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CHAPTER 10

Adverse Consequences of Vaccination

OUTLINE

Adverse Events
Hypersensitivity Responses
Residual Virulence
Other Issues
Errors in Manufacture and Administration
Human Illness
Reporting

Vaccination is the only safe, reliable, and effective way of protecting animals against the major infectious diseases. Society does not remember the devastating toll taken by infectious diseases before the development of modern vaccines. Exaggerated fear of negative side effects has discouraged owners from having their pets (and themselves) from being vaccinated. The rise of the Internet and the development of social media have enabled those who oppose vaccination to spread their opinions. Those who resist vaccination for themselves or their children are unlikely to be enthusiastic about vaccinating their pets. Much of this resistance is a result of adverse events and controversy regarding effectiveness associated with the earliest vaccines. In spite of the fact that these problems have long been solved, it takes a considerable time before confidence is restored. There is a lack of awareness of the rigorous safety tests that modern vaccines must undergo before they are marketed. Good manufacturing practices and the quality control procedures used by the biologics industry, together with rigorous regulatory controls, serve to minimize the occurrence of these events. Past issues have been corrected and vaccine safety has steadily improved. Modern vaccines are safe to use and overwhelmingly beneficial. Adverse events associated with vaccination that might compromise the health of an animal are usually rare, mild, and transient. Hypothetical, speculative, or historical adverse effects sometimes dominate perceptions. Nevertheless, it has been truly said, "The most dangerous vaccine is the one not given." In reading this chapter the reader should be aware that the events described here are rare, somewhat historical, and relatively unimportant when compared with the benefits of vaccination.

Drivers of vaccine usage differ significantly between companion animals and commercial livestock. Owners of companion animals are concerned for the health and well-being of their pets and are intolerant of any adverse events that cause discomfort, pain, or sickness. Livestock producers in contrast vaccinate to maintain livestock health, prevent disease spread, maximize economic return, and to minimize zoonotic disease risks. Vaccines that cause a drop in milk production, decreased feed conversion, increased time to market, or a decline in carcass quality may have significant economic consequences and will not be used.

ADVERSE EFFECT PRINCIPLES

In determining whether a vaccine causes an adverse effect, the following three principles should apply. First, is the effect consistent? The clinical responses should be the same if the vaccine is

given to a different group of animals, by different investigators, and irrespective of the method of investigation. Second, is the effect specific? The association should be distinctive and the adverse event linked specifically to the vaccine concerned. It is important to remember that an adverse event may be caused by vaccine adjuvants and components other than the major antigens. Finally, there must be a temporal relationship. Administration of the vaccine should precede the earliest manifestations of the event or a clear exacerbation of a continuing condition.

The US Centers for Disease Control and Prevention (CDC) has classified adverse events as follows:

1. Vaccine-induced events: These are events that would not occur in the absence of vaccination and are therefore attributed to the vaccine. An example would be an allergic response to a vaccine component such as egg protein.
2. Vaccine potentiated reactions: These are events that might have occurred anyway but may have been precipitated by the vaccine. One possible example is purpura hemorrhagica in horses.
3. Programmatic error: Events that occur in response to technical errors in vaccine storage, preparation, handling, and administration.
4. Coincidental events: These are simply events that happen by chance or result from some underlying illness.

Adverse Events

The use of vaccines is not free of risk, and an owner has reason to be upset if their healthy animal is sickened by the administration of a vaccine. Residual virulence and toxicity, allergic responses, disease in immunodeficient hosts, neurological complications, and harmful effects on the fetus are potential risks associated with the use of vaccines (Table 10.1). Veterinarians should use only licensed vaccines, and the manufacturer's recommendations must be carefully followed. Before using a vaccine, the veterinarian should consider the likelihood that an adverse event will happen, and also the possible consequences or severity of this event. These factors must be weighed against the benefits to the animal. A common but mild complication requires a very different consideration than a rare, severe complication (Table 10.2).

The issue of the risk associated with vaccination remains in large part a philosophical one because the advantages of vaccination are well documented and extensive, whereas the risk for adverse effects is poorly documented, and in many cases, largely speculative. Nevertheless, established facts should be recognized, unsubstantiated allegations rebutted by sound data, and uncertainties acknowledged. For example, there is absolutely no evidence that vaccination itself leads

TABLE 10.1 ■ **The Classification of Adverse Events**

Classification	Features
Certain	Event with appropriate time course No other explanation Consistent definitive signs
Probable	Reasonable time relationship Unlikely to be caused by something else
Possible	No other reasonable explanation Reasonable time relationship
Unlikely	No reasonable time relationship Other plausible explanations
Unknown	Insufficient data Cannot be verified

TABLE 10.2 ■ **Frequency of Adverse Reactions as Defined by the European Medicines Agency**

	Frequency
Very common	More than 1 in 10 animals showing adverse reactions (>10%)
Common	Greater than 1 but less than 10 animals per 100 animals vaccinated (1%–10%)
Uncommon	More than 1 but less than 10 animals per 1000 animals vaccinated (0.1%–1%)
Rare	More than 1 but less than 10 animals per 10,000 animals vaccinated (0.01%–0.1%)
Very rare	Less than 1 animal in 10,000 reported (<0.01%)

BOX 10.1 ■ Canine Autism and Vaccination

Autism spectrum disorder is a chronic developmental disorder in children. Its causes are largely unknown. It usually becomes apparent in young children over one year of age at around the same time they receive their initial vaccinations. In a paper published in 1998, a physician studied 12 children with autism. He asked the parents if the children had been vaccinated, with the measles, mumps, and rubella vaccine, within the previous two weeks. Eight said yes, so the author went on to assert in his paper that this vaccine caused autism. He postulated that autism resulted from measles infection. The paper was eventually retracted and the author lost his medical license. Subsequent population-based studies have failed to demonstrate any link between vaccination and autism. Thousands of children are vaccinated every year and large amounts of data are available for analysis. All these show the same thing. There is no link between vaccination and autism risk. However, the word was out. The Internet and Twitter spread the word. Additionally, pet owners began to claim that their dog's behavior had changed after vaccination—canine autism. The British Veterinary Association felt obliged to issue a statement regarding these claims.

"There is currently no reliable scientific evidence to indicate autism in dogs or a link between vaccination and autism. Vaccinations save lives and are an important tool in keeping our pets healthy. All medicines have potential side-effects but in the case of vaccines, these are rare and the benefits of vaccination in protecting against disease far outweigh the potential for an adverse reaction."

to ill health. Although difficult to prove, a negative, competent statistical analysis has consistently failed to demonstrate any general adverse effect of vaccination.

Identification of an adverse event is based on the clinical judgment of the attending veterinarian and is therefore subject to bias. Standard case definitions of a vaccine-associated adverse event are not yet available. It still is often difficult to distinguish association from causality (Box 10.1).

Traditionally, adverse events resulting from vaccine administration have been reported by veterinarians to manufacturers or government agencies. The resulting numbers have been difficult to analyze satisfactorily for two major reasons. First, reporting is voluntary, so significant underreporting occurs. Adverse events are often regarded as insignificant, or it may be inconvenient to report them. Second, very little data has been available on the number of animals vaccinated. Although manufacturers know the number of doses of vaccine sold, they are unable to measure the number of animals vaccinated.

It has, however, proved possible by examining the electronic medical records of a very large small animal general practice, to determine the prevalence of vaccine-associated adverse events in over a million dogs. The use of a standardized reporting system within a very large population has permitted objective analysis of the prevalence of adverse events occurring within three days of vaccine administration. Out of 1,226,159 dogs receiving 3,439,576 vaccine doses, 4678 adverse events were recorded (38.2/10,000 dogs); 72.8% of these events occurred on the same day the vaccine was administered, 31.7% were considered to be allergic reactions, 1.7% were classified as anaphylaxis, and 65.8% were considered "vaccine reactions" and were likely caused by innate immune responses. Three dogs died. The lowest rate of such events was associated with *Bordetella*

vaccination and the highest rate with Lyme disease vaccine. Additional analysis indicated that the risk of adverse events was significantly greater for small dogs than for large dogs (Fig. 10.1); for neutered than for sexually intact dogs; and for dogs that received multiple vaccines on one occasion. Each additional vaccine dose administered increased the risk of an adverse event occurring by 27% in dogs under 10 kg and by 12% in dogs heavier than 12 kg (Fig. 10.2). High-risk breeds included dachshunds, pugs, Boston terriers, miniature pinschers, and Chihuahuas.

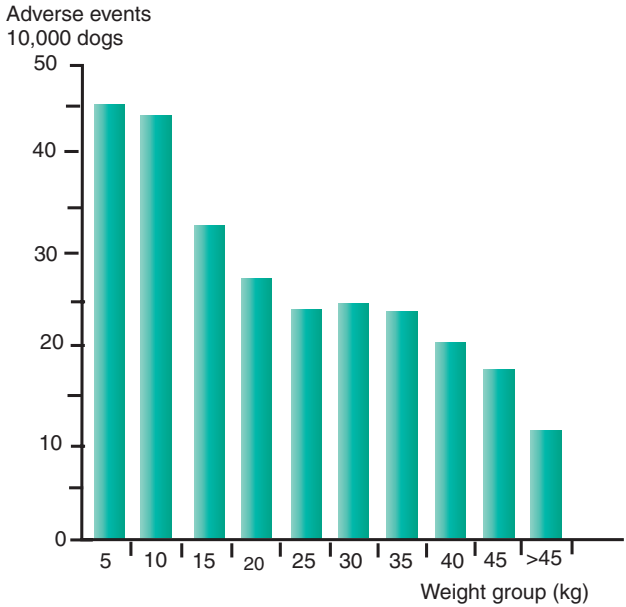

Fig. 10.1 The mean vaccine associated adverse event rates occurring within 3 days of vaccination in dogs of different weights. This survey was undertaken using data from 1,226,159 dogs at 360 veterinary hospitals in 2002 and 2003. Small dogs receiving a relatively higher vaccine dose react accordingly. (From Moore, G.E., Guptil, L.F., Ward, M.P., et al. [2005]. Adverse events diagnosed within three days of vaccine administration in dogs. *JAVMA*, 227, 1102–1108. Fig. 1. With permission.)

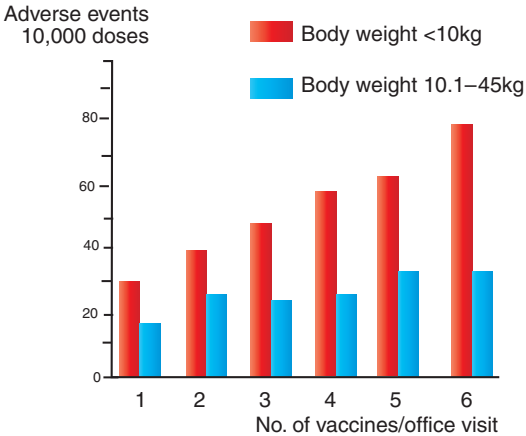

Fig. 10.2 The increase in adverse events associated with multiple vaccines given at a single office visit. This survey was undertaken using data from 1,226,159 dogs at 360 veterinary hospitals in 2002 and 2003. Presumably this reflects the additive effects of these vaccines on the innate immune response. (From Moore, G.E., Guptil, L.F., Ward, M.P., et al. [2005]. Adverse events diagnosed within three days of vaccine administration in dogs. *JAVMA*, 227, 1102–1108. Fig. 4. With permission.)

Overall, the increased prevalence of adverse events in young adult, small-breed, neutered dogs and their relationship to multiple dosing suggests that veterinarians should look carefully at the practice of giving the same vaccine dose to all dogs irrespective of their size.

In another report, from Japan 351 dogs showed an adverse event out of 57,300 vaccinated (62.7/10,000 doses). (Vaccines used included canine parvovirus, canine distemper, canine adenovirus 2, canine coronavirus, and leptospirosis.) Of these 351 dogs, 1 died, 41 had anaphylaxis, 244 developed dermatological signs, and 160 showed gastrointestinal signs. About half the anaphylaxis events occurred within 5 minutes of vaccination. Additional analysis of these anaphylaxis cases reported 87% collapse, 77% cyanosis, and both collapse and cyanosis in 71% of affected dogs. Breeds affected included miniature dachshunds (50%; these accounted for about 30% of all the anaphylaxis cases), Chihuahuas (10%), mixed breeds (5%), and toy poodles (5%). Miniature Schnauzers also appeared to be unusually prone to anaphylaxis. The highest frequency of adverse reactions occurred in dogs under 5 kg. Most adverse events were observed within 12 hours after vaccination. The adverse event rate in Japan as reported here (62.7/10,000 doses) is much higher than in the United Kingdom (0.093/10,000 doses), or in the United States (38.2/10,000 dogs).

INNATE IMMUNE REACTIONS

Vaccines may elicit mild transient injection site reactions as a result of inflammation. These inflammatory responses may manifest themselves within two to three days. As pointed out in Chapter 2, some degree of inflammation is required for the efficient induction of protection. This may cause pain or pruritus. The sting produced by some vaccines may present problems, not only to the animal being vaccinated, but also to the vaccinator, if the animal reacts violently. Lethargy, anorexia, soreness, minor behavioral changes, and tenderness at the vaccine site are normal postvaccinal responses and should resolve within 12 to 24 hours. Swellings may develop at the reaction site less commonly. These may be firm or edematous and may be warm to the touch. They appear within 24 hours and can last for about a week. Unless an injection-site abscess develops, these swellings leave little trace.

Vaccines containing killed gram-negative bacteria may be intrinsically toxic owing to the presence of pathogen-associated molecular patterns such as endotoxins, lipids, muramyl peptides, and porins that can bind to pattern recognition receptors and provoke cytokine release. In extreme cases this may lead to anorexia, and fever. Although such reactions are usually only a temporary inconvenience to male animals, they may be sufficient to provoke early embryonic deaths in pregnant females. It may be prudent to avoid vaccinating pregnant animals unless the risks of not giving the vaccine are considered to be too great. Vaccination with either immune-stimulating complex (ISCOM) vaccines or live recombinant vectored vaccines against influenza and tetanus may induce an acute-phase response in horses.

Innate immune responses may reduce an animal's growth rate and diminish its feed efficiency. This growth suppression can be mimicked by injection of interleukin (IL)-1 and tumor necrosis factor (TNF)-α. These cytokines act on the brain to reduce appetite while at the same time, causing degradation of skeletal muscle.

Intranasal vaccines such as those containing *Bordetella bronchiseptica* and some viruses may cause transient cough or sneezing. This simply reflects the mild innate response triggered as the vaccine organisms invade the upper respiratory tract.

Hypersensitivity Responses

TYPE I HYPERSENSITIVITIES

Vaccines have the potential to cause rare but serious allergic reactions (type I hypersensitivity). For example, allergic responses may occur when an animal produces immunoglobulin (Ig)E in

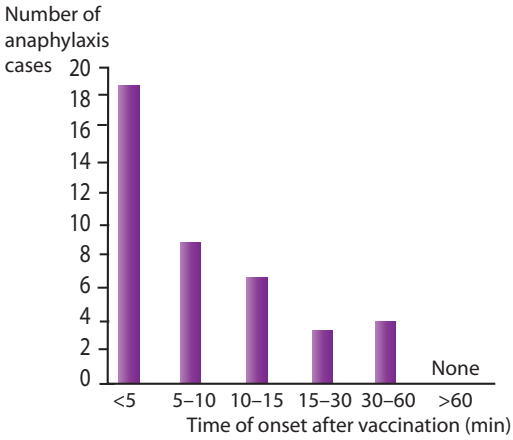

Fig. 10.3 The time of onset of vaccine-associated anaphylaxis in Japanese dogs. A total of 359 dogs showed vaccine-associated adverse events. The great majority develop within 10 minutes reflecting an immediate hypersensitivity whereas 299 occurred within 12 hours. (From Miyaji, K., et al. [2012]. Large-scale survey of adverse reactions to canine non-rabies combined vaccines in Japan. *Vet Immunol Immunopathol*, 145, 447–452. With permission)

response, not only to the immunizing antigen, but also to other components in vaccines. The most significant allergens are often vaccine excipients. For example, reactions are most likely to occur after injection of vaccines that contain trace amounts of fetal calf serum (specifically bovine serum albumin), egg proteins (ovalbumin), or gelatin. (Gelatin and serum albumin are added to vaccines as stabilizers to protect the vaccine antigens during the freeze-drying process.) Some vaccines may also contain antibiotics such as neomycin to which an animal may be sensitized. Severe allergic responses have been associated with the use of killed foot-and-mouth disease, rabies, and contagious bovine pleuropneumonia vaccines in cattle. Signs include angioedema, affecting mainly the head and ears, urticaria, pruritus, acute-onset diarrhea, vomiting, dyspnea, and collapse. All forms of hypersensitivity are more commonly associated with multiple injections of antigens and therefore tend to be associated with the use of killed vaccines.

It is important to emphasize that a type I hypersensitivity reaction is an immediate response to an antigen and occurs within a few minutes after exposure to an antigen (Fig. 10.3). It is good practice to keep an animal in the clinic for 15 to 25 minutes after vaccination to ensure that any immediate problems can be promptly recognized and treated (Box 10.2). Reactions occurring more than two or three hours after administration of a vaccine are likely not type I hypersensitivity reactions.

TYPE II HYPERSENSITIVITIES

In type II hypersensitivity reactions, antibodies directed against an animal's own cells act together with complement to cause cell lysis. These antibodies are usually induced by the presence of animal cells in the vaccine.

Hemolytic Disease of the Newborn

Natural hemolytic disease of the newborn (HDN) in calves is very rare, but it has resulted from vaccination against anaplasmosis or babesiosis. These vaccines contain pooled red cells from infected calves. In the case of *Anaplasma* vaccines, for example, the blood from infected donors is pooled, freeze-dried, and mixed with adjuvant before being administered to cattle. The vaccine against babesiosis consists of fresh, infected calf blood. Both vaccines cause infection, and consequently, the development of immunity in recipients. They also stimulate the production of antibodies against the injected red cells. If cows sensitized by these vaccines are then mated with bulls

BOX 10.2 ■ The Treatment of Acute Anaphylaxis

Anaphylaxis is a life-threatening medical emergency. Deterioration can occur very rapidly and time is of the essence. Initiate treatment immediately. If an animal is undergoing acute anaphylaxis take the following steps:

1. Stop administering the vaccine.
2. In the case of dogs and cats, administer epinephrine 1:1000 at 0.01 mg/kg intramuscularly. Repeat every 5–15 minutes if necessary. If very severe and shock has developed, place an intravenous catheter and administer 0.1 mg/kg of 1:10,000 epinephrine by slow intravenous infusion and monitor blood pressure and perfusion. Alternative routes of administration include intracardiac or intratracheal. Avoid subcutaneous administration because epinephrine is a potent vasoconstrictor and absorption is delayed.

   In the case of foals administer epinephrine 1:1000 at 0.01 to 0.02 mg/kg (0.5–1ml for a 50 kg foal) given slowly intravenously or intramuscularly. In adult horses administer epinephrine at 0.01 mg/kg (3–8 ml for a 450 kg horse) slowly intravenously. If the condition is mild, this dose may be administered intramuscularly. Repeat every 10–20 minutes if necessary.
3. Secure the airway, intubate if necessary, and administer oxygen to animals showing respiratory symptoms.
4. Provide isotonic shock crystalloid fluids (normal saline or lactated Ringer solution) intravenously to help restore adequate blood pressure in hypotensive animals. The volume required depends on the animal's response, but may be as high as 90ml/kg for dogs and 60ml/kg for cats.
5. Administer an H1-antihistamine such as diphenhydramine every 8–12 hours if necessary.
6. Once the animal is stabilized consider administering a fast acting glucocorticosteroid by the slow intravenous route to prevent late-phase responses.

carrying the same blood groups, they can transmit these antibodies to their calves through colostrum. The calves that drink this colostrum may then develop hemolytic disease. HDN in piglets had a similar pathogenesis when sows were immunized with a hog cholera vaccine containing pig blood.

Bovine Neonatal Pancytopenia

Beginning in 2007, multiple outbreaks of an unexplained hemorrhagic disease in newborn beef calves were reported from many countries in Western Europe. Affected calves showed sudden onset bleeding including nasal hemorrhage, petechiation on mucus membranes, and excessive bleeding from minor wounds such as injection, or ear-tag sites. The disease appeared 7 to 8 days after birth and affected calves could die within 48 hours. It is now called bovine neonatal pancytopenia (BNP). Investigation showed an early drop in platelets, monocytes, and neutrophils was followed by drops in erythrocyte and lymphocyte numbers. The net result was a profound pancytopenia. The bone marrow could be completely aplastic. Mortality was as high as 90% in severely affected calves, but there were also many subclinical cases.

Because this disease only occurred in suckled calves and developed within hours of first suckling, it appeared to result from the consumption of colostrum. Further investigations showed that the colostrum from these cows contained antibodies directed against the major histocompatibility complex (MHC) class I molecules expressed on neonatal leukocytes and bone marrow stem cells. Cells of the thrombocyte, lymphocyte and monocyte lineages, and precursors of neutrophil, erythrocyte, and eosinophil lineages were affected.

Further investigations showed that the disease was triggered by administration of a specific vaccine against bovine virus diarrhea (BVD). This vaccine—Pregshure—contained inactivated bovine viral diarrhea virus (BVDV) grown in bovine kidney cells. A potent, oil-in-water emulsion adjuvant containing Quil A, cholesterol, and mineral oil was then added. Immunization with this

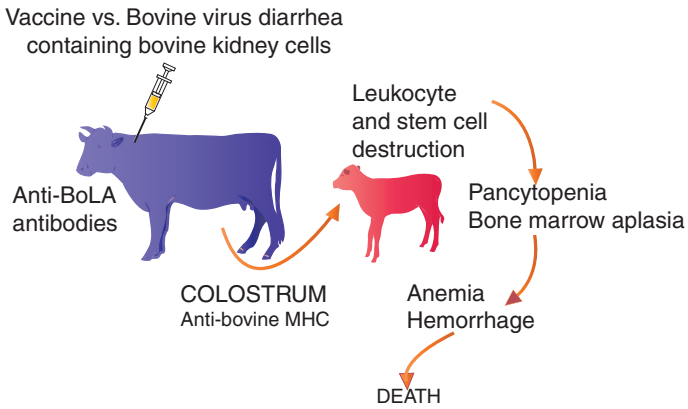

Fig. 10.4 The pathogenesis of bovine pancytopenia. Inoculation of a vaccine containing bovine kidney cells results in the production of antibodies against MHC antigens. When ingested by drinking colostrum, these antibodies destroy bone marrow stem cells in their calves. This results in a loss of all their white blood cells including platelets. *MHC,* Major histocompatibility complex.

vaccine induced antibodies against the bovine kidney cells in some cows. These antibodies, when transferred to calves via colostrum, bound to their leukocytes and bone marrow stem cells, killed them, and so induced pancytopenia (Fig. 10.4). Not all calves born from cows that received this specific vaccine developed clinical disease. The quantity and specificity of their antibody response determined the risk to their calves. Antibody levels remained high in some cows for many years and were boosted by each pregnancy. As a result, BNP cases occurred for many years after Pregshure was removed from the market in 2010.

TYPE III HYPERSENSITIVITIES

Type III hypersensitivity reactions (immune-complex-mediated) may be induced by vaccination. The deposition of immune-complexes in tissues may cause local inflammation or cause a generalized vasculitis such as purpura. Some rabies vaccines may also induce a local complement-mediated vasculitis in the skin resulting in ischemic dermatitis and local alopecia. This may occur at the injection site or at remote locations such as the ear tips, footpad, tail, or scrotum. This vasculitis is most often seen in small dogs such as dachshunds, miniature poodles, bichon frises, and terriers.

Blue Eye

In dogs infected with canine adenovirus-1 (CAV-1, infectious canine hepatitis), an immune-complex-mediated uveitis and a focal glomerulonephritis both develop. The uveitis, commonly called "blue-eye," is seen both in dogs with natural infections and in those vaccinated with live attenuated CAV-1 vaccine (Fig. 10.5). The uveitis results from the formation of virus-antibody complexes in the anterior chamber of the eye and in the cornea with complement activation and consequent neutrophil accumulation. The neutrophils release enzymes and oxidants that damage corneal epithelial cells, leading to edema and opacity. The condition resolves spontaneously in about 90% of affected dogs. Replacing CAV-1 with CAV-2 in vaccines has largely eliminated this problem.

Purpura Hemorrhagica

See Chapter 15.

Fig. 10.5 Blue-eye in a coyote puppy. This is a form of type III hypersensitivity reaction to Canine adenovirus-1. (Courtesy of Dr. G.J. Costanzo)

TYPE IV HYPERSENSITIVITIES

Type IV hypersensitivity (delayed) reactions are T-cell-mediated inflammatory responses. They may occur at the injection site in response to vaccination, but a more common reaction is local granuloma formation. This may be in response to persistent adjuvants containing alum or oil. Vaccines containing a water-in-oil adjuvant produce larger and more persistent lesions at injection sites than vaccines containing alum or aluminum hydroxide. These lesions may develop into sterile abscesses and if the injection site is dirty, these abscesses may become infected. Injection site lesions are of major concern in the meat industries.

Residual Virulence

Modified live vaccines must be able to establish themselves transiently in a vaccinated animal yet at the same time not cause disease. They must be safe in animals and their human companions. They must be as stable as possible to enable long-term storage. They must be environmentally safe. It may be possible to achieve minimal virulence with maximal immunogenicity, but this may be unattainable in animals with any defects in their immune function. The normal distribution of immunological competence in an outbred population is such that some animals will inevitably be susceptible to an otherwise avirulent organism. This immunosuppression may result from minor stresses, but equally important some common viral infections such as canine distemper, feline pancytopenia, or feline leukemia also cause immunosuppression to a degree that an animal may become susceptible to otherwise avirulent vaccinal agents.

It is also appropriate to point out that modified live vaccines are attenuated for a specific target species for administration by a specified route. If administered to the wrong species or in the wrong way residual virulence may cause disease. Thus some modified live vaccines may retain the ability to cause disease. A good example is *Brucella abortus* strain 19. Although highly immunogenic in cattle, S19 can cause severe reactions in vaccinated cows. Swelling, fever, anorexia, depression, and a drop in milk yield have been reported. S19 can also cause abortion in pregnant cows and orchitis in bulls and humans. Safer attenuated Brucella vaccines are now available. Similar residual virulence hazards are associated with the soremouth vaccine and the sheep

Toxoplasmosis vaccine. Some modified live herpes vaccines or calicivirus vaccines given intranasally may spread to the oropharynx and result in persistent infection. In these cases, the vaccine virus may infect (and protect) other animals in contact.

Because live vaccine strains may be released into the environment, safety issues involving not only the animal but also its environment must be addressed. Are there changes in the tissue tropism of the virus? Are there changes in the carrier through the incorporation of new foreign genes? Is there reversion to virulence through the incorporation of complementation genes? Is there exchange of genetic information with other wild type or vaccine strains of the carrier? Will the carrier spread unwanted genes such as antibiotic resistance into the environment? These questions are highly relevant in the aquaculture industry where modified live vaccine viruses may escape into the aquatic environment (Chapter 21).

Postvaccinal canine distemper encephalitis is a rare complication that may develop in dogs and ferrets after administration of modified live canine distemper vaccines. Affected animals may show neurologic signs such as aggression, incoordination, and seizures, or die suddenly. The pathogenesis of this condition is unclear. It may be the result of residual virulence, increased susceptibility, or triggering of a latent paramyxovirus by the vaccine.

FETAL ABNORMALITIES

Vaccination during pregnancy carries uncertain risks, especially when live vaccines are used. The fetal immune system may not have developed sufficiently to defend itself against the vaccine strain of the virus. MLV bluetongue virus vaccine has been reported to cause malformations in the offspring of ewes vaccinated while pregnant. The severity of the lesions depends upon the stage of pregnancy at vaccination. For example, MLV bluetongue administered to ewes between 50 and 100 days of gestation has caused hydranencephaly and retinal dysplasia in lambs. Live *Erysipelothrix rhusiopathiae* vaccines have been reported to cause abortions in sows. The stress from this type of vaccination may also be sufficient to reactivate latent infections; for example, reactivation of equine herpesviruses has been triggered by vaccination against African horse sickness. A modified live virus (MLV) parvovirus vaccine administered during pregnancy has been reported to cause hydranencephaly and cerebellar hypoplasia in kittens.

IMMUNOSUPPRESSION

Many viruses promote their own survival by suppressing their host's immune system. Although immunosuppression is greatest in virulent strains, some MLVs may remain somewhat immunosuppressive. For example, some MLV canine parvovirus strains may depress T cell responses to mitogens in puppies for two to five weeks following administration, or even cause a lymphopenia. Similarly, MLV canine distemper may cause immunosuppression and thrombocytopenia. In view of this it may be best to avoid performing elective surgery on dogs for at least one week postvaccination.

MLV bovine viral diarrhea (MLV-BCD) vaccines may suppress neutrophil functions and lymphocyte blastogenesis in vaccinated calves. As a result, they may potentiate intercurrent infections. MLV-BVD may also induce mucosal disease 7 to 20 days after vaccination. Vaccination with an MLV-BHV1 vaccine has been shown to exacerbate the lesions of experimental Moraxella-induced pinkeye (Chapter 16).

Several vaccine combinations may also result in transient immunosuppression. For example, a combination of distemper and adenovirus vaccines can reduce canine lymphocyte counts and their responsiveness to mitogens, although the individual components are not detectably immunosuppressive. This T cell suppression may be accompanied by simultaneous enhancement of

B cell responses and raised immunoglobulin levels. Many of these cases of "immunosuppression" attributed to vaccines may however simply reflect alterations in the Th1/Th2 balance or transient alterations in lymphocyte recirculation patterns. They are rarely of clinical significance.

REVERSION TO VIRULENCE

As pointed out in an earlier chapter, older vaccine viruses were attenuated by prolonged passage in tissue culture or eggs. In some cases, it is possible to reverse the attenuation process by back-passage through their natural hosts. For example, attenuated distemper strains cannot grow in canine lung macrophages. Back-passage of the canine distemper virus (CDV) Rockborn strain for as few as three passages in puppies resulted in the virus regaining this ability. By four passages the virus could cause weight loss. By five passages, immunosuppression returned. The virus that had been back-passaged six to seven times had regained its virulence. The use of genetically defined, gene deleted attenuated vaccines has largely eliminated this type of problem.

OTHER ISSUES

AUTOIMMUNE DISEASE.

Louis Pasteur's first rabies vaccine contained dried rabbit brain tissue. When injected into patients it induced antibodies against myelin basic protein and an acute demyelinating encephalomyelitis developed in about 0.1% of recipients. Rabies vaccines have had an undeserved bad reputation ever since. In 2011, it was proposed that a new syndrome existed that linked diverse human autoimmune diseases with the use of adjuvanted vaccines. It was called autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA). This syndrome has been investigated to determine whether it is an insignificant clinical term or whether there is an underlying mechanism that links adjuvants to autoimmunity. Aluminum-containing adjuvants were claimed to be the "cause" of ASIA. However, patients receiving allergen-specific immunotherapy receive up to 500 times more injected aluminum than regular vaccine recipients and have a lower incidence of autoimmune disease. Current data does not support the causation of ASIA by vaccine adjuvants. There is a lack of any reproducible evidence for any link between adjuvants and autoimmunity. One obvious problem with this proposed syndrome is that vaccination is so commonplace whereas autoimmunity remains uncommon. After all, huge numbers of people receive influenza vaccines annually without untoward effect.

There is a single animal study that appears to show that a link might exist between vaccination and the development of autoimmunity. A retrospective analysis of the history of dogs presenting with immune-mediated hemolytic anemia (IMHA) showed that 15 of 58 (26%) dogs with IMHA had been vaccinated within the previous month, compared with a randomly selected control group of 70 dogs in which 5% had been vaccinated. Dogs with IMHA that developed within a month of vaccination differed in some clinical features from dogs with IMHA unassociated with prior vaccination. Some studies using very large databases have tended to confirm this effect, in that they showed an approximately three-fold increase in diagnoses of autoimmune thrombocytopenia, and a two-fold increase in diagnoses of IMHA in dogs in the 30 days following vaccination, compared with other time periods. Other studies have failed to show any association between vaccination and IMHA. The overall prevalence of these diseases remains low, and they can be diagnosed at times not temporally associated with vaccination. Vaccination may therefore serve as a trigger for these diseases in some dogs—a vaccine potentiated reaction.

Contaminating thyroglobulin found in some vaccines (usually from the presence of fetal bovine serum) may lead to the production of antithyroid antibodies in vaccinated dogs. Lymphocytic

thyroiditis has been found in 40% of Beagles on necropsy, but there was no association detected between vaccination and the development of this thyroiditis.

In the 1970s, a swine influenza vaccine induced Guillain-Barré syndrome (an autoimmune polyradiculoneuritis) in about 1 case per 100,000 human recipients. (Current influenza vaccines have a risk of about 1:1 million. It appears that the older influenza vaccine was unique in this respect.) Cases of this syndrome in dogs have been rarely reported. In some animals, the administration of potent, adjuvanted vaccines may stimulate the transient production of autoantibodies to connective tissue components such as fibronectin and laminin.

VACCINE-ASSOCIATED OSTEODYSTROPHY

Vaccination of some Weimaraner puppies may lead to the development of a severe hypertrophic osteodystrophy. The disease appears within 10 days of administration of MLV canine distemper vaccine. Systemic signs include anorexia, depression, fever, and gastrointestinal, nervous, and respiratory symptoms, in addition to symmetrical metaphyseal lesions with painful swollen metaphyses. Radiological examination shows radiolucent zones in the metaphyses, flared diaphyses, and formation of new periosteal bone. It is possible that the condition is triggered by the vaccine in genetically susceptible animals. These dogs may have a preexisting immune dysfunction with low concentrations of one or more immunoglobulin classes, recurrent infections, and inflammatory disease. It has been suggested that Weimaraners are especially susceptible to this condition and that they therefore receive only killed virus vaccines.

A mild transient polyarthritis has been reported in some dogs following vaccination. The dogs show a sudden onset of lameness with swollen and painful joints within two weeks of vaccination. The dogs recover within two days. No specific breed or vaccine has been associated with this problem. Vaccination against calicivirus has been associated with polyarthritis and a postvaccination limping syndrome in cats.

OVERVACCINATION

A search of web sites regarding vaccination of pets reveals that a large number express great concern regarding the practice of overvaccination. By this is meant the use of unnecessary vaccines and by implication a significant threat to the health of pets. Conversely a search of PubMed, the NCBI web site, reveals only a single scientific paper regarding this subject. The paper describes renal disease in a spaniel that received seven doses of vaccine from its owner, one vaccine per month, in the absence of any veterinary supervision. As a result, the dog developed immune-complex lesions in its kidney glomeruli. This was very likely a type III hypersensitivity nephropathy.

Clearly administration of excessive and unneeded vaccines is inappropriate. There are no health benefits and each additional dose of vaccine carries with it the chances of an untoward event. As pointed out throughout this text, the risk/benefit assessment of any vaccination procedure must be a subject for discussion between a veterinarian and the pet owner. There are many reasons why a veterinarian may suggest that it may be beneficial to vaccinate an animal and it is inappropriate to blame those vets who choose to vaccinate animals more frequently than currently recommended without a full knowledge of each specific case. This is called clinical judgment.

INJECTION SITE SARCOMAS

These are discussed in Chapter 14.

Errors in Manufacture and Administration

VACCINE CONTAMINATION

Modified live vaccines cannot contain preservatives (except antibiotics in viral vaccines). As a result, occasional cases of vaccine contamination have occurred. These have been a major issue in the past when viral identification required culturing. Modern identification techniques such as the polymerase chain reaction have made such contamination a thing of the past. There are numerous examples of such contamination. For example, Mycoplasma contamination was a feature of many live virus veterinary vaccines. The pestivirus of Border disease contaminated some soremouth and pseudorabies vaccines; bovine leukemia virus has contaminated bovine blood vaccines such as those against babesiosis and anaplasmosis. Bluetongue virus has contaminated some canine vaccines.

INJECTION SITE LESIONS

Injection site selection should include consideration of potential adverse reactions in addition to the hypersensitivity reactions described earlier. For example, injection in the gluteal muscles/hip region of cattle should be discouraged because gravitational drainage along fascial planes can occur. Should an abscess develop, considerable tissue damage may occur and result in eruptions in undesirable locations with lesions that require prolonged time to heal. They may result in unacceptable blemishes in meat destined for human consumption (Chapter 16).

Human Illness

Veterinarians and other vaccine users may be inadvertently exposed to animal vaccines as a result of unintended inoculation or spraying. Some of these vaccines may cause sickness. Veterinarians, their assistants, and other animal handlers should be especially careful when administering injectable vaccines to avoid needle-stick and eye injuries. If an individual is accidentally self-injected with a mineral oil-adjuvanted vaccine, seek immediate medical treatment regardless of the dose injected. With the notable exception of Brucellosis, these events are rarely reported. Nevertheless, accidents do occur and veterinarians should be fully aware of these risks.

Brucellosis is an existential hazard to veterinarians. The CDC has established a passive surveillance registry. In the two years 1998 to 1999, 21 individuals reported needlestick injury related exposure to the Brucella vaccine strain RB51, five were splashed in the eye, and one was splashed into an open wound. Although most received antibiotics, 19 reported clinical disease. Approximately 4 to 5 million doses of Brucella vaccines were administered annually in 1997 to 2000. It is estimated these would have resulted in at least 8000 needle-stick injuries, suggesting that exposure to RB51 is substantially under-reported.

A vaccinia recombinant rabies vaccine bait has been air-dropped across many states in the United States to vaccinate wildlife. Several instances of human exposure to these baits have been reported. (The vaccine baits have toll-free numbers printed on them.) In Ohio, there were 160 reports of bait contact and 20 of these involved contacts with the vaccine. One individual developed a severe vaccinia infection and had to be hospitalized.

Bordetella bronchiseptica causes respiratory disease in dogs and atrophic rhinitis in pigs. Infection of humans is rare but has been documented. In at least one case a young boy was inadvertently sprayed in the face with a "kennel cough vaccine." He had been holding his dog but the dog moved. He developed a pertussis-like respiratory disease that lasted several months despite antibiotic treatment. There have been reports of clients experiencing respiratory difficulty following administration of an intranasal vaccine to their dogs.

Needle-stick injuries are not uncommon and many involve vaccines. A woman was inadvertently inoculated with the Sterne anthrax vaccine while vaccinating her horse. She did not develop anthrax but did develop a local reaction within 24 hours. Serious inflammatory reactions are associated with injected *Mycobacterium paratuberculosis* vaccine. Self-injections appear to be a major issue in the aquaculture industry where workers have to work fast to vaccinate slippery fish.

Reporting

Veterinarians are encouraged to report all adverse reactions to the vaccine's manufacturer and the regulatory authorities. This provides both with the critical information that is used to evaluate and monitor vaccine safety in the field. In this way vaccine safety can be progressively improved.

Adverse reactions should be reported to the vaccine manufacturer first. After that, they should be reported to the appropriate regulatory authorities.

UNITED STATES

In the United States, adverse vaccine events should also be reported to the US Department of Agriculture APHIS Center for Veterinary Biologics at 1-800-752-6255. They have an online electronic report form. Reports can also be made by fax or mail. Vaccine lot and serial numbers should be noted in vaccination records because this will facilitate an investigation. The use of standardized reporting systems is encouraged.

Web: http://www.aphis.usda.gov/animal_health/vet_biologics/vb_adverse_event.shtml

Fax or mail: Download the PDF form at http://www.aphis.usda.gov/animal_health/vet_biologics/publications/adverseeventreportform.pdf and fax to (515) 337-6120 or mail to the Center for Veterinary Biologics (CVB), 1920 Dayton Avenue, PO Box 844, Ames, Iowa 50010, USA. Telephone: (800) 752-6255

In Canada, suspected adverse events (SAE) should be reported to the Canadian Center for Veterinary Biologics (CCVB) in Ottawa at 1-855-212-7695. As stipulated by the Health of Animals Regulations, all reports that indicate "serious expected" or "serious unexpected" adverse events related to the use of a veterinary biologic, including lack of efficacy, must be reported to CCVB within 15 days of that information becoming known to the permit or license holder. Follow-up reports, including case conclusions, must be submitted to CCVB in a timely manner. All other reports should be investigated by the license/permit holder, summarized in a summary update report, and submitted to CCVB every six months. Summary update reports should be submitted within 60 days of the end of the reporting period. SAE related to veterinary biologics are categorized as one of the following: adverse event (AE), serious AE, unexpected AE, and lack of efficacy. A causality assessment should also be assigned to each SAE. Each case should be classified as probable, possible, unlikely, or unknown.

Form CFIA/ACIA 2205, Notification of Suspected Adverse Events to Veterinary Biologics, may be found at http://inspection.gc.ca/english/for/pdf/c2205e.pdf.

UNITED KINGDOM

In the United Kingdom adverse events should be reported to the Veterinary Medicines Directorate. Forms can be obtained at their website at www.vmd.defra.gov.uk or by calling their Pharmacovigilance team at 01932 338427. The Veterinary Medicines Directorate (VMD), an agency of the Department for Environment, Food, and Rural Affairs, is responsible for the Suspected Adverse Reaction Surveillance Scheme (SARSS) for veterinary medicines. Adverse reactions in animals in the United Kingdom should be reported at http://www.vmd.defra.gov.uk/adversereactionreporting/default.aspx.

Suspected human reactions to veterinary medicines in the United Kingdom should be reported at http://www.vmd.defra.gov.uk/adversereactionreporting/default.aspx, or contact the VMD at Freepost KT4503, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3BR, UK. Telephone: 01932 338427 Fax: 01932 336618

AUSTRALIA

In Australia, adverse events should be reported to the Australian Pesticides and Veterinary Medicines authority on their website at https://apvma.gov.au/node/309.

NEW ZEALAND

In New Zealand adverse event reports should be made to the Ministry for Primary Industries, PO Box 2526, Wellington, 6140, or online at ACVM-adverseevents@mpi.govt.nz.

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Abstract: The importance of adverse effects from vaccination must not be overstated. Vaccine benefits greatly exceed any risks from the procedure. Neither must they be minimized. Unnecessary vaccination must be discouraged. Hypersensitivity reactions to vaccine components are real and must be guarded against. Residual virulence, although a concern tends to be more a hypothetical than a real problem. Progressive improvements in animal vaccines have significantly reduced the chances of adverse effects occurring, although some issues persist. One such example is injection-site sarcomas in cats. Another issue is the influence of animal size on the prevalence of adverse events in dogs.

Keywords: allergies, hypersensitivities, residual virulence, contamination, immunosuppression, sarcomas, inflammation, overvaccination.