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Mechanistic Bases for Adverse Vaccine Reactions and Vaccine Failures

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- I. Introduction
- II. Adverse Vaccine Reactions
 - A. Contamination of Vaccines with Extraneous Agents
 - B. Failure to Inactivate the Vaccine Organism in a Killed Vaccine
 - C. Adverse Vaccine Reactions Due to Residual Virulence of Vaccine Organisms
 - D. Adverse Vaccine Reactions Due to Vaccine-Induced Immune Suppression
 - E. Adverse Vaccine Reactions Due to Excessive Induction of Cytokine Release
 - F. Hypersensitivity Responses to Vaccine Antigens
 - G. Vaccine-Induced Triggering or Exacerbation of Hypersensitivity Disease to Nonvaccine Antigens
 - H. Vaccine-Induced Neoplastic Disease
 - I. MLV BVD Vaccine Triggering Mucosal Disease in Persistently Infected Cattle
 - J. Adverse Reactions Due to Multiple Vaccines Administered Concurrently
 - K. Injection Site Lesions
- III. Vaccine Failure
 - A. Insufficient Time to Develop Immunity
 - B. Vaccine Failure Due to Alterations in the Vaccine
 - C. Host Factors Responsible for Vaccine Failure
 - D. Vaccine Failure Due to Exposure to an Overwhelming Challenge Dose
 - E. Vaccine Failure Due to Inadequate Duration of Immunity
 - F. Vaccine Failure Due to Antigenic Differences between Vaccine and Field Strains
 - G. Vaccine Failure Due to Interference When Multiple Vaccines Are Administered Concurrently
- IV. Summary
- References

I. Introduction

Vaccines have proven to be very beneficial for controlling diseases in domestic animals. Their widespread use has dramatically reduced the incidence of severe and fatal diseases in companion animals (canine distemper, canine parvovirus, infectious canine hepatitis, and feline panleukopenia). They have also enabled the intensification of livestock production, thus enabling great increases in efficiency in animal origin food and fiber production. In addition, animal vaccines have improved human health through control of zoonotic diseases such as rabies, brucellosis, and leptospirosis. Indeed, it can be argued that animal vaccines have had a profound impact on modern society. Without effective rabies vaccines many people would not opt to keep companion animals in their homes, and without effective vaccines for controlling major diseases in food-producing animals the availability of animal proteins for human consumption would be greatly reduced. However, in spite of the success of animal vaccines, vaccines sometimes induce adverse reactions in animals and sometimes they fail to protect animals. When making decisions regarding vaccination programs for animals, veterinarians and animal owners must weigh the risks of vaccinating vs. the risks of not vaccinating. They must also use vaccines in a manner that induces optimal protection. This article provides an overview of some of the reasons why vaccines occasionally produce adverse reactions (Table I) and reasons why vaccines sometimes fail to protect animals from disease (Table II).

To produce protective immunity, a vaccine must stimulate a reaction in the animal. There usually must be a reaction both at the site of injection and systemically in order to produce an effective immune response. This reaction involves extensive activity by antigen-presenting cells, production of a variety of cytokines, and alterations in the trafficking of lymphocytes within the body. In addition, if the vaccine contains live organisms, they probably need to replicate to induce effective immunity. Live viruses must infect and replicate within cells. These essential reactions to a vaccine may induce observable clinical signs. Hopefully, the reaction to the vaccine will be mild and either unnoticeable or acceptable to the animal owner.

To understand vaccine safety and efficacy, it is important to understand the process by which vaccines are developed and tested by vaccine producers, and licensed by the United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics (CVB). The federal government regulations for the United States of America regarding veterinary vaccines

TABLE I

POTENTIAL MECHANISMS RESPONSIBLE FOR ADVERSE VACCINE REACTIONS

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- Contamination with extraneous agents
 - Failure to inactivate agent in killed vaccine
 - Residual virulence of vaccine organisms
 - Vaccination of immunosuppressed animal
 - Immune suppression induced by the vaccine
 - Excessive induction of cytokine release
 - Multiple vaccines administered concurrently
 - Hypersensitivity to vaccine antigens
 - Type I—immediate type
 - Type II—cytotoxic type
 - Type III—immune complex type
 - Type IV—delayed type
 - Triggering or exacerbation of hypersensitivity to nonvaccine antigens
 - Allergies
 - Autoimmune disease
 - Induction of neoplastic changes
 - MLV BVD vaccine triggering mucosal disease in persistently infected cattle
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are found in the Virus Serum Toxin Act (VSTA) in Title 9 of the Code of Federal Regulations (9 CFR). The VSTA gives the USDA the authority to regulate veterinary vaccines in the United States. According to the 9 CFR a USDA licensed biological must be “pure, safe, potent, and efficacious, and not be worthless, contaminated, dangerous, or harmful.” To understand this statement, it is important to understand what is meant by *safe* and *efficacious*. The definition found in the 9 CFR for safe or safety regarding veterinary biologics is “freedom from properties causing undue local or systemic reactions when used as recom-

TABLE II

POTENTIAL REASONS FOR VACCINE FAILURE

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- Insufficient time after vaccination to develop immunity
 - Something happened to the vaccine to make it ineffective
 - The physiologic status of the animal impaired the response to the vaccine
 - The animal was immunosuppressed at some point after vaccination
 - The animal was exposed to an overwhelming challenge dose of infectious agent
 - The duration of immunity after vaccination was not adequate
 - Important antigenic differences exist between the vaccine and field strains
 - Interference when multiple vaccines are administered concurrently
-

mended or suggested by the manufacturer." This definition has two important qualifiers for the term *safety*. It does not state that a vaccine should produce no reaction, rather it states that a vaccine should not cause "undue local or systemic reactions." This is a recognition of the fact that stimulating a potent immune response is likely to produce at least a mild local and systemic reaction in the animal. The second important point is that according to the definition the safety of the vaccine is only ensured when it is used as recommended or suggested by the manufacturer. The recommendations and suggestions can be found on the label for the vaccine. Most vaccine label statements will indicate that a particular vaccine is only for use in healthy animals of a particular species. Healthy is defined as "apparently normal in all vital functions and free of signs of disease."

The 9 CFR definition for efficacious or efficacy is "specific ability or capacity of the biological product to effect the result for which it is offered when used under the conditions recommended by the manufacturer." The label found on the vaccine will indicate the "result for which the vaccine is offered" and will also indicate the conditions under which the vaccine is recommended for use. Therefore, it is very important to read and follow label instructions in order to achieve maximum safety and efficacy from vaccine usage.

II. Adverse Vaccine Reactions

When animals develop adverse clinical signs within a few days to weeks after vaccination it is important to determine whether those clinical signs were vaccine induced or were not due to vaccination and only coincidentally occurred after the vaccine was administered. Animals commonly experience adverse clinical signs from a wide variety of causes and animals are commonly vaccinated. Therefore, it is to be expected that occasionally adverse clinical signs will occur after animals have been vaccinated for reasons unrelated to vaccine administration. There are also many reasons why vaccines may induce adverse reactions in the animal. It is important to differentiate true adverse vaccine reactions from false adverse vaccine reactions. Some of the causes of true adverse vaccine reactions are summarized in Table I and explained next.

A. CONTAMINATION OF VACCINES WITH EXTRANEIOUS AGENTS

A prominent example of this occurred when it was discovered that some lots of the live oral human poliomyelitis vaccine were contami-

nated with live simian virus 40 (SV40) in the 1950s (Pennisi, 1997; Shah and Nathanson, 1976). Millions of people were potentially exposed to live SV40 through administration of polio vaccine. To date, there is no solid epidemiologic evidence that any adverse health effects can be attributed to exposure to this agent. The SV40 virus had not yet been discovered when the human polio vaccine was produced. This raises the question of how does one test for all potential known and unknown viruses in each production lot of modified live virus vaccines. There have been numerous examples of extraneous agents contaminating veterinary vaccines. A list of these examples with appropriate references is given in Table III.

B. FAILURE TO INACTIVATE THE VACCINE ORGANISM IN A KILLED VACCINE

A dramatic example of this cause of adverse vaccine reactions occurred with the killed poliovirus vaccine in people. Formaldehyde, used to inactivate the poliovirus in the vaccine, failed to completely inactivate the vaccine virus (Gard and Lycke, 1957; Nathanson and Langmuir, 1963). This resulted in several cases of poliomyelitis in people that had received the vaccine. There have also been cases where formaldehyde failed to inactivate the foot-and-mouth disease virus (Beck and Strohmaier, 1987; King *et al.*, 1981) and the Venezuelan equine encephalitis virus (Kinney *et al.*, 1992) in their respective vaccines. In both of these cases the vaccine was shown to induce disease because of the lack of complete inactivation of the virus by the formaldehyde (Brown, 1993). An example of a failure to completely inactivate a bacterial pathogen in a killed bacterin occurred when thimerosal was used to inactivate *Haemophilus somnus* in an *H. somnus* vaccine. The thimerosal failed to kill the *H. somnus*. Approximately half the ani-

TABLE III

EXAMPLES OF ADVERSE VACCINE REACTIONS DUE TO EXTRANEIOUS AGENTS IN VACCINES

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- Live SV40 in human polio vaccine (Pennisi, 1997; Shah and Nathanson, 1976)
 - Killed hog cholera virus in pseudorabies vaccine (Jensen, 1981)
 - Live *Mycoplasma* in multiple live virus veterinary vaccines (Thornton, 1986)
 - Live border disease virus in Orf vaccine (Loken *et al.*, 1991)
 - Live bovine leukemia virus in babesiosis and anaplasmosis vaccines (Rogers *et al.*, 1988)
 - Live bovine viral diarrhea virus in hog cholera vaccine (Wensvoort and Terpstra, 1988)
 - Live border disease virus in pseudorabies vaccine (Vannier *et al.*, 1988)
 - Live blue tongue virus in a canine vaccine (Evermann *et al.*, 1994; Wilbur *et al.*, 1994)
 - Live bovine viral diarrhea virus in bovine vaccines (Lohr *et al.*, 1983; Neaton, 1986)
-

mals on one farm that were injected with vaccine shortly after its production developed thromboembolic meningoencephalitis and died.

C. ADVERSE VACCINE REACTIONS DUE TO RESIDUAL VIRULENCE OF VACCINE ORGANISMS

Modified live vaccine organisms have been attenuated to have reduced virulence. The attenuation must be shown to be stable when passaged through animals; therefore, reversion to virulence is thought to be a rare event. However, the attenuated vaccine strains may be capable of producing disease in immunosuppressed animals. Induction of disease by the vaccine organism has occasionally been reported when modified live virus (MLV) vaccines have been administered to healthy animals. However, it has occurred much more frequently when MLV vaccines are administered to unhealthy animals, by a nonrecommended route of exposure, to animals younger than the intended age for use of the vaccine, or when the vaccine is used in other than the intended species. Examples of MLV vaccines occasionally causing disease in healthy animals of the recommended species without apparent predisposing causes include the induction of rabies in dogs and cats after administration of an MLV rabies vaccine (Bellinger *et al.*, 1983; Esh *et al.*, 1982; Erlewein, 1981; Whetstone *et al.*, 1984; Pedersen *et al.*, 1978) and the induction of ovarian lesions and infertility in seronegative heifers administered MLV bovine herpesvirus 1 (BHV1) vaccine during estrus (Smith *et al.*, 1990; Chiang *et al.*, 1990; Miller *et al.*, 1989; Van der Maaten *et al.*, 1985). Since most heifers already have antibody to BHV1 due to either vaccination or previous exposure, this is thought to be a rare occurrence.

An example of vaccine-induced disease resulting from administration of vaccine to unhealthy animals is the induction of encephalitis by MLV canine distemper virus vaccine in dogs infected with canine parvovirus (Krakowka *et al.*, 1982). An example of adverse vaccine reaction after exposure of an animal to an MLV vaccine by a nonrecommended route of exposure is the induction of clinical feline viral rhinotracheitis after inadvertent exposure by the intranasal route to an MLV vaccine that was intended for intramuscular administration only (Povey and Wilson, 1978). MLV vaccines that have been shown to be safe in older animals may not be safe in neonatal animals. An MLV BHV-1 vaccine induced fatal BHV1 infection in neonatal purebred Salers calves (Bryan *et al.*, 1994). This may have been partially due to the breed of the animals since there are other reports that MLV BHV1 vaccines are apparently safe in neonatal calves (Schuh and Walker, 1990).

There have been several examples of MLV vaccines inducing lethal disease when administered to a species other than the target species. An MLV pseudorabies virus vaccine produced fatal pseudorabies in lambs (Clark *et al.*, 1984; Van Alstine *et al.*, 1984). This occurred when a syringe that had been used to administer the pseudorabies vaccine to pigs was used without proper disinfection to vaccinate lambs with another vaccine 3 days later. The MLV canine distemper virus vaccine has been shown to induce canine distemper infection in gray foxes (Halbrooks *et al.*, 1981), kinkajous (Kazacos *et al.*, 1981), and lesser pandas (Bush *et al.*, 1976). An MLV rabies vaccine has been shown to induce rabies in a pet skunk (Debbie, 1979). An MLV feline panleukopenia vaccine induced cerebellar hypoplasia when given experimentally to neonatal ferrets (Duenwald *et al.*, 1971).

D. ADVERSE VACCINE REACTIONS DUE TO VACCINE-INDUCED IMMUNE SUPPRESSION

An MLV bovine viral diarrhea (BVD) virus vaccine has been shown to suppress neutrophil function and lymphocyte blastogenesis in cattle (Roth and Kaerberle, 1983). This correlates with the observation that cattle tend to be somewhat more susceptible to bacterial pneumonia after administration of MLV BVD vaccines, especially if the animals are stressed at the time of vaccination. Several commercially available canine vaccines have been shown to be capable of inducing lymphopenia and suppressing blastogenesis of peripheral blood lymphocytes (Phillips *et al.*, 1989; Mastro *et al.*, 1986; Kesel and Neil, 1983). Lymphopenia and suppression of blood lymphocyte blastogenesis must be interpreted with caution, however, because it may only be an indication of changes in lymphocyte trafficking between the blood and lymphatic systems rather than an indication of depressed lymphocyte function. Vaccination with an MLV BHV1 vaccine has been shown to exacerbate the lesions of infectious bovine keratoconjunctivitis after experimental intraocular challenge with *Moraxella bovis* (George *et al.*, 1988).

E. ADVERSE VACCINE REACTIONS DUE TO EXCESSIVE INDUCTION OF CYTOKINE RELEASE

Interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF- α) are potent proinflammatory cytokines that are released by macrophages and other cells in response to infection, endotoxin and other bacterial components, and some vaccine adjuvants. These proinflammatory cytokines can induce a wide range of clinical signs. They may induce

acute inflammation at the local site of production, they may induce rapid synthesis and secretion of acute phase proteins by the liver, they may act on the hypothalamus to induce fever and malaise, they may reduce rate of gain and feed efficiency, and in sufficiently high concentrations they may induce hypoglycemia, reduce cardiac output, cause hypovolemic shock, and cause disseminated intravascular coagulation. Lipopolysaccharide (or endotoxin) from gram-negative bacteria is one of the most potent inducers of the proinflammatory cytokines (Cullor, 1994; Ellis and Yong, 1997; Galanos and Freudenberg, 1993). A number of other bacterial components, listed in Table IV, have also been shown to induce proinflammatory cytokine production (Erdos *et al.*, 1975; Henderson and Wilson, 1995; Allison and Eugui, 1995). These components are generally the most active if they are released from the degraded bacterial cell. Killed bacterins that contain excessive amounts of these bacterial components can induce clinical signs due to excessive induction of cytokine release. This is more likely to occur if multiple killed bacterins are administered at the same time and if these bacterins contain adjuvants that also induce cytokine release. The production of small amounts of proinflammatory cytokines is beneficial to the induction of a protective immune response. However, overproduction of the proinflammatory cytokines can have mild to very severe adverse side effects.

F. HYPERSENSITIVITY RESPONSES TO VACCINE ANTIGENS

Animals may develop any of the four types of immune-mediated hypersensitivity reactions to vaccine antigens. Systemic anaphylaxis

TABLE IV

BACTERIAL COMPONENTS THAT INDUCE
PROINFLAMMATORY CYTOKINES

-
- Lipopolysaccharide
 - Lipid A
 - Porins
 - Muramyl peptides
 - Peptidoglycan
 - Mycoplasma lipoproteins
 - Teichoic acid
 - Lipoteichoic acids
 - Lipoarabinomannans
 - Protein A
 - Superantigens
-

due to type I (immediate type) hypersensitivity is the most dramatic type of adverse vaccine reaction. This can occur as a result of the induction of IgE class antibody to essentially any component of a vaccine (Bonin *et al.*, 1973; Wilson *et al.*, 1968; Erdos *et al.*, 1975). As with all of the hypersensitivity reactions, the animal will not react on first exposure to an antigen (unless it has received passive antibody responsible for the reaction). It will only react after there has been sufficient time to produce the sensitizing antibody or memory T cells.

A local type I hypersensitivity reaction may occur due to IgE induced against infectious agents by the vaccine. Immunization against bovine respiratory syncytial virus under experimental conditions was shown to induce IgE antibodies specific for BRSV which apparently contributed to the development of symptoms following aerosol challenge with BRSV (Stewart and Gershwin, 1989a,b).

Vaccine-induced type II (cytotoxic type) hypersensitivity reactions can occur when vaccines are used that contain normal cell antigens. For example, vaccines that contain erythrocyte antigens may induce anti-erythrocyte antibodies leading to immune-mediated hemolytic anemia.

Type III (immune complex type) hypersensitivity can occur when circulating antibody specific for vaccine antigens is present at the time of vaccination. This can lead to an Arthus reaction at the site of injection due to complement fixation and neutrophil recruitment to the site. This mechanism is commonly responsible for the local inflammatory reaction at the site of injection, especially when administering booster vaccinations with killed vaccines. Sometimes, hypersensitivity can be one component of a more complex adverse vaccine reaction. Antibody induced by the vaccine may lead to immune complex type hypersensitivity reactions after the animal becomes infected when the antibody binds to replicating infectious agents. Examples include anterior uveitis and corneal edema (blue eye) after vaccination with canine adenovirus (Carmichael *et al.*, 1975; Wright, 1976) and the sensitization to the effusive form of feline infectious peritonitis after vaccination with experimental killed vaccines (Pedersen and Black, 1983).

Sometimes, hypersensitivity may be one component of a more complex adverse vaccine reaction. Bacterins for *Pasteurella haemolytica* which were marketed and widely sued for several years were of marginal efficacy and were even capable of increasing the severity of lesions in animals either experimentally (Wilkie *et al.*, 1980) or naturally exposed (Bennett, 1982) to the *P. haemolytica*. There are at least two hypothesized mechanisms by which the immune response induced by the bacterin could potentiate pneumonia after *P. haemolytica* challenge. First, the high concentration of complement-fixing antibody in-

duced by vaccination with a bacterin could rapidly activate complement if a large number of *P. haemolytica* organisms were introduced into the lung either naturally or artificially. This could cause a type III hypersensitivity response leading to acute inflammation in the lung and severe pneumonia. Second, antibody against cell surface antigens will opsonize the *P. haemolytica* in the lung and enhance phagocytosis by alveolar macrophages and neutrophils. Because there may be insufficient leukotoxin-neutralizing antibody or cell-mediated immunity to activate phagocytes, the bacteria present in the alveoli and ingested by phagocytes are not efficiently killed and may produce leukotoxin that could destroy the phagocytes. This destruction would cause the phagocytes to release their hydrolytic enzymes into the lung.

G. VACCINE-INDUCED TRIGGERING OR EXACERBATION OF HYPERSENSITIVITY DISEASE TO NONVACCINE ANTIGENS

In the last few years concern has been expressed that vaccination may trigger or exacerbate autoimmune disease or allergies (hypersensitivities), especially in dogs and cats (see article by Dr. Jean Dodds in this volume). Vaccination has been shown to augment production of IgE antibody to pollen in inbred atopic dogs (Frick and Brooks, 1983). Remember that animals with allergies or autoimmune diseases are not healthy animals, and that vaccines are only recommended for use in healthy animals. Dr. Harm HogenEsch addresses the topic of vaccine-induced autoimmunity in another article in this volume.

H. VACCINE-INDUCED NEOPLASTIC DISEASE

In recent years, an increased incidence of fibrosarcoma occurring at sites commonly used for vaccination in cats has been observed (Hendrick *et al.*, 1992, 1994; Kass *et al.*, 1993). The causal relationship and mechanistic basis for vaccine-associated fibrosarcomas in cats has not been firmly established (Ellis *et al.*, 1996).

I. MLV BVD VACCINE TRIGGERING MUCOSAL DISEASE IN PERSISTENTLY INFECTED CATTLE

Shortly after MLV BVD vaccines were introduced, it was recognized that a very small percentage of cattle developed a syndrome 7–20 days after vaccination that closely resembled BVD mucosal disease (Lambert, 1973; Peter *et al.*, 1967). Based on the current understanding of the pathogenesis of mucosal disease (Bolin *et al.*, 1985; Brownlie *et al.*, 1984) this was almost certainly due to the cytopathic BVD virus in the

vaccine triggering mucosal disease in calves that were immunotolerant to, and persistently infected with, a noncytopathic BVD virus. The mechanistic basis for the induction of the lesions of mucosal disease is not clearly understood. This unique syndrome is primarily due to abnormalities in the animal rather than to a defect in the vaccine.

J. ADVERSE REACTIONS DUE TO MULTIPLE VACCINES ADMINISTERED CONCURRENTLY

Vaccines are tested for safety and efficacy when administered to healthy animals in the formulation in which they are packaged to be sold. Vaccines are not required to be tested for safety and efficacy when administered concurrently with other vaccines. This would not be practical since there are too many possible vaccines that may potentially be used in combination. An example of a safety problem that occurred when two different vaccines were administered concurrently involved a newly developed MLV canine coronavirus and parvovirus vaccine given at the same time as an MLV canine distemper–hepatitis virus vaccine. The evidence indicated that the other MLV components allowed the canine coronavirus in the vaccine to induce neurologic disease in some vaccinated animals (Wilson *et al.*, 1986).

K. INJECTION SITE LESIONS

Injection site lesions are a common occurrence and are of great concern in food-producing animals. They may lead to unacceptable blemishes in, or decreased quality of, meat intended for human consumption. There are many possible causes of injection site lesions, including organisms introduced with a contaminated needle, live contaminating organisms in the vaccine, adjuvant induced reactions, cytokine release, hypersensitivity reactions (types I, II, III, or IV), trauma, and hemorrhage (Straw *et al.*, 1985, 1990; Droual *et al.*, 1993; Littledike, 1993; Stokka *et al.*, 1994; Dexter *et al.*, 1994; Apley *et al.*, 1994; Straw, 1986).

III. Vaccine Failure

Vaccines that are licensed by the USDA have been tested to determine that they are safe and effective. However, “effective” is a relative term. It does not mean that the vaccine must be able to induce complete immunity under all conditions which may be found in the field. This would not be realistic since the immune system is not capable of such potent protection under adverse conditions.

To be federally licensed, the vaccine must have been tested under controlled experimental conditions. The vaccinated group must have had significantly less disease than the nonvaccinated control group. This testing is typically done on healthy, nonstressed animals under good environmental conditions and with a controlled exposure to a single infectious agent. Vaccines may be much less effective when used in animals that are under stress, incubating other infectious diseases, or exposed to a high dose of infectious agents due to overcrowding or poor sanitation.

It is important to remember that for most diseases the relationship between the infectious agent and the host is sufficiently complicated that vaccination cannot be expected to provide complete protection. The vaccine can increase the animal's resistance to disease, but this resistance can be overwhelmed if good management practices are not followed. Some of the causes for vaccine failure are summarized in Table II and explained next.

A. INSUFFICIENT TIME TO DEVELOP IMMUNITY

The host requires several days after vaccination before an effective immune response will develop. If the animal encounters an infectious agent near the time of vaccination, the vaccine will not have had time to induce immunity. The animal may come down with clinical disease resulting in apparent vaccination failure. In this situation, disease symptoms will appear shortly after vaccination and may be mistakenly attributed to vaccine virus causing the disease (McKercher *et al.*, 1968).

B. VACCINE FAILURE DUE TO ALTERATIONS IN THE VACCINE

Improperly handled and administered vaccines may fail to induce the expected immune response in normal, healthy animals. Modified live bacterial and viral vaccines are only effective if the agent in the vaccine is viable and able to replicate in the vaccinated animal. Observing proper storage conditions and proper methods of administration are very important for maintaining vaccine viability. Failure to store the vaccine at refrigerator temperatures, or exposure to light, may inactivate the vaccine. Even when stored under appropriate conditions, the vaccine loses viability over time. Therefore, vaccines that are past their expiration date should not be used. The use of chemical disinfectants on syringes and needles can inactivate modified live vaccines if there is any residual disinfectant.

The use of improper diluent or the mixing of vaccines in a single syringe may also inactivate modified live vaccines. Diluents for lyophilized vaccines are formulated specifically for each vaccine. A diluent that is appropriate for one vaccine may inactivate a different vaccine. Some vaccines and diluents contain preservatives that may inactivate other modified live vaccines. For these reasons, multiple vaccines should not be mixed in a single syringe unless that particular combination has been adequately tested to ensure there is no interference.

C. HOST FACTORS RESPONSIBLE FOR VACCINE FAILURE

Vaccine failures may occur because a vaccinated animal is not able to respond appropriately to the vaccine. Vaccine failure in young animals may be due to the presence of maternal antibody which prevents adequate response to vaccination. It can also be due to immunosuppression from a variety of causes.

Maternal antibodies derived from colostrum are a well-known cause of vaccine failure (Greene, 1990). These antibodies in the young animal's circulation may neutralize or remove the antigen before it can induce an immune response. Typically, virulent infectious agents are capable of breaking through maternal immunity earlier than modified live or killed vaccines. This means that even if young animals are immunized frequently, there still may be a period when they are vulnerable to infection. Vulnerability occurs between the time that young animals lose their maternal antibody and before they develop their own active immune responses. This period can be shortened by the use of less-attenuated and/or higher titered modified live vaccines or the use of killed vaccines with high antigenic mass and strong adjuvants (Smith-Carr *et al.*, 1997; Larson and Schultz, 1996).

A high challenge dose of infectious agents will break through maternal immunity sooner than low exposure to infectious agents. Therefore, overcrowding and poor sanitation exacerbate the problem of inducing immunity in young animals before they come down with clinical disease.

Veterinarians commonly recommend that puppies and kittens be vaccinated every 3 weeks between approximately 6 and 18 weeks of age. However, for large domestic animals, a single vaccination is commonly recommended to induce immunity during the first few weeks or months of life. There is no inherent difference between large and small domestic animals in their responses to vaccination in the face of maternal immunity. The frequent vaccinations recommended in pup-

pies and kittens minimizes the period of vulnerability to infectious diseases.

Because only one vaccination is commonly recommended for large domestic animals, the timing of vaccination is important. If the vaccine is administered too soon, it may be ineffective because of the presence of maternal antibody. If the vaccine is administered after all maternal antibodies are gone from animals in the group, there may be a prolonged period of vulnerability before they develop their own immune response. The optimal age to vaccinate young animals is highly variable. It will depend on the antibody titer of the mother and the amount of colostrum ingested. It is impossible to predict an optimal age to vaccinate a young animal, unless its antibody titers are determined. Most veterinarians and producers decide that because of time and expense considerations it is impractical to vaccinate young food-producing animals frequently to minimize their period of vulnerability to infection. However, frequent vaccination may be justified in cases of unusually high disease incidence in young animals.

Immunosuppression due to a variety of factors including stress, malnutrition, concurrent infection, or immaturity or senescence of the immune system may also lead to vaccination failure. If the immunosuppression occurs at the time of vaccination, the vaccine may fail to induce an adequate immune response. If the immunosuppression occurs sometime after vaccination, then disease may occur due to reduced immunity in spite of an adequate response to the original vaccine. Therapy with immunosuppressive drugs (e.g., glucocorticoids) may also cause this to occur.

D. VACCINE FAILURE DUE TO EXPOSURE TO AN OVERWHELMING CHALLENGE DOSE

Most vaccines do not produce complete immunity to disease. They provide an increased ability to resist challenge by infectious agents. If a high-challenge dose of organisms is present due to overcrowding or poor sanitation, the immune system may be overwhelmed, resulting in clinical disease.

E. VACCINE FAILURE DUE TO INADEQUATE DURATION OF IMMUNITY

The peak response to a vaccine typically occurs 2–6 weeks after vaccination. The level of immunity then begins to gradually decline. A common recommendation is to revaccinate annually. However, if the animal did not have a strong initial immune response due to stress at

the time of vaccination, or if it is stressed and exposed to a high-challenge dose several months after vaccination, there may not be enough residual immunity to protect the animal. This is especially true for certain killed vaccines. Under these circumstances, it may be necessary to revaccinate more frequently than once per year.

F. VACCINE FAILURE DUE TO ANTIGENIC DIFFERENCES BETWEEN VACCINE AND FIELD STRAINS

For certain types of infectious agents, particularly bacteria that are vulnerable to control by the development of antibodies against surface components and viruses which use RNA as their genetic material and consequently have high mutation rates, there are often several antigenic variants of each agent. For antibody-mediated protection to be effective, the antibodies formed must bind the important strain-specific antigens on the surface of the bacteria or virus. Cell-mediated immunity is usually not as strain specific as antibody-mediated immunity. To determine if a vaccine's failure to protect is due to antigenic differences between the vaccine and field strains it is necessary to isolate the field strain and compare it to the vaccine strain. Antigenic differences between strains leading to lack of vaccine efficacy are usually more of a problem with killed vaccines than modified live vaccines.

G. VACCINE FAILURE DUE TO INTERFERENCE WHEN MULTIPLE VACCINES ARE ADMINISTERED CONCURRENTLY

As mentioned earlier, vaccines are tested for safety and efficacy when administered singly to animals. However, multiple vaccines are commonly administered concurrently to animals. Very little published data are available concerning the efficacy of vaccines when used in combination. One study demonstrated that there was no detrimental effect on the antibody response to a bovine respiratory syncytial virus vaccine when administered in combination with up to 17 different immunogens (Carmel *et al.*, 1992). In contrast, an MLV BHV1 vaccine when administered in combination with an experimental *Pasteurella haemolytica* vaccine containing outer membrane proteins and genetically attenuated leukotoxin significantly reduced the antibody response to the leukotoxin and the efficacy of the *P. haemolytica* vaccine in preventing morbidity and mortality due to bovine respiratory disease (Harland *et al.*, 1992).

IV. Summary

Mild local and systemic reactions to vaccines are to be expected as a natural consequence of vigorously stimulating the immune system. Dramatic adverse reactions to vaccines are occasionally due to mistakes during the production or handling of vaccines. More often, they are due to not following label instructions, particularly the restriction to only use vaccines in healthy animals. It is important to publish well-documented instances of adverse vaccine reactions so that producers and users of vaccines can all learn from the experience and avoid similar problems.

Vaccine failure to protect from disease is usually due to problems with either client education or compliance with good animal management practices. It is important for clients to understand the proper timing and method of vaccine administration, what to realistically expect for vaccine efficacy, and the importance of minimizing immunosuppressive factors and exposure to high doses of infectious agents in vaccinated animals.

Veterinary vaccines have produced dramatic benefits in terms of animal health, human health, and efficiency of food production. Advances in research and the accumulating experience with vaccines are leading to safer and more effective vaccines. Proper usage of vaccines and adherence to good management practices will continue to be essential to achieve maximal vaccine safety and efficacy.

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