haematologically, the occurrence of fibrin thrombi, lymphopenia, reduction in platelets, and failure of other blood clotting factors leads to multiple organ failure through generalized circulatory dysfunction. Disseminated intravascular coagulation is a characteristic feature of the pathogenesis of RHD (Carrasco *et al.* 1990, Carrasco *et al.* 1991, Di Guardo 1991, Plassiart *et al.* 1992, Ueda 1992, Ueda *et al.* 1992, Guelfi *et al.* 1993).

Aetiology: the virus

The earliest investigations of RHD established that a small virus was responsible for the disease, but there was initial controversy over its classification. Chinese and American workers described it as a parvovirus (Gregg & House 1989, Du 1991, Gregg *et al.* 1991), but European and Korean studies, on both European and Chinese isolates (Park *et al.* 1993), considered the agent to be more like a picornavirus (Lee & Park 1987) and finally identified it as a previously unknown member of the caliciviridae. Subsequent work in many laboratories has confirmed the characterization of the virus as a calicivirus on the basis of capsid morphology, physical chemistry, protein composition, nucleic acid type and replication strategy (Granzow *et al.* 1989, Ohlinger *et al.* 1989, Capucci *et al.* 1990, Ohlinger *et al.* 1990, Parra & Prieto 1990, Erber *et al.* 1991, Glavits *et al.* 1991, Park *et al.* 1991, Le Gall *et al.* 1992, Liebermann *et al.* 1992, Moussa *et al.* 1992, Park *et al.* 1992, Fuller *et al.* 1993). In particular, the virus particle consists of an unenveloped icosahedral 35–40 nm diameter capsid, composed primarily of a major 60 kDa polypeptide species, containing a positive sense single strand RNA genome of approximately 7.4 kb. Virus particles are resistant to treatment with ether, chloroform and low pH, and are comparatively stable, remaining viable for several weeks in adverse conditions of humidity and temperature (Smid *et al.* 1991, Gorski *et al.* 1994). RHD virus agglutinates erythrocytes from chickens, sheep and geese, but this reaction, inhibited by specific antiserum, is optimal with human red cells (Xu 1991). Virus can usually be found in several tissues in rabbits that have died of RHD, and there can be a viraemic stage, but it grows to high titres in the spleen and especially the liver. With the exception of a report on one Chinese isolate (Ji *et al.* 1991) numerous attempts have failed to adapt the RHD calicivirus to continuous growth in primary or secondary rabbit cells or other culture systems, including embryonated eggs (Du 1990, Nowotny *et al.* 1990, Erber *et al.* 1991, Gregg *et al.* 1991, Mizak *et al.* 1991a).

All known isolates of RHD virus appear to belong to one serotype (Berninger & House 1995) and viruses from widespread locations are generally indistinguishable on the basis of the established properties. One or two isolates that exhibit temperature dependent differences in haemagglutination characteristics have been described recently (Chasey *et al.* 1995, Capucci *et al.* 1996).

RHD virus does not cross-react with other established members of the caliciviridae

(Nowotny *et al.* 1990, Rodak *et al.* 1990a), but it is antigenically related to a calicivirus that causes a similar hepatic disease, European brown hare syndrome (EBHS), in hares of the species *Lepus europaeus* and *Lepus timidus* (Marcato *et al.* 1989, Capucci *et al.* 1991, Chasey *et al.* 1992, Steineck & Nowotny 1993). (EBHS is not addressed specifically in this review but comparative features are discussed in many of the quoted references, and particular descriptions can be found in Eskens & Volmer 1989, Henriksen *et al.* 1989, Lavazza & Vecchi 1989, Gavier-Widen & Morner 1991, Poli *et al.* 1991, Duff *et al.* 1994.) Although the aetiology of EBHS has only recently been determined, sporadic outbreaks have been observed over many years in Europe before the emergence of RHD and it is likely that the two diseases share a common ancestry. Despite one or two reports to the contrary (Di Modugno & Nasti 1990, Morisse *et al.* 1990) experimental attempts to cross-infect rabbits and hares with heterologous virus have failed to induce disease (Kolbl *et al.* 1990, Capucci *et al.* 1991, Mizak *et al.* 1991a, Smid *et al.* 1991, Chasey *et al.* 1992, Jurcik *et al.* 1992, Nauwynck *et al.* 1993), and these results are supported by observations on wild populations (Gavier-Widen & Morner 1993). The two viruses have also failed to cross-protect in immunization experiments (Capucci *et al.* 1991, Chasey *et al.* 1992, Nauwynck *et al.* 1993).

The RHD virus appears to affect only rabbits, and other small mammals and rodents such as mice, hamsters, chinchillas, guineapigs, dogs, cats and piglets are resistant to infection (Mizak *et al.* 1991a, Smid *et al.* 1991, Nowotny *et al.* 1992).

Genome characteristics

The 7.4 kb genome of the RHD virus is organized as one long open reading frame that codes for the major 60 kDa (VP60) capsid protein, a putative minor one of 12 kDa, and three non-structural proteins, including an RNA polymerase and a protease. The VP60 is probably produced from transcription of a 2.2 kb subgenomic RNA which is also synthesized in virus replication. Non-structural proteins are produced by proteolytic cleavage of a large precursor (Meyers *et al.* 1991a, Meyers *et al.* 1991b, Boga *et al.* 1992, Parra *et al.* 1993, Boniotti *et al.* 1994, Rasschaert *et al.* 1994, Wirblich *et al.* 1995, Alonso *et al.* 1996). The organization of the genome as one long single open reading frame differentiates RHDV from other caliciviruses such as feline calicivirus (FCV) and the human hepatitis E virus, tentatively classified as a calicivirus (Tam *et al.* 1991), but it does resemble EBHS virus and the human enteric calicivirus in this respect (Wirblich *et al.* 1994, Liu *et al.* 1995).

Comparisons of different RHD viral isolates reveals close overall homology in terms of genome sequence with few or no consequent predicted changes in amino acid composition; viruses from Germany, France, Spain and Egypt differ by between 2% and 5% corresponding to between one and ten amino acid substitutions in the capsid VP60 protein from the different isolates (Milton *et al.* 1992, Boga *et al.* 1994, Rasschaert *et al.* 1994, Guittre *et al.* 1995).

Consistent with the antigenic relationship between RHD virus and EBHS virus, sequence comparison shows a 76% homology between the two major capsid proteins, equivalent to 135 changes in amino acids. Homology with other unrelated caliciviruses has generally been reported to be considerably lower. There is a 24–26% correspondence with San Miguel sealion virus, 25% with FCV and only 18% with the human enteric Norwalk virus (Wirblich *et al.* 1994). On the other hand, however, some strains of human enteric caliciviruses from Japan are apparently more closely related genetically to the RHD virus than to other isolates of human origin (Matson *et al.* 1995).

Diagnosis and virus detection

RHD can be confirmed by detection of the virus or viral antigen, in tissues from rabbits that have died of the disease. The liver is the organ of choice in view of the large quantities of virus produced there, and semi-purified or crude extracts of homogenized tissue provide the basic material for diagnostic tests. Characteristic calicivirus particles can be detected, usually in large numbers, by direct

negative stain electron microscopy, and these can be specifically identified further as RHD virus by conventional immunological labelling using RHD-specific antiserum or monoclonal antibodies (Capucci *et al.* 1991, Erber *et al.* 1991, Park *et al.* 1991, Biermann *et al.* 1992, Chasey *et al.* 1992, Valicek *et al.* 1992, Alexandrov *et al.* 1993, Lavazza & Capucci 1993, Chasey *et al.* 1995). Haemagglutination assays (HA), with human type 'O' erythrocytes, are still commonly used as convenient tests whose specificity can also be demonstrated by inhibition with RHD virus-specific antisera (Capucci *et al.* 1991, Erber *et al.* 1991, Biermann *et al.* 1992, Chasey *et al.* 1995). HA may occasionally produce false negative or false positive results, and also fail to detect infection in instances where virus particles have undergone proteolytic degradation (Capucci *et al.* 1991).

Enzyme linked immunosorbent assays (ELISA) have to some extent superseded other tests (Capucci *et al.* 1991, Zimmer *et al.* 1992, Chasey *et al.* 1995). These involve coating assay plates, either with polyclonal antibodies to the virus or with monoclonal antibodies (mabs) that recognize different epitopes on the RHD viral capsid. The use of mabs in ELISAs or Western immunoblots also enables distinction to be made between the related viruses of RHD and EBHS, and has contributed to antigenic characterization studies (Rodak *et al.* 1990b, Capucci *et al.* 1991, Capucci *et al.* 1995).

Although not of prime importance in routine diagnosis, immunohistochemical labelling methods can identify viral antigen in histological sections of infected organs (Alexandrov *et al.* 1992, Park & Itakura 1992, Stoerckle-Berger *et al.* 1992). Cytoplasmic localization of antigen is consistent with calicivirus morphogenesis, and virus particles have been observed by electron microscopy (Marcato *et al.* 1989, Lucidi 1991, Park *et al.* 1992, Park *et al.* 1993).

The application of the reverse transcriptase polymerase chain reaction (RT-PCR) to the detection of RHD virus-specific nucleic acid has recently been described (Guittre *et al.* 1995). This methodology is probably unnecessarily sensitive for routine diagnosis of clinical disease (10^4 times more sensitive than ELISA), but is appropriate, particularly, for studies on molecular epidemiology.

Control

RHD can be controlled in domestic and commercial rabbit colonies by a combination of slaughter, disinfection and vaccination. (It is not feasible to control the disease in populations of wild rabbits.) Where RHD has occurred, all infectious material should be removed and the premises disinfected with solutions of either formalin (1–2%) or sodium hydroxide (10%) before re-stocking, if necessary with rabbits that have been quarantined for a short period. (Xu & Chen 1989, Erber *et al.* 1991). A rigorous slaughter and disinfection regime, in conjunction with movement restrictions, sentinel rabbits and subsequent surveillance, was successfully employed on a large scale in the eradication of RHD from Mexico (Gregg *et al.* 1991).

Virus antigen, harvested from experimentally infected rabbits, can be inactivated, usually with formalin or β-propiolactone, to produce effective killed vaccines, which are now commercially available. Oil or aluminium hydroxide adjuvanted vaccines induce a good immune response that protects older animals from fatal infection when administered parenterally. Immunity develops in the first few days after inoculation and, although this may persist for several months, booster vaccinations are commonly given at half yearly intervals to cover the productive life of breeding and fur-producing rabbits (Mocaari *et al.* 1989, Xu & Chen 1989, Haralambiev *et al.* 1990, Pages Mante & Costa Quintana 1990, Haralambiev *et al.* 1991, Mizak *et al.* 1991b, Smid *et al.* 1991, Arguello Villares 1991, Huang 1991, Arguello *et al.* 1992, Gorski *et al.* 1994). Antibody levels in serum can be measured and monitored by haemagglutination inhibition levels (HI), immunoblotting or ELISAs which have been developed for general examination of RHD serology (Rodak *et al.* 1990a, Capucci *et al.* 1991, Collins *et al.* 1995, Ruvoen-Clouet *et al.* 1995).

Since RHD virus has not been successfully adapted to growth *in vitro*, vaccine antigen has to be produced in rabbits, but this is

clearly not ideal. Studies on the expression of virus capsid protein in baculoviruses have demonstrated that non-infectious capsid particles, structurally and antigenically identical to RHD virions, can be assembled artificially. These are immunogenic and may lead to improved methods of vaccine manufacture (Laurent *et al.* 1994, Nagesha *et al.* 1995, Marin *et al.* 1995, Sibilia *et al.* 1995).

The administration of immune serum is also effective in producing a rapid, but short-lived, protection against challenge with RHD virus (Pages Mante 1989, Huang 1991, Peschlejski *et al.* 1991).

Epidemiology

RHD can spread rapidly by various routes and vectors. Natural infection commonly occurs through direct animal to animal contact and the virus, present in excretion products such as faeces (Nowotny *et al.* 1993), enters usually by the oral or respiratory route. The stability of the virus leads to local contamination of the environment and RHD can be spread by contact with feedstuffs and bedding materials (Loliger *et al.* 1989, Xu & Chen 1989). The passive transmission of the virus over short distances by insects, such as flies, may also occur (Erber *et al.* 1991, Gehrmann & Kretzschmar 1991), and there is significant risk of disease spread to new areas through movement of people, equipment and other wild and domestic animals, including rabbits (Fioretti *et al.* 1991, Xu 1991, Nowotny *et al.* 1992, Fuller *et al.* 1993). There is evidence that foxes can seroconvert to RHD after ingestion of the virus (Leighton *et al.* 1995) and, although there is probably little or no replication within these animals, foxes and dogs may readily bring infection to previously unexposed colonies of wild rabbits (Simon *et al.* 1994). Scavenging foxes on the west coast shoreline of the USA are also known to seroconvert to the San Miguel sealion calicivirus (Prato *et al.* 1977). The role of other rabbit predators, such as the polecat in which low titre antibody to the RHD virus may occur (Chasey & Trout, unpublished observations), is not clear.

Rabbit products, such as pelts, have also been implicated in the spread of the disease, and rabbit meat is a potential source of infectivity. Outbreaks of RHD on Reunion Island were attributed to the importation of contaminated meat, and the Mexico epidemic was linked circumstantially to frozen rabbit carcasses from China introduced illegally through the USA. Direct experimental confirmation of disease transfer from infected meat products was, however, never demonstrated (Morisse *et al.* 1991).

Aerosol spread over large distances as a result of local meteorological conditions, and transmission by birds, particularly rabbit predators such as gulls, may also be significant factors in the dissemination of the disease (Chasey 1994).

Where RHD is established in the wild, the combination of breeding patterns, immunity in surviving adults and unaffected, but subsequently protected juveniles, can lead to a two-year cycle of disease. However, there are few published data on RHD in wild rabbits (Villafuerte *et al.* 1994, Simon *et al.* 1995). Unlike myxoma-infected animals, rabbits with RHD tend to die underground and outbreaks of disease may not be easily recognized particularly where predator activity is high.

Serology: natural immunity

A significant feature of RHD in Europe is the existence of rabbits that are seropositive before exposure to the virus, an observation also made initially in China (Huang 1991). Pre-existing cross-reacting 'natural' antibody occurs in farmed, laboratory bred animals and wild rabbits (Ohlinger *et al.* 1989, Rodak *et al.* 1990a, Smid *et al.* 1991, Chasey *et al.* 1995), and retrospective examination of older sera indicates that antibodies were widespread several years before the recognition of RHD as a clinical syndrome in 1984 (Rodak *et al.* 1990a, Chasey 1994). In addition, seronegative rabbits will seroconvert after contact with seropositive rabbits (Capucci *et al.* 1991) and these observations have led to the supposition that there are non-pathogenic RHD or 'RHD-like' strains of virus circulating.

Natural cross-reacting antibody titres are not usually high, and some reports consider

< 1/80 as non-specific, but these titres nevertheless protect against challenge with virulent RHD virus in experimental conditions (Rodak *et al.* 1991, Smid *et al.* 1991, Chasey *et al.* 1995). A recent study (Chasey & Trout, unpublished observations) has shown directly that seropositive wild rabbits, previously unexposed to the disease, are also protected against fatal infection when experimentally challenged. This is consistent with the relatively slow natural spread of RHD through the UK which overall has a high proportion of seropositive wild rabbits (Chasey & Trout 1995). Similarly high numbers of seropositive wild rabbits have been reported in Spain (Simon *et al.* 1995).

Australia

While countries of the northern hemisphere have occupied themselves with the control of RHD, Australia, realizing the potential of the disease as a rabbit control agent, began a scientific research programme in 1991 to establish the feasibility of virus introduction. This included aspects of susceptibility in other species, effectiveness of virus spread and welfare. High security laboratory studies commenced with an imported European strain of RHD virus, and a field trial of the disease in a warren system under controlled quarantine conditions followed on an isolated island off the South Australian coast. However, in late 1995 the disease, possibly carried from the island by insects or air currents, appeared on the mainland, and attempts to halt the spread were unsuccessful. Over a 2-month period several million wild rabbits have been estimated to have died over an area the size of Spain (Westbury, personal communication). Unlike European wild rabbits, many of which contain pre-existing protective antibody, no such protection exists in Australian rabbits, and this undoubtedly is a contributing factor in the rapid dissemination of the disease.

Concluding remarks

Although RHD continues to cause considerable damage amongst domestic and commercial rabbits in several countries, the disease can be controlled through effective slaughter and vaccination regimes. The disease in wild rabbit populations may have ecological implications for other species of fauna and flora.

European wild rabbit populations overall have not been affected to the dramatic extent that was observed with the appearance of myxomatosis. To a large extent, this is related to the existence of cross-reacting protective antibody, although the origin of this immunity is unclear. Despite the difficulties of obtaining accurate data on wildlife diseases it is not considered likely that clinical RHD has been present, but undetected, in wild rabbits before its initial description in 1984. A preferred explanation is that apathogenic RHD-like viruses have been circulating generally for some time, maintaining varying levels of antibody within rabbit populations. The finding of seropositive animals within laboratory rabbit colonies with no history of clinical RHD also implies the existence of silent infections, but seropositive laboratory bred rabbits are at least protected if subsequently challenged. In Australia, however, where the rabbit has been separated from its European origin for over 100 years, there appears to be no cross-reacting antibody or natural immunity to RHD. As a consequence the effect of the disease in Australia may, in the short term, be markedly more dramatic.

Continuing investigation of the RHD virus should shed some light on its origins, and its relationship with other diverse members of the calicivirus group.

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