Novel bivalent vectored vaccine for control of myxomatosis and rabbit haemorrhagic disease

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Context
Rabbit haemorrhagic disease (RHD) and myxomatosis are two almost invariably fatal viral diseases affecting the European rabbit. Myxomatosis, caused by myxoma virus, a poxvirus of the genus Leporipoxvirus, became endemic in Europe after the virus had been released in France in the 1950s. Since its release the virus has coevolved with the wild rabbit population and, although less virulent strains of the virus have arisen and wild rabbits have acquired some genetic resistance, domesticated rabbits remain susceptible to infection. Biting insects are recognised as an important vector for the transmission of myxoma virus, but the virus is also able to spread efficiently between rabbits in the absence of insect vectors.

RHD is a highly contagious disease of the European rabbit with a high morbidity and mortality in susceptible animals. After its emergence in China in the 1980s it has spread naturally throughout most of the rest of the world. The aetiological agent of the disease is a small positive-strand RNA virus, and the disease is somewhat unusual in that animals younger than approximately 10 weeks of age are almost completely resistant. The mechanism of this resistance remains to be fully elucidated.

Vaccination against myxomatosis has been available for some time. All vaccines are live vaccines based either on attenuated myxoma virus strains or on a closely related poxvirus, Shope fibroma virus. Each has its advantages and disadvantages. Shope fibroma virus-based vaccines may be considered less immunogenic, while attenuated myxoma virus-based vaccines may be immunosuppressive, particularly in young rabbits. Such immunosuppression in animals kept in large rabbitries can lead to serious problems of bacterial respiratory infection. The claimed duration of protection of live attenuated myxoma virus vaccines is usually around four to six months.

Current vaccines for RHD consist of inactivated virus preparations derived from infected rabbit livers, combined with an adjuvant. These products are able to stimulate effective immune responses; however, the adjuvants used may sometimes cause unwanted injection site reactions, particularly in dwarf and show animals.

Main conclusion
This paper describes a number of safety and efficacy studies with a novel, recombinant myxoma virus-RHD virus (RHDV) vaccine (Nobivac Myxo-RHD; MSD Animal Health) in specific pathogen-free rabbits, and demonstrates that the vaccine is able to provide protection from challenge with myxoma virus or RHDV for one year following vaccination with a single dose of vaccine.

Approach
Efficacy against myxoma virus challenge, efficacy against RHDV challenge, dissemination, vaccine virus shedding and vaccine safety were analysed in a number of separate studies. In all studies, rabbits were housed in groups and vaccinated subcutaneously with 1.0 ml of vaccine material. Studies designed to examine vaccine efficacy used the minimum dose of $10^5$ focus-forming units (ffu), whereas safety was determined by administering doses of up to $10^7$ ffu.

To demonstrate that the vaccine was able to protect rabbits against myxomatosis and RHD, vaccinated and control rabbits were challenged with either virulent myxoma virus or virulent RHDV. The animals were monitored closely for clinical signs; control animals were euthanased when disease was clearly apparent but before overt signs of distress. Virus isolation from tissues taken from rabbits vaccinated with high doses of vaccine was carried out to determine the propensity for the vaccine to disseminate in the animal, skin from the sites of virus predilection (eyes, ears and genitals), together with a number of internal organs, were analysed.

The potential for biting insects to spread virus via the blood of vaccinated rabbits was addressed by isolating lymphocytes from vaccinated animals and determining their virus content.

Results
In the myxomatosis efficacy study, all five unvaccinated control rabbits developed clinical signs of myxomatosis and had to be euthanased. In contrast, 10 of the 11 vaccinated animals remained completely normal and healthy. The 11th vaccinated rabbit did not show any signs typical of myxomatosis but developed acute enteritis; this was not attributable to the challenge but was typical of mucoid enteropathy, which was present sporadically in the animal unit.

In the RHD efficacy study, all of 11 RHDV-challenged vaccinated rabbits survived and showed no clinical signs, whereas all five unvaccinated controls died within 72 hours as a result of the challenge. The dissemination studies revealed that virus was not present in any of the tissues of the vaccinated rabbits, with the exception, occasionally, of the skin around the site of injection and the nearest draining lymph node. Furthermore, when virus could be isolated from these tissues, the amounts were very low. The virus was not isolated from any of the lymphocyte preparations.

Interpretation
Vaccination with a single dose of the vaccine elicited an immune response that provided protection against both myxomatosis and RHD. Virus could occasionally be recovered from the skin around the injection site and from the nearest draining lymph node; however, the absence of myxoma virus in the tissues from vaccinated rabbits indicates that the virus is unable to replicate extensively and disseminate within the animal.

Significance of findings
These studies show that Nobivac Myxo-RHD is able to provide protection against both myxomatosis and RHD after a single vaccination, which is the first time that this possibility has been available to rabbit owners. Additional studies have shown that immunity persists for at least 12 months. Furthermore, the vaccine is able to achieve this protection without extensive replication within, or shedding of vaccine virus from, the rabbit.
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