**Vaccination against and immune response to viral haemorrhagic disease of rabbits: a review of research in the People’s Republic of China**

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**Summary:** Viral haemorrhagic disease (VHD) of rabbits is an acute entity with high mortality which affects adult rabbits. Several vaccines have been developed in China and extensive use of these vaccines in the field has controlled the spread of the disease. Formalin inactivated tissue vaccine induces solid immunity on the third to fourth day post vaccination and immunity lasts for at least six months. The oil-emulsion tissue vaccine which has been developed has longer lasting potency. Successful adaptation of VHD virus (VHDV) to cultured cells and preliminary immunisation will provide the possibility of large-scale production of cell-cultured virus vaccine.

Passive, emergency immunisation with hyperimmune antiserum provides short-term protection of threatened rabbits as well as treatment of infected rabbits in the field.

Histopathological and pathophysiological studies reveal that immune cells and organs are the most affected targets in infected rabbits; owing to the damage to the endothelial system of blood vessels, extensive disseminated intravascular coagulation (DIC) occurs in the parenchymal tissues. Destruction of the immune system and the occurrence of DIC lead to acute illness and sudden death post infection.

Experimental immunological studies demonstrate that the induction of rapid immunity is coordinated by macrophages and T and B lymphocytes in the initial, post-immunisation stage, whereas humoral immunity plays the main role in long-term protection against VHDV infection. The positive association of post-vaccination protection with haemagglutination inhibition antibody can also be observed. Interferon probably takes effect as an anti-VHDV agent soon after vaccination.

**KEYWORDS:** Histopathology - Immunogenicity - Immunological response - Interferon - Monoclonal antibodies - Passive immunisation - Pathophysiology - Vaccination - Vaccine development - Viral haemorrhagic disease of rabbits.

**INTRODUCTION**

In the People’s Republic of China, viral haemorrhagic disease (VHD) of rabbits was first reported as a new entity in 1984 (33). Rapid spread and early mortality were
the principal epidemiological characteristics. In the first stage of VHD spread, the Chinese veterinary services and rabbit industry were alerted to the economic losses caused by VHD. Scientists in the People's Republic of China at once developed inactivated vaccine from infected rabbit tissue treated with formalin. Experimental and field results show that the vaccine can rapidly induce solid immunity against VHD virus (VHDV) infection (14, 30, 41, 50, 56, 57, 63, 70) and that extensive use in the field for prophylaxis has resulted in the control of VHD spread in the People's Republic of China since 1986 (11, 64, 65). Certain modified adjuvant vaccines have also been developed (16, 32, 46, 70). In 1990, VHDV was adapted to cultured cells and, according to preliminary immunisation results (36; Ji et al., personal communication), cell culture could possibly be used to develop an inactivated or attenuated vaccine. Hyperimmune antiserum plays an effective part in passive emergency protection and treatment in the field (20, 38, 48, 55, 56, 58). Since the discovery of a means to control VHD, Chinese scientists have been attempting to clarify the mechanisms of pathogenesis and immunogenesis, and numerous research papers on these subjects have been, and are still being, published in Chinese journals and research collections. This review paper will give a general presentation of this work.

DEVELOPMENT OF VHD VACCINES

When the first outbreaks of VHD were discovered in the People's Republic of China and various antibacterial agents were found to be ineffective in controlling the spread of the disease, it was suggested that the causative pathogen might be a virus. An inactivated tissue vaccine for emergency vaccination was consequently developed, although no knowledge of VHDV characteristics existed. Because quickly-induced solid immunity can protect vaccinated rabbits from VHDV infection, a national vaccination programme was implemented in areas where VHDV was prevalent. At present, VHD is only found sporadically or is limited, as far as possible, to small areas.

It is evident that VHD is a worldwide disease of economic importance in the rabbit industry (15). Practical experience with formalin inactivated VHD vaccine for rabbits reveals that the key to controlling the disease is vaccination. Certain modified and improved vaccines are being developed in the People's Republic of China for use, if needed, in sporadically-infected areas or in other countries.

Inactivated tissue vaccines

Seed virus

The virus seeds used for production of inactivated tissue vaccines are liver tissue virus by in vivo serial passages. The virus strains collected from different epidemic regions and in different periods have proved, through vaccine cross protection determination and the haemagglutination inhibition (HI) cross-reaction test (1, 52), to have the same antigenicity. This explains why the rapid control of VHD spread with the same strain vaccine is possible without having to consider the field-prevalent virus type. Seed virus LD_{50} and the haemagglutination (HA) titre are usually higher than 1:10^7 and 1:320, respectively. Seed virus in liver tissue should be stored in a frozen or freeze-dried condition.
Inactivation

The different results obtained in inactivation experiments have been detailed in published papers. Wang et al. (53) conducted an inactivation test for VHDV strain HC-84 using seven different final concentrations of formalin in the infected liver tissue suspension. The result shows that 1.0-1.4% concentrations could completely inactivate the infectivity of the virus; however, 0.4-0.8% resulted in incomplete inactivation. Identical findings were obtained by Xu (63), Zhang (74), Wu (57), Zhan (71), Cao (1) and Tong (46). However, in the study conducted by Li et al., 0.625% formalin inactivation proved effective. The formalin inactivated tissue vaccine has good immunogenicity and no adverse clinical reaction occurs. The vaccine may normally be stored at 4°C for more than one year or at 15°C-20°C for half a year.

Collection of infected tissue

The liver and spleen, and sometimes the kidney, have the highest HA titres in controlled conditions (13); these are collected in a sterile state from dying or recently dead rabbits which have been experimentally infected. Five or ten percent suspensions of ground tissues are treated with formalin and then used as vaccine after serial quality control tests. Tenfold dilution of the prepared vaccine also induces solid immunity (46, 51).

Vaccination

It has been proved that the virus principally infects rabbits older than two months (26, 39). One of the characteristics of VHD is that younger rabbits are either resistant or infected subclinically (11, 13, 19, 31). In the laboratory as well as in the field, the author has found that the sturdier rabbits often suffer the highest morbidity and mortality, but that there is no difference in susceptibility between sexes or among breeds (64, 65). Successful practice in the field with formalin treated tissue vaccine shows that solid immunity may be acquired in adult rabbits. Emergency vaccination can suppress VHD spread within three to four days (42, 57, 63). Normally, a 1 ml dose is inoculated subcutaneously in the neck of each rabbit. The vaccine is very safe for pregnant rabbits (54).

Duration of immunity

Numerous challenge tests indicate that immunity in adult rabbits, induced with one dose of the vaccine, may reach a 100% protection rate in the sixth post-vaccination (p.v.) month (46, 50, 56, 73). In other studies, the duration was found to last until the eighth or ninth month (70). Thus, it is necessary that breeding and fur-producing rabbits, and those kept for covering, be vaccinated twice a year.

Adjuvant vaccines

Aluminium hydroxide gel vaccine has a potency comparable to non-adjuvant vaccine (46). However, longer immunity can be induced by the same, or a smaller, dosage of oil-emulsion vaccine. It appears that the HI antibody titres are higher, and duration longer, in rabbits vaccinated with oil-emulsion vaccine than with non-adjuvant vaccine (16, 70). The use of either alumina gel or oil-emulsion vaccine is advisable because the smaller doses of vaccine are absorbed within one month without any influence upon the quality of the meat and fur. In the twelfth month p.v., the average HI titre for oil-emulsion vaccine is still 1:2^{2.1}, though there is no HI titre for non-adjuvant vaccine (70).
**Combined vaccines**

Polyvalent vaccines combined with VHD have been tested successfully in the People's Republic of China. The combined vaccines include bivalent vaccines (VHD/pasteurellosis, VHD/clostridiosis and VHD/bordetellosis) (5, 22, 32, 44, 45) and a trivalent vaccine (VHD/pasteurellosis/clostridiosis) (Y.K. Wang, personal communication). In the combined vaccines mentioned above, the other vaccine components have been found not to influence VHDV immunogenicity, and the VHDV components not to interfere with other vaccine activities. The oil-emulsion combined vaccines induce better and longer protection (32).

**Post-exposure treatment**

It is known that vaccinated rabbits quickly produce solid immunity against VHDV infection. When VHD occurs in rabbitries, emergency strategies primarily focus on vaccination of all live rabbits, whether or not they have been infected. It is sometimes found that rabbits with light clinical signs, or with none at all, will recover after emergency inoculation with inactivated tissue vaccine. Huang (21) demonstrated that the majority of rabbits, after having been experimentally infected with a virulent virus for 18 to 24 h and then given three- to fourfold doses of VHD vaccine, could resist VHD, although their recovery from clinical signs took longer. The explanation for this is at present unclear.

**Cell-adapted cultured VHDV vaccine**

To characterise VHDV and industrialise large-scale production of the vaccine, Chinese laboratories have made many attempts since 1984 to adapt VHDV to cultured cells (2, 36, 47, 59; Ji et al., personal communication). VHDV 7- to 8- passage propagation with cytopathic effect (CPE) has been obtained, respectively, on a newborn rabbit kidney diploid cell and the M-104 cell line. CPE disappears if further propagation is conducted (23, 59). The mixed suspensions of CPE-positive cultures are inactivated with formalin and used to vaccinate rabbits. The vaccine elicits complete protection with high dosage, but protection is incomplete with normal or low dosage (59). Ji et al. (23) have successfully used a suckling rabbit kidney transformed cell line (DJRK) to propagate VHDV. The immunofluorescent test, the VHD replication test in rabbits and electron microscopic observation have proved that VHDV can be readily adapted to DJRK. The fifth, tenth (23) and sixteenth (Ji et al., personal communication) passage viruses can still cause typical VHD pathological lesions and death. Inactivated culture suspensions may induce a good immunological response to, and even solid immunity against, VHDV virulent challenge; in addition, the other three cell types (VERO E6, LLCMK2 and L929) have also been used to adapt VHDV successfully. VHDV has been propagated in more than 60 passages (36). Experiments on cell-adapted VHDV vaccine are now being conducted.

In preliminary experiments on cell-cultured VHDV vaccine, the HI titre in vaccinated rabbits can quickly reach 1:2^{10} on the third day p.v. and 1:2^{14-15} on the seventh to fourteenth days. Progressive drop in the titre starts from the 21st day. On the fourteenth day challenge, 100% protection is observed (23). The result shows that elicited HI antibody titres are significantly higher at different post-vaccination stages with cell-cultured vaccine than with tissue vaccine. Tests on the duration of immunity are presently being conducted.
Although VHDV has been adapted to cultured cells, the progressive loss of virulence as passage times on cultured cells increase has been found to postpone death in inoculated rabbits (23). This tendency will result in the possibility of developing an attenuated live VHDV vaccine strain.

VHD PASSIVE IMMUNISATION WITH HYPERIMMUNE ANTISERUM

Hyperimmune antiserum has been successfully used for emergency inoculation in many infectious animal diseases so that endangered animals can quickly produce short-term immunity and infected animals can be treated by neutralising pathogenic agent action. In the People's Republic of China, such attempts have been made for VHD emergency control in the field (20, 22, 38, 55, 56, 57, 58). It is certain that passively acquired immunity with homogeneous antiserum, which has been extensively used in the field, acts solidly against infection in emergency situations (20, 55, 56, 58). A dose of 0.2-0.5 ml antisera normally protects against virulent challenge for no less than one month (11, 13). Passive administration of antiserum is a valuable treatment for infected rabbits with light, or no, clinical signs, but has no effect on dying rabbits. Additionally, some reports indicate that heterogeneous antisera (bovine, ovine and caprine) provide passive protection to some extent, but the cure and protection rates are somewhat lower than those of homogeneous antisera (22, 38, 57). Traditional Chinese veterinary medicine herbal preparations, injected or administered orally, can enhance nonspecific antiserum treatment and short-term immunity (37).

Hybridomas which secrete monoclonal antibody (MAb) against VHDV have been identified in several laboratories in the People's Republic of China (34, 35, 36, 72, 76). It has been proved that three MAbs can protect passively inoculated rabbits from VHDV challenge and that the MAbs are effective in both HI and gel precipitation (72). So far, there have been no reports on MAb field application in the People's Republic of China.

HISTOPATHOGENESIS AND IMMUNOGENICITY

Histopathogenesis

The pathogenesis of any infectious disease reveals the balance between the ability of the host to resist microbial invasion and the capacity of the microbe to inflict damage. VHD is an acute infection clinically characterised by high fever, haemorrhagic septicaemia, shock and high mortality (11, 33, 64). Clinical, histopathological and histochemical studies demonstrate that VHDV can replicate at extremely high speed and heavily interfere with the metabolism of target cells and organs (60, 61). The immune system is one of the most heavily damaged systems. In the spleen and lymph nodes of infected rabbits, the macrophages of different tissues have been observed to phagocytose some red blood cells and necrotic lymphocytes. According to acid alpha-naphthyl acetate esterase (ANAE) staining, T lymphocytes in the blood are significantly reduced in experimentally infected rabbits (3, 18, 72). The situation
continues to deteriorate as the course of the disease develops (18, 72). The average reduction rate is 37.1% in lymphocytopenia (Du et al., personal communication). In addition, T lymphocytes in peripheral lymphatic organs and tissues are destructively influenced (18). Spleen and lymph nodes become progressively atrophic and the functions of haematopoietic systems are disordered, which are the main causes of lymphocytopenia and leukocytopenia (67). Infected rabbits are therefore unable to mount an effective immune response against the viral infection, and this leads to further deterioration.

Pathophysiological and histopathological reports (24, 29, 60, 67, 75) explain that the VHD virus first invades target systems, including the immune and endothelial systems, and then activates endogenous thrombin pathways. In the 6th h following infection, microthrombi have been observed in the kidney, lung, heart, liver and adrenal tissues. Extensive disseminated intravascular coagulation (DIC) occurs in the parenchymal tissues of dying rabbits (4, 62, 66).

Rabbit thymus lymphocyte antigen (RTLA) and rabbit bursal equivalent lymphocyte antigen (RABELA) are, respectively, T-cell and B-cell specific markers (6, 15). In the study by Deng et al. (8), RTLA and RABELA cells with complement dependent antibody-mediated cytotoxicity were detected in different immune tissues in the initial post-immunisation (p.i.) stage. The results show that the increasing potency of RTLA cells can be seen in spleen and lymph nodes in the 24th h p.i.; the peak occurs in the 48th h, which indicates that RTLA cells actively join anti-viral reactions, perhaps directly killing virus or/and helping B cell response. As the immunological response continues, RABELA cells start to increase progressivly and exceed the level of RTLA cells in the 120th h p.i. At this stage, the enhanced B cells quickly differentiate, mature and then secrete specific antibodies. This finding is consistent with the other studies by Deng et al. (9) on antibody-forming cells (AFC) and antibody-secreting cells (ASC). Therefore, in the initial p.i. stage, specific immunity results from coordinated interaction of T and B lymphocytes. To some extent, the study provides evidence for the histopathological observations in infected rabbits.

**Immunological response and immunity**

It is known that the capture and treatment of antigen by macrophages, and interaction among macrophages, T cells, B cells and various lymphokines, will induce specific and protective immunity. Additionally, this immunity includes certain nonspecific factors. Some scientists in the People’s Republic of China have provided an account of present knowledge, but much remains to be discovered.

**Macrophage activity**

Capture and phagocytosis of foreign pathogens by macrophages are the first stage in cellular and humoral responses. Following this stage, macrophages present the treated antigens to helper T and effector T cells, and B cells receive the antigens presented by helper T cells; humoral and cellular responses start at this point. The macrophages are therefore among the most important cells in the immunological response. Deng et al. (personal communication) detected some phagocytic characteristics of abdominal macrophages in vivo with VHDV-coated red blood cells (RBC) as target markers. The phagocytic index was found to increase from 7.8 to 9.5% in the 48th h p.i. (Fig. 1). In the 72nd and 120th h, the indexes were 16.8 and 45.7%, respectively. The number of engulfed RBCs in a macrophage also rose from
1-2 to 3-5. Only in the 72nd h was a typical RBC-macrophage rose ring formed. The interaction between macrophages and VHDV can greatly reduce phagocytosis and inhibit the rose-ring formation, which suggests that specific contact exists between macrophages and VHDV-coated RBCs. Therefore, it is possible that the binding of macrophage AFC receptors and a few antibodies in the initial stage of vaccination will strengthen macrophage phagocytosis. It is also estimated that macrophages take an active part in the initial anti-viral immunity. The author tried to duplicate *in vitro* the anti-VHDV-serum mediated VHDV opsonisation, but found no significant phagocytosis and rose-ring formation. The binding may require certain *in vivo* environmental conditions before macrophage activation starts.

**FIG. 1**

Dynamic changes in the phagocytic index of three categories of macrophages at different times
Humoral response

Many vaccines can be readily assessed by comparing serum antibody titres before and after immunisation. At present, the established HI test (40) demonstrates well the dynamic change of antibody production (43, 68, 72), and the relationship between HI antibody titre and protection has also been observed (13, 17, 25, 28, 40, 41, 42, 77). Because it is simple and convenient to carry out, the method has been widely used to monitor post-immunisation antibody response. Generally, it is thought that HI antibody titre of more than 1:20 is resistant to challenge (41).

In the studies by Yu et al. (70), non-adjuvant tissue vaccine and oil-emulsion vaccines were compared in terms of HI antibody response after the first and booster vaccinations (Figs. 2 and 3). Both vaccines induced typical immunological responses, but the response by oil-emulsion vaccine was stronger than that of non-adjuvant vaccine. Four different inactivated VHD vaccines also showed the same immunological responses (16). In challenge tests, non-adjuvant vaccine induced the earliest protective immunity on the third day p.i., and all four vaccines conferred the same protection on the seventh day. The duration of immunity of adjuvant vaccines is obviously longer than that of non-adjuvant vaccine (70).

![Graph showing HI antibody response](image-url)
Antibody-forming cells (AFC) in the spleen are first detected by the indirect immunofluorescent technique in the 24th h p.i. and in lymph nodes in the 48th h; they then rise continuously in both organs until the 120th h. According to monolayer liquid-phase haemagglutination assay (10), antibody-secreting cells (ASC) first appear in the spleen in the 48th h and in lymph nodes in the 72nd h, and then ASC rapidly increase in quality. In the 120th h, ASC tend to maintain a stable status in the spleen, while in the thymus, lower levels of both AFC and ASC can be observed from, respectively, the 24th and 48th to the 120th h p.i. with no increase occurring. In the appendix, only a very limited number of ASC is measured at the 72nd and 120th h p.i., and no ASC are detected from the 24th to 120th h p.i. among the blood lymphocytes (Fig. 4) (9).
FIG. 4

Post-immunisation dynamic changes of antibody-forming cells (AFC, a) and antibody-secreting cells (ASC, b) in several lymphatic organs of rabbits immunised with inactivated VHD vaccine.
In an experiment involving ten rabbits with no HI-antibody titre, it has been observed (70) that, in the seventh month p.v. with oil-emulsion vaccine, nine still had solid protective immunity against virulent challenge. The rabbits, post challenge, had a significant rise in body temperature; at the same time, HA titre could be detected in the blood. The rabbits recovered and HA titre disappeared in the 72nd h post challenge. It must be pointed out that this situation occurs only in vaccinated rabbits. A rabbit passively immunised, and in which HI antibody disappears, cannot resist the virus challenge (41). All this illustrates that other factors besides HI antibody participate in protective immunity, which has to be determined by the virus neutralisation test on cell culture. At present, however, HI antibody detection is still used to evaluate and monitor the vaccine effect. In addition, it has been recorded that the indirect haemagglutination test (68, 69) and agarose gel immunodiffusion test (7) have been used for detecting VHD antibodies.

With his colleagues, the author has found that rabbits which have recovered from VHD have a low HI antibody level. When they are vaccinated or re-infected with virulent virus, only a small increase in HI titres can be observed as compared with titres of vaccinated or boosted rabbits. This difference is associated with the virulent damage done to the immune system by the first infection.

In epidemiological investigations, HI antibody can occasionally be detected in rabbit stocks never influenced by an attack of VHD. In addition, low HI antibody titres also exist in some hare (49), calf and human sera (12). We still do not know whether these HI antibodies are evoked by cross-antigens of other microbes or by VHD virus.

**Cellular immunity**

Rabbits inoculated with specific transfer factor (TF) prepared from vaccinated rabbit spleen cannot produce effective protection against a challenge in the 18th h post inoculation (28). In addition, T lymphocyte transformation in the different post-vaccination stages is determined by the [3H]-thymidine radioactive (TdR) microdroplet lymphocyte transformation test. The transformation index starts to rise only on the 17th day p.v. (28). Before that time, humoral response has been evoked in the vaccinated rabbits, indicating that humoral immunity is formed faster than cellular immunity. There is no denying that cellular immunity is important in the immunological response; as with most acute viral diseases, however, VHD immunity is mainly a humoral response.

**Role of interferon (IFN)**

Interferon is a family of broad-spectrum, nonspecific antiviral products and plays an important role in antiviral responses. According to the cytopathic effect inhibition (CPEI) test, there is a high concentration of IFN in the blood of vaccinated and VHD-recovered rabbits, but only a low level in infected dying rabbits (Fig. 5). Rabbits administered only with IFN inducer poly-I:C can produce solid short-term protection against virus challenge in the 6th h post administration, while the rabbits used as controls die (27). The study by Li (28) states that a high concentration of IFN in the blood can interfere with VHDV pathogenesis and provide nonspecific protection. Some virus vaccines have been shown to elicit IFN production quickly, which indicates that IFN contributes to the initial antiviral activities post vaccination; active immunisation will then offer specific and long-term immunity (13). It has been noticed that, in VHD-recovered rabbits, high-titre IFN peaks in the 18th h following infection.
Individual rabbits which have high levels of IFN or which can produce high titres of IFN very quickly as soon as IFN inducer exists, will usually recover from VHD (27). The initial immunity induced by inactivated vaccines is associated not only with the fast, specific immunological response, but also with IFN.

**FIG. 5**
Dynamic levels, at different times post inoculation, of interferon in the blood of rabbits dead or recovered from, or vaccinated with, VHDV (28)
PROSPECTS

There is little doubt that considerable progress in the molecular biology, immunology, pathology, vaccinology, epidemiology and comprehensive control of VHD has been made since the disease investigated by Liu et al. (33) was first recorded; much, however, remains to be done. Studies on VHD and VHDV are currently at an exciting stage of development, and the author heartily hopes that Chinese scientists and colleagues of other countries and regions will collaborate closely to realise their common objective: to control and, finally, eradicate VHD throughout the world as rapidly as possible.

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LA MALADIE HÉMORRAGIQUE VIRALE DU LAPIN : ÉTAT DES RECHERCHES SUR LA VACCINATION ET LA RÉPONSE IMMUNITAIRE EN RÉPUBLIQUE POPULAIRE DE CHINE. – Hai-Bo Huang.

Résumé : La maladie hémorragique virale du lapin (VHD) est une maladie qui se présente sous forme aiguë avec une mortalité élevée n’affectant que les lapins adultes. Plusieurs vaccins ont été mis au point en République populaire de Chine, et l’usage extensif de ces vaccins a permis d’empêcher la propagation de la maladie. Le vaccin à base de tissus virulents inactivés par le formol induit, dès le 3e ou 4e jour suivant la vaccination, une bonne immunité qui persiste pendant au moins six mois. Le vaccin avec adjuvant huileux qui a été mis au point confère une protection plus durable. Le succès de l’adaptation du virus VHD (VHDV) en culture cellulaire ainsi que des essais de vaccinations préliminaires, permettront la production industrielle de vaccin en culture cellulaire. En cas d’urgence, l’utilisation d’antisérum hyperimmun confère une immunité passive de courte durée aux lapins menacés, et constitue un traitement efficace des lapins infectés. Les études histopathologiques et physio-pathologiques montrent que les cellules et organes immuns sont les premières cibles chez les lapins infectés. Les lésions du système endothélial des vaisseaux sanguins sont responsables de la coagulation intravasculaire disséminée (CIVD) que l’on peut observer au niveau des parenchymes. La destruction du système immunitaire et l’apparition d’une CIVD conduisent à une mort subite. Les études d’immunologie expérimentale ont démontré que l’immunité peut s’installer rapidement grâce à l’action coordonnée des macrophages et des lymphocytes T et B dans la phase initiale suivant l’immunisation, tandis que l’immunité humorale joue un rôle essentiel dans la protection à long terme contre la maladie. On peut également observer que la protection vaccinale est associée aux anticorps inhibant l’hémagglutination (HI). L’interféron agit probablement en tant qu’agent anti-VHDV peu après la vaccination.
Resumen: La enfermedad hemorrágica viral del conejo (VHD) se presenta en forma aguda con alta mortalidad; sólo afecta a los conejos adultos. Varias vacunas han sido puestas al punto en la República Popular de China y su extensiva aplicación en el terreno ha logrado impedir la propagación de la enfermedad. La vacuna, a base de tejidos virulentos inactivados por formol, induce una sólida inmunidad a partir del tercer o cuarto día post-vacunación, manteniéndose la inmunidad durante seis meses como mínimo. Se desarrolló también una vacuna con adyuvante oleoso, que confiere una protección más duradera. La exitosa adaptación del virus VHD (VHDV) en cultivo de células, conjuntamente a los ensayos de vacunaciones preliminares, permitirán la producción industrial de vacuna en el cultivo celular del virus. La utilización, en caso de urgencia, de un suero hiperinmune confiere una inmunización pasiva y de corto plazo a los conejos expuestos; este suero se utiliza también para el tratamiento de los conejos infectados. Los estudios histopatológicos y fisiopatológicos han demostrado que las células y órganos inmunes son los más atacados por la infección. Produce en los parénquimas un fenómeno de coagulación intravascular diseminada (CID), debido a las lesiones del sistema endotelial de los vasos sanguíneos. La destrucción del sistema inmune y la aparición de una CID conducen a la muerte súbita del animal infectado. Los estudios de inmunología experimental han demostrado que una inmunidad puede instalarse rápidamente gracias a la acción coordinada de los macrófagos y de los linfocitos B y T durante la fase inicial que sigue la inmunización, mientras que la inmunidad humoral asegura una protección a largo plazo contra la infección por VHDV. Se observa también que la protección post-vacunación está asociada a los anticuerpos inhibidores de la hemaglutinación. Se piensa que el interferón empieza a actuar como agente anti-VHDV rápidamente después de la vacunación.


REFERENCES


