The Administration of Vaccines

Although vaccine manufacturers produce high quality products, these will not be effective if administered by the wrong route, in the wrong dose, or at the wrong time. Thus careful and appropriate administration is required if maximum benefit is to be afforded by vaccination.

One must not lose sight of the objectives of vaccination. Vaccines are given to protect animals against significant infectious diseases to which they have a risk of exposure. Vaccines should therefore only be given when these benefits are obvious and outweigh any possible adverse effects. Potential risks include adverse reactions, the likelihood of acquiring the disease, and the severity of the disease. On the other hand, benefits include protection from infection and death, reduction in disease severity, and any contribution to herd immunity. Vaccines should be administered no more frequently than necessary to confer protection. It is of course equally inappropriate to vaccinate animals in such a way that any immunity conferred is insufficient to protect them. Veterinarians assessing vaccine risk must also consider any benefits to human health that might result from protection against zoonotic infections.

Since the 1990s, there has been a concerted effort to classify vaccines into those essential for animal health and thus mandatory (CORE vaccines) and those whose use depends upon specific risk assessment (nonCORE vaccines). That terminology is used here although it may be considered a false dichotomy. The use of every vaccine should be based on an objective and thorough risk assessment. The veterinarian must make their own professional judgment and an informed decision regarding vaccine use. Designation of core vaccines does not absolve them from their professional responsibilities in this respect.

Veterinarians should only use effective vaccines licensed by their national authorities and the vaccines must be used in accordance with the label directions. They should not be used unless the veterinarian has either diagnosed a specific disease or is aware of its presence in an area, because otherwise it is not possible to determine the benefits and risks of vaccination.

Vaccination Principles

VACCINATION SCHEDULES

Certain principles are common to all methods of active immunization. Most vaccines require an initial series in which the immune system is primed and protective immunity initiated, followed by revaccination (booster shots) at intervals to ensure that this protective immunity remains at an adequate level.

Initial Series

Because maternal antibodies passively protect newborn animals, it is not usually possible to vaccinate very young animals successfully. If protection is deemed necessary at this stage, the mother may be vaccinated during pregnancy. Maternal vaccinations should be timed so that peak antibody levels are achieved at the time of colostrum formation. Once an animal is born, successful active immunization is effective only after maternal antibodies have waned. Animals should be revaccinated 12 months later or at 1 year of age. It is unclear whether maternal antibodies can always block antibody responses to intranasal vaccines. Despite high levels of circulating maternal antibodies, maternal interference does not always occur and nasal antibody production is often unimpaired.

The timing of initial vaccinations may also be determined by disease epidemiology. Some diseases are seasonal, and vaccines may be given before outbreaks are anticipated. Examples of these include the vaccine against the lungworm, *Dictyocaulus viviparus,* given in early summer just before the anticipated lungworm season; the vaccine against anthrax given in spring; and the vaccine against *Clostridium chauvoei* given to sheep before turning them out to pasture. Bluetongue of lambs is spread by midges and is thus a disease of midsummer and early fall. Vaccination in spring will therefore protect lambs during the susceptible period. Similar considerations apply to mosquito-borne/wet season diseases.

Vaccination Intervals

When deciding on the optimal interval between the first immunization and the booster shot it is important to consider how B cells and T cells differentiate. These cells respond rapidly to antigen and generate effector cells or plasma cells. Once this phase is over, most effector cells die while the survivors differentiate into memory cells. Memory T cells may take several weeks after the primary immune response to reach maximal numbers. Only when this memory phase develops can a significant secondary response be induced. As a general rule it is better to wait for as long as possible between prime and boost. Boosting too soon may well result in suboptimal secondary responses. (But boosting too late may open a window of vulnerability). Excessive boosting of mice appears to drive T cells toward terminal differentiation and deplete the population of central memory cells. Similar considerations apply to B cell responses. They need time to develop memory cells and premature boosting runs the risk of generating suboptimal memory. Computer modeling suggests that an interval of several weeks is necessary to obtain optimal secondary responses. In children, 4 to 8 weeks is considered to be the minimal interval between the first two doses by the Centers for Disease Control and Prevention (CDC), whereas six months is the recommended interval between the second and third vaccine doses. Studies on revaccination with Clostridial vaccines in sheep also suggest that an interval of 8 weeks between vaccine doses is optimal. A study on boosting cattle with rabies vaccine suggested that the optimal response was obtained with a 180-day interval between vaccine doses.

Although experimental data suggest that vaccination intervals be somewhat longer than currently recommended, one must also remember that it is essential not to leave a window of susceptibility between vaccine doses. For practical purposes, it is generally recommended that in dogs and cats the minimal interval should be 2 to 3 weeks. For larger animals such as horses it is generally a minimum of 3 to 4 weeks. In general, the longer the interval between booster shots, the better it is for the induction of a maximal protective response. Decisions on vaccination frequency however must be at the discretion of the vaccinating veterinarian.

Revaccination

It is the persistence of memory cells after vaccination that provides an animal with long-term protection. The presence of long-lived plasma cells is associated with persistent antibody production

so that a vaccinated animal may have antibodies in its bloodstream for many years after exposure to a vaccine.

Revaccination schedules depend on the duration of effective protection. This in turn depends on specific antigen content, whether the vaccine consists of living or dead organisms, and its route of administration. In the past, relatively poor vaccines may have required frequent administration, perhaps as often as every six months, to maintain an acceptable level of immunity. Modern vaccines usually produce a long-lasting protection, especially in companion animals. Many require revaccination only every three or four years, whereas for others, immunity may persist for an animal's lifetime. Even inactivated viral vaccines may protect individual animals against disease for many years. Unfortunately, the minimal duration of immunity has rarely been measured, until recently, and reliable figures are not available for many vaccines. Although serum antibodies can be monitored in vaccinated animals, tests have not been standardized, and there is no consensus regarding the interpretation of these antibody titers. Even animals that lack detectable antibodies may have significant cell-mediated resistance to disease. Nor is there much detailed information available regarding long-term immunity on mucosal surfaces. In general, immunity against feline panleukopenia, canine distemper, canine parvovirus, and canine adenovirus is considered to be relatively long lasting (>5 years). On the other hand, immunity to feline herpesvirus, feline calicivirus, and *Chlamydia* is believed to be relatively short. One problem in making these statements is the variability among individual animals and among different types and brands of vaccine. Thus recombinant canine distemper vaccines may induce shorter duration immunity than conventional, modified live vaccines. There may be a great difference between the shortest and longest duration of immunological memory within a group of animals. Duration of immunity studies are confounded by the fact that many older animals have increased innate resistance. Different vaccines within a category may differ significantly in their performance, and although all vaccines may induce immunity in the short term, it cannot be assumed that all confer long-term immunity. Manufacturers use different master seeds and different methods of antigen preparation. A significant difference exists between the minimal level of immunity required to protect most animals and the level of immunity required to ensure protection of all animals.

Annual revaccination was once the rule for most animal vaccines because this approach was administratively simple and had the advantage of ensuring that an animal was seen regularly by a veterinarian. It is clear, however, that modern vaccines such as those against canine distemper or feline herpesvirus induce protective immunity that can last for many years and that annual revaccination using these vaccines is excessive. A growing body of evidence now indicates that most modified live viral vaccines induce lifelong sterile immunity in dogs and cats. In contrast, immunity to bacteria is of much shorter duration and often may prevent disease but not infection. Old dogs and cats rarely die from vaccine-preventable disease, especially if they have been vaccinated as adults. In contrast, young animals die from such diseases, especially if not vaccinated or vaccinated prematurely.

A veterinarian should always assess the relative risks and benefits to an animal in determining the timing of any vaccination. It is therefore be good practice to use serum antibody assays such as rapid test ELISAs (enzyme-linked immunosorbent assays) or lateral flow assays, if available, to provide guidance on revaccination intervals. Persistent antibody titers determine whether an animal requires additional protection. These tests not only identify those animals that have responded to vaccination, they can determine if an animal is a nonresponder. They can determine if an animal that previously suffered from an adverse event really requires revaccination. They can determine whether an animal with an undocumented vaccine history needs to be vaccinated and with which vaccines. They can determine which animals in a shelter undergoing a disease outbreak are susceptible and so require vaccination. They can also determine whether revaccination is really necessary at three years. It should be pointed out, however, that animals with low or undetectable serum antibody levels may still be protected as a result of persistence of

memory B and T cells capable of responding rapidly to reinfection. "Blind" revaccination should be avoided if appropriate serum antibody assays are available.

Notwithstanding this discussion, animal owners should be made aware that protection against an infectious disease can only be maintained reliably when vaccines are used in accordance with the protocol approved by the vaccine-licensing authorities. The duration of immunity claimed by a vaccine manufacturer is the minimum duration of immunity that is supported by the data available at the time the vaccine license is approved. This must always be taken into account when discussing revaccination protocols with an owner.

MATERNAL IMMUNITY

Mothers transfer antibodies to their offspring through feeding colostrum in most domestic mammals (Fig. 8.1). Once absorbed from the intestine, these maternal antibodies inhibit neonatal antibody synthesis by acting through regulatory pathways that ensure that the body does not make more antibodies than it needs. They inhibit B cells, not T cells. As a result, they prevent the successful vaccination of very young animals. This inhibition may persist for many months. Its duration depends primarily on the amount (titer) of antibodies transferred and the half-life of the immunoglobulins involved. This problem can be illustrated using the example of vaccination of puppies against canine distemper.

Maternal antibodies, absorbed from the puppy's intestine, reach maximal levels in serum by 12 to 24 hours after birth. These levels then decline slowly through normal protein catabolism. The catabolic rate of proteins is exponential and is expressed as a half-life. The half-life of specific antibodies against distemper and canine infectious hepatitis is 8.4 days. Experience has shown that, *on average*, the level of maternal antibodies to distemper in puppies declines to insignificant levels by about 10 to 12 weeks, but this may range from 6 to 16 weeks. (The titer of maternal antibodies, not the animal's age is the determining factor.) In a population of puppies, the proportion of susceptible animals therefore increases gradually from a very few or none at birth, to most puppies at 10 to 12 weeks. Consequently, very few newborn puppies can be successfully vaccinated, but most can be protected by 10 to 12 weeks. Rarely, a puppy may reach 15 or 16 weeks before it can be successfully vaccinated. If virus diseases were not so common, it would
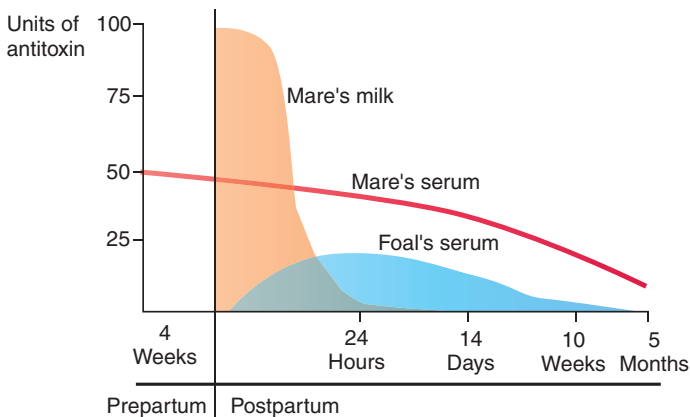

Fig. 8.1 The transfer of maternal antibodies from mares to foals. In this case antibodies to *Cl. perfringens* were measured in mare's serum, colostrum, and milk, and also in their foal's serum from birth to five months. (From Jeffcott, L.B. [1974]. Studies on passive immunity in the foal. I. γ-globulin and antibody variations associated with the maternal transfer of immunity and the onset of active immunity. *J. Comp. Pathol,* 84, 93–101.).

be sufficient to delay vaccination until all puppies were about 12 weeks old, when success could be almost guaranteed. In practice however, a delay of this type means that an increasing proportion of puppies, fully susceptible to disease, would be without immune protection—an unacceptable situation. Nor is it feasible to vaccinate all puppies repeatedly at short intervals from birth to 12 weeks, a procedure that would also ensure almost complete protection. Therefore a compromise must be reached.

The earliest recommended age to begin vaccinating a puppy or kitten with a reasonable expectation of success is at six weeks. Colostrum-deprived orphan pups lacking maternal antibodies, may be vaccinated at two weeks of age. Because it is impossible to predict the exact time of loss of specific maternal antibodies, any initial vaccination series will generally require administration of at least three doses. Current guidelines for essential canine and feline vaccines, for example, indicate that the first dose of vaccine should be administered as early as 6 to 8 weeks of age, and revaccinated at 2 to 4 week intervals until they are about 16 weeks of age. Strictly speaking these are not booster doses. They are simply designed to trigger a primary response as soon as possible after maternal antibodies have declined. Rabies is a core vaccine that should be given at 14 to 16 weeks. In kittens the half-life of maternal antibodies to feline panleukopenia is 9.5 days. The appropriate protocol would be to use three doses of the core vaccines (herpesvirus, calicivirus, and panleukopenia) at 8 to 9 weeks, 3 to 4 weeks later, and at 14 to 16 weeks; feline leukemia vaccine can be given at 8 weeks and 3 to 4 weeks later; and rabies vaccine can be given at 8 to 12 weeks, depending on the type of vaccine used (Fig. 8.2).

Similar considerations apply when vaccinating large farm animals (Fig. 8.3). The prime factor influencing the duration of maternal immunity is the level of antibodies in the mother's colostrum. In foals, maternal antibodies to tetanus toxin can persist for six months and antibodies to equine arteritis virus for as long as eight months. Antibodies to bovine viral diarrhea virus may persist for up to nine months in calves. The half-lives of maternal antibodies against equine influenza and equine arteritis virus antigens in the foal are 32 to 39 days respectively. As in puppies, a young foal may have nonprotective levels of maternal antibodies long before it can be vaccinated. Maternal antibodies, even at low titers, effectively block immune responses in young foals and calves, so premature vaccination may also be ineffective. The effective response to vaccines increases progressively after the first six months of life. A safe rule is that calves and foals should be vaccinated no earlier than three to four months of age, followed by one or two revaccinations at four-week intervals. The precise schedule will depend on the vaccine used and the species to
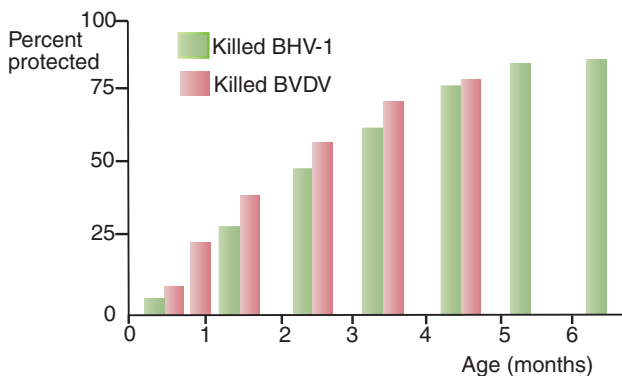

Fig. 8.2 The response of vaccinated calves to two different inactivated viral vaccines on calves between birth and six months of age. It is clear that vaccination before four to five months results in significantly reduced protection. *BHV,* bovine herpesvirus-1; *BVDV,* bovine virus diarrhea virus. (From data kindly provided by Dr. R.J. Schultz)
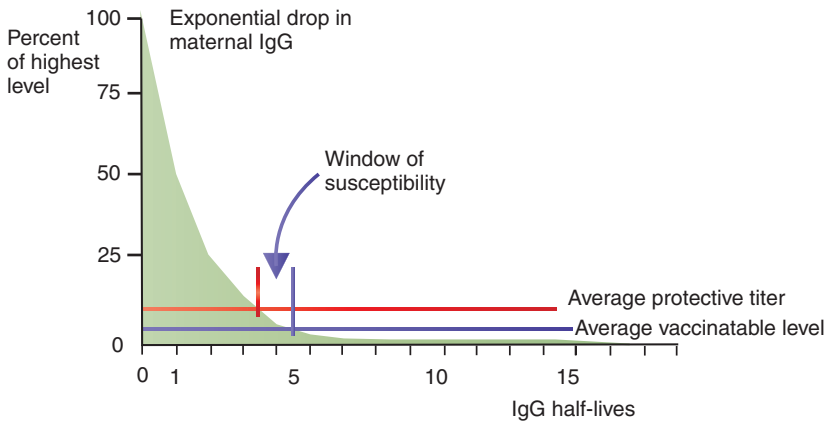
Fig. 8.3 The effect of maternal antibodies on the response of young animals such as puppies. Although immunoglobulins decline exponentially based on their half-life, the precise time at which they lose immunity and the time when they can be vaccinated depend upon the antibody titer. This protective titer varies between infectious agents and thus the time when the animal becomes susceptible will also vary. The presence of maternal antibodies also suppresses the puppy immune response to vaccination. The higher the maternal antibody titer, the greater the suppression. The time when a puppy can respond to a vaccine may not be the same as the time when it becomes disease susceptible. *Ig,* Immunoglobulin.

be vaccinated. Animals vaccinated before six months of age should always be revaccinated at six months or after weaning, to ensure protection.

Some live recombinant vaccines such as canarypox-vectored distemper in dogs or influenza in horses appear to be able to prime young animals in the presence of significant maternal antibodies. DNA vaccines against pseudorabies also appear to be effective in priming cell-mediated responses in piglets in the face of maternal immunity, whereas a DNA plasmid vaccine against bovine respiratory syncytial virus vaccine is not. Thus the ability of DNA vaccines to overcome maternal antibodies varies among species and agents.

Vaccination Strategies

Although the principles of vaccination have been known for many years, vaccines and vaccination procedures are continuing to improve in efficacy and safety. The earliest veterinary vaccines were often of limited efficacy and some had significant adverse effects, although these were considered acceptable when measured against the risks of acquiring disease. The vaccination protocols developed at that time reflected the inadequacies of these vaccines. Ongoing developments in vaccine design and production have resulted in great improvements in both safety and effectiveness. These improvements permit a reassessment of the relative risks and benefits of vaccination. Vaccination is not always a totally innocuous procedure. For this reason, the use of any vaccine should be accompanied by a risk/benefit analysis conducted by the veterinarian in consultation with the animal's owner. Vaccination protocols should be determined for each individual animal, giving due consideration to the seriousness of the disease, the zoonotic potential of the agent, the animal's susceptibility and exposure risk, and any legal requirements relating to vaccination. The success of mass vaccination programs depends both on the proportion of animals vaccinated and on the efficacy of the vaccine. Neither of these factors will reach 100%, so it is essential to target the vaccine effectively. It is also the case that vaccines do not confer immediate protection, so the strategy employed will depend on the rate of spread of an infection.

HERD IMMUNITY

The main purpose of vaccinating animals, especially companion animals, is to protect each individual animal. It is expected that clinical disease will be minimized. It is also expected that vaccinated animals will shed fewer pathogens. In an animal population such as a herd or flock, the benefits of vaccines result from the collective impact of the procedure on all individuals and the collective decline in pathogen shedding. This decline in shedding, together with collective immunity, contributes to herd immunity (Fig. 8.4).

When vaccines are used to control disease in a population of animals rather than in individuals, herd immunity must be considered. Herd immunity refers to the resistance of an entire group of animals to a disease as a result of the presence of many immune animals in that group. Herd immunity reduces the probability of a susceptible animal meeting an infected one so that the spread of disease is slowed or prevented. If it is acceptable to lose individual animals from disease while preventing epizootics, it may be possible to do this by vaccinating only a proportion of the population. Veterinarians should seek to ensure that as many animals as possible are vaccinated to maximize herd immunity.
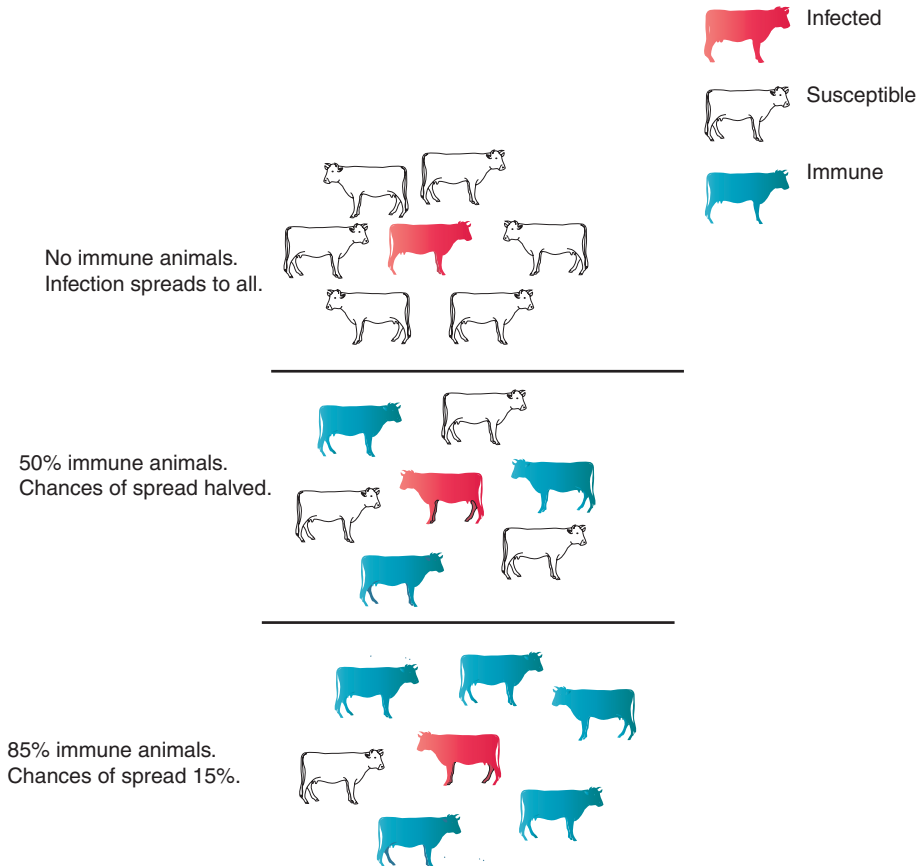

Fig. 8.4 The principle of herd immunity. This figure is based on an infectious agent that is highly efficiently transmitted. If the agent has a low R_0, herd immunity need not be 100% for its transmission to be completely blocked.

The spread of an infectious disease is, of course, dependent upon the close proximity of susceptible individuals. Solitary animals are much less likely to encounter other infected individuals. On the other hand, animals living in herds, flocks, or shelters will encounter numerous individuals. If all these other animals lack immunity, then there is nothing to prevent the spread of infection. If all these other individuals are soundly immune then the infection cannot spread. This is not, however, an all-or-nothing phenomenon. If most of the animals in the herd are immune then the chances of an infected animal encountering a susceptible one are reduced and the chances of the disease spreading is drastically reduced.

The most important factor that influences herd immunity is the basic reproductive number of the disease, termed R_0 and pronounced "R nought". R_0 is the expected number of secondary cases resulting from each primary case in a completely susceptible population. In other words, the probability of transmission of an infectious agent.

R_0 is not a constant. For example, it will vary according to population density, animal behavior, and seasonality. An R_0 of 1 indicates that each individual primary case generates one secondary case and the prevalence of the disease will remain static. An R_0 of less than 1 means that one case will on average, generate fewer secondary cases. As a result, the prevalence of disease will decline. Conversely, an R_0 greater than 1 means that each primary case will generate an increased number of secondary cases, then the numbers of such cases will increase. The higher the R_0 the more difficult it is to prevent an infectious disease. R_0 depends on the effective contact rate between individuals over time, the size of the population, and the duration of infectivity. Thus R_0 will vary as a result of stocking density, environmental effects, any biosecurity practiced, the introduction of susceptible animals, and the nature of the production system.

Vaccines, by reducing the number of susceptible animals in a population, reduce the number of contacts between infectious and susceptible animals. This reduction will be determined by the efficacy of the vaccine in reducing transmission and the amount of vaccination coverage within the population. As a result, the "effective population density" of susceptible animals is reduced and the quantity of pathogen available to infect the nonvaccinated animals decreases. Each vaccinated individual therefore contributes to herd immunity and a reduction in the effective reproductive number, R will occur. R is similar to R_0 but does not assume complete susceptibility in a population. It is not necessary for all the animals in a herd to be protected in order for R to be reduced to less than 1 and so result in disease elimination. R may be calculated by multiplying the R_0 by the proportion of susceptible animals. For example, if a vaccine protects 80% of a herd then the organism can only infect the unprotected 20% and R will drop by 80%. If there are insufficient susceptible animals in a population, R may drop to less than 1, transmission will be interrupted, and the disease will be eliminated.

The level of herd immunity needed to bring R to this level is called the "herd immunity threshold (HIT)" and is calculated by HIT $= 1-1/R_0$. The HIT is useful in that it provides a target for vaccination coverage. The HIT has been calculated for the major human infectious diseases. It ranges from 90% to 95% for measles and rubella, to about 85% for rubella and diphtheria, to 70% to 80% for smallpox. It has not been widely calculated for animal diseases. A figure of 70% is widely quoted for canine rabies (Box 8.1).

Although vaccination is a powerful tool for the control of infectious disease, its potential to prevent the spread of or eliminate a disease depends on selecting the correct control strategies. If an infectious disease outbreak, such as one caused by foot-and-mouth virus, is to be rapidly controlled by vaccination, it is vitally important to select the correct population to be vaccinated. The success of any mass vaccination program depends both on the proportion of animals vaccinated and on the efficacy of the vaccine. Neither of these factors will reach 100%, so it is essential to target the vaccine effectively. It is also the case that vaccines do not confer immediate protection, so the strategy employed will depend on the rate of spread of an infection. Vaccines may thus be given prophylactically, in advance of an outbreak, or reactively, in response to an existing outbreak.

Both strategies have advantages and disadvantages. In general, prophylactic vaccination greatly reduces the potential for a major epidemic of a disease such as foot-and-mouth disease by reducing the size of the susceptible population. The effectiveness of this approach can be greatly enhanced by identifying high-risk individuals and ensuring that they are protected in advance of an outbreak.

It is generally not feasible to vaccinate an entire population of animals once a disease outbreak has occurred. However, two effective reactive vaccination strategies are *ring vaccination,* which seeks to contain an outbreak by establishing a barrier of immune animals around an infected area, and *predictive vaccination,* which seeks to vaccinate the animals on farms likely to contribute most to the future spread of disease. Reactive vaccination in this way can ensure that an epidemic is not unduly prolonged. A prolonged "tail" to an epidemic commonly results from the disease "jumping" to a new area. Well-considered, predictive vaccination may prevent these jumps. Thus a combination of prophylactic and reactive vaccination will likely yield the most effective results.

Safety and Efficacy

The two major factors that determine vaccine use are safety and efficacy. We must always be sure that the risks of vaccination do not exceed those associated with the chance of contracting the disease. Thus it may be inappropriate to use a vaccine against a disease that is rare, is readily treated by other means, or is of little clinical significance. Because the detection of antibodies is a common diagnostic procedure, unnecessary use of vaccines may complicate diagnosis based on serology and perhaps make eradication of a disease impossible. On the other hand, serologic tests may make it possible to determine animal susceptibility and rationalize vaccine usage. The decision to use vaccines for the control of any disease must be based not only on the degree of risk associated with the disease, but also on the availability of superior alternatives.

The second major consideration is vaccine efficacy. Vaccines may not always be effective. In some diseases, such as equine infectious anemia, Aleutian disease in mink, and African swine fever, poor or no protective immunity can be induced and vaccines are not available. In other diseases, such as foot-and-mouth disease in pigs, the immune response may be transient and relatively ineffective, and successful disease control is sometimes difficult to achieve.

As a result of these considerations, animal vaccines should be ranked based on their importance. The first category consists of core "essential" vaccines—those that are required because they protect against common, dangerous diseases and because a failure to use them would place an animal at significant risk of disease or death. In other words, a high benefit/risk ratio. Determination of which vaccines are core will vary based on local conditions and disease threats. A second

category consists of optional vaccines. These are directed against diseases for which the risks associated with not vaccinating may be low. In many cases, risks from these diseases are determined by the location or lifestyle of an animal. The use of these optional vaccines should be determined by a veterinarian on the basis of exposure risk. A third category consists of vaccines that may have no application in routine vaccination but are only used under special circumstances. These are vaccines directed against diseases of little clinical significance or vaccines whose risks do not significantly outweigh their benefits. Of course, all vaccine use should be conducted on the basis of informed consent. An animal's owner should be made aware of the risks and benefits involved before seeking approval to vaccinate. This is especially important if using a vaccine in a manner different from that recommended by the manufacturer.

COMBINED AND POLYVALENT VACCINES

It is increasingly uncommon for vaccines directed against a single agent to be employed in domestic species. In practice, it is usual to employ complex mixtures of organisms within single vaccines. For example, in dogs, distemper vaccine is combined with canine adenovirus 2, canine parvovirus, canine parainfluenza, coronavirus, leptospirosis, and *Borrelia burgdorferi* vaccines. In controlling the respiratory disease complex of cattle, bovine virus diarrhea vaccines may be combined with infectious bovine rhinotracheitis, parainfluenza 3, bovine respiratory syncytial virus, leptospirosis, *Campylobacter fetus*, *Histophilus somni*, *Pasteurella multocida*, and *Mannheimia hemolytica* vaccines. These vaccine combinations protect animals against several diseases with economy of effort. However, it can also be wasteful to use vaccines against organisms that may not be causing problems. When different antigens in a mixture are inoculated simultaneously, competition occurs between antigens. Manufacturers of combined vaccines take this into account and adjust their components accordingly. Vaccines should never be mixed indiscriminately because one component may dominate the mixture or interfere with the response to the other components.

Some have questioned whether the use of complex vaccine combinations leads to less than satisfactory protection or increases the risk for adverse side effects. They are concerned that the use of 5- or 7-component vaccines in their animals will somehow overwhelm the immune system, forgetting that our animals encounter hundreds of different antigens in daily life. The suggestion that these combined vaccines can overload the immune system is unfounded, nor is there any evidence to support the contention that the risk for adverse effects increases disproportionately when more components are added to vaccines. The success of a 15-component bluetongue vaccine in sheep or a 23-component pneumococcal vaccine in acquired immunodeficiency syndrome patients, should serve as a reassurance that multiple component vaccines are not overwhelming. Certainly such vaccines should be tested to ensure that all components induce a satisfactory response. Licensed vaccines provided by a reputable manufacturer will generally provide satisfactory protection against all components.

Administration

VACCINE STORAGE AND HANDLING

Always check the package insert or the manufacturer's recommendations regarding storage. Vaccines should be stored in a refrigerator or freezer as appropriate. Refrigerated vaccines should be stored between 2°C and 8°C with a mid-range of about 5°C (40°F). Ideally check the temperature twice daily with a max/min thermometer. A signed log recording this should be maintained to ensure that this is not ignored. Make sure that vaccines do not warm or freeze inadvertently by storing them in the middle, not the front or back of the shelves. Do not store in

vegetable drawers or in the door where temperature variation may be considerable. Liquid vaccines that contain an aluminum adjuvant will lose potency if frozen. Never store food in a refrigerator holding vaccines. Do not overstock a refrigerator because this may affect temperature control. A study of farm refrigerators in the United Kingdom suggests that most failed to store vaccines under the recommended conditions. Many (40%) inadvertently froze the vaccine, and 59% had a temperature that rose above 8°C at least once. This part of the cold chain is very vulnerable.

A designated person should be the vaccine coordinator, to oversee receipt of vaccines, their storage, and handling. This individual should maintain a vaccine inventory log that documents the details of each vaccine batch: name, manufacturer, lot number, expiration date, vendor, quantity, and arrival condition.

All other appropriate staff members should also receive training. A practice should have documented standard operating procedures available with respect to storage and handling posted close to the vaccine storage units and make sure that the staff knows where they are. All new employees should be trained and then refreshed annually. Make sure that staff members are instructed when recommendations are updated or when new vaccines are added.

Vaccines must be organized according to their expiration date so that the oldest products are used first. Obviously, the refrigerator should be reliable and should it fail promptly move them to a working one or to a refrigerated container. Discard vaccines that have been exposed to temperatures outside the manufacturers recommended range, whether too high or frozen. When transporting vaccines to clients make sure they are carried in a refrigerated container with a thermometer to ensure the vaccines do not warm. A cool pack may not be sufficient to maintain cold temperatures over a full day in a hot climate.

Always store vaccines in their original packages with lids closed until ready for use. Protect them from light. Store diluent with the corresponding vaccine. Clearly label where each type of vaccine and diluent are stored.

INJECTION

Most vaccines are administered by injection. Care must be taken not to injure or introduce infection into any animal. All needles used must be clean and sharp and of the appropriate size. Dirty or dull needles can cause tissue damage and infection at the injection site. The skin at the injection site must be clean and dry, although excessive alcohol swabbing should be avoided. Vaccines are provided in a standard dose, and this dose should not be divided to account for an animal's size. Vaccine doses are not yet formulated to account for body weight or age. There must be a sufficient antigen to trigger the cells of the immune system and provoke a protective immune response. This amount is not related to body size. Vaccination by subcutaneous or intramuscular injection is the simplest and most common method of administration. This approach is obviously excellent for small numbers of animals and for diseases in which systemic immunity is important.

Although this may seem obvious, it is essential that proper aseptic technique should always be followed when administering vaccines. Always follow manufacturer's instructions because these are based on the actual methods employed when the vaccine was shown to be efficacious. The site of injection should be cleaned as much as possible. Each animal should be vaccinated with a new needle and a new needle should be used for each vaccine product to ensure that they are not cross contaminated when the needle is inserted into the vaccine vial. A new needle also prevents the possible transmission of blood-borne pathogens. Vaccines must only be given by their approved route. For example, intranasal vaccines should never be injected. To facilitate treatment of any sarcomas that may arise, cats should not be vaccinated subcutaneously into the interscapular furrow in the neck (Chapter 10). Always observe the meat or milk withdrawal period of vaccines in food-producing animals. This is commonly 21 days, but sometimes it is considerably longer.

Draw up vaccines only at the time of administration because once the vaccine is inside syringes, it may be difficult to identify. Syringes are not designed for storage. Remember that once reconstituted, vaccines should be administered within 1 hour. Any reconstituted vaccines held for longer than an hour should be discarded. Do not rely on preservatives to prevent contamination of multidose vaccine containers. Never mix vaccines with other medicines and follow all manufacturer's instructions. Always dispose of used needles in a sharps box. If a vaccine is spilled, clean off the fur with alcohol swabs and disinfect any surfaces.

If an animal cannot be approached closely, it may be injected by the use of a jab stick or syringe pole. This is in effect a syringe at the end of a long (15–50 inch) rod to provide extended reach. They may simply be push rods where the syringe is pushed into the animal and the plunger continues to be pushed to inject the vaccine. Alternatively, the plunger may be pushed using a thumb-operated trigger that does not exert additional pressure on the animal. Anesthetized animals should not be vaccinated because of the risks of hypersensitivity and vomiting.

Proper documentation of vaccination is essential. Permanent medical records should include the date, the identity of the animal vaccinated, the administering veterinarian, the type and proprietary name of the vaccine(s) administered, batch number, expiry date, manufacturer, route, and the site of inoculation. Veterinarians should also offer the owner of a vaccinated animal, a vaccination certificate also containing this data. Ideally the recommended date of revaccination should also be on this certificate in addition to the details of the administering veterinarian and the practice.

Mucosal Vaccination

Most infectious agents invade the body through mucosal surfaces, especially the respiratory and digestive tracts. It makes sense therefore for vaccine antigens to be administered by the same route. Presumably, by mimicking the natural route, vaccines will trigger immune responses on these surfaces and ideally, block pathogen invasion.

When a systemic immune response is triggered by injected antigen, effector T cells in the spleen are activated. The spleen is a central lymphoid organ not associated with any body surface. As a result, splenic T cells have a "promiscuous" homing pattern and travel to many different sites including mucosal surfaces. Because most current vaccines are delivered parenterally, they rely on generating this strong systemic response. In such cases, protection of the mucosa is mediated by a migration of T cells into mucosal tissues or by antibodies entering damaged areas once the pathogen has breached the mucosal barrier. This indirect protection may work, but direct immunization of the mucosal lymphoid tissues is expected to be much more efficient. It is therefore logical to prevent such infections by administering vaccines in such a way that they either stimulate the intestinal or the nasopharyngeal lymphoid tissues.

ORAL VACCINATION

By far the greatest numbers of immune cells are associated with the gastrointestinal tract. The immune system functions on the basis that microorganisms that invade the body must be eliminated before they cause damage. Organisms that penetrate the epithelial barriers are promptly detected, attacked, and destroyed by both innate and adaptive mechanisms (Fig. 8.5). Immunoglobulin (Ig)A antibodies predominate in surface secretions. At least 80% of all plasma cells are found in the intestinal lamina propria, and together they produce more IgA than all other immunoglobulin isotypes combined. IgA is found in enormous amounts in saliva, intestinal fluid, nasal, and tracheal secretions, tears, milk, colostrum, urine, and the secretions of the urogenital tract.
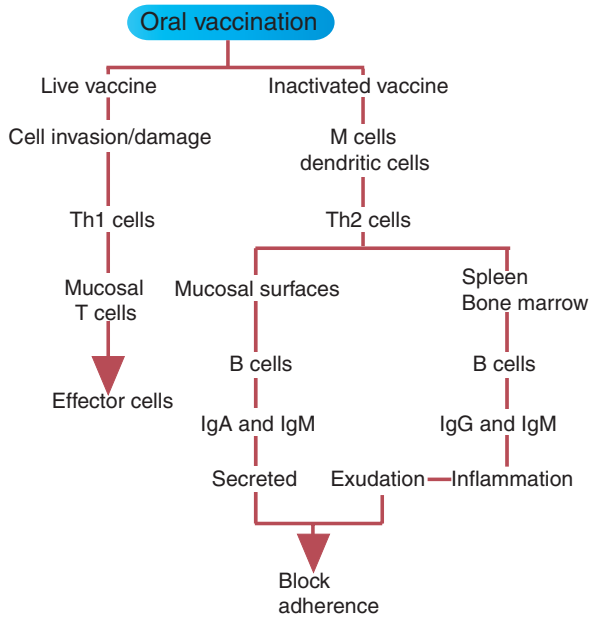
Fig. 8.5 The mechanism of action of oral vaccines. *Ig,* Immunoglobulin.

When animals are vaccinated against organisms that invade the intestinal or respiratory tracts, it makes sense to stimulate a mucosal IgA response. Because of the abundant intestinal microbiota however, intestinal IgA responses also have a high threshold, tend to lack memory, and fade rapidly. The body tightly regulates antigen import across epithelial cells. Regulatory effects on IgA production constantly adapt the IgA response to the intestinal microbiota. Once a protective IgA response has been generated, other difficulties may arise. For example, secondary immune responses are sometimes difficult to induce on surfaces, and multiple doses of vaccine may not increase the intensity or duration of the local immune response. This is not caused by any intrinsic defect but occurs because high levels of IgA can block antigen absorption and so prevent it from reaching antigen-presenting cells and memory cells.

To trigger an IgA response, the vaccine antigen can simply be ingested or inhaled. Unfortunately, such vaccines are not always effective. Inactivated antigens administered orally fail to trigger an IgA response because they are immediately washed off or simply digested when applied to mucous membranes. The only way a significant IgA response can be triggered is to use live vaccines, in which the vaccine organism can invade mucous membranes. The vaccine must persist for a sufficient time to trigger an immune response yet not cause significant damage.

The nature of the intestinal immune responses to enteroinvasive organisms depends on the sites of invasion. Enteropathogenic viruses can be divided into two broad types (type 1 and type 2) depending on their infection site in the intestine. Thus immunity to viruses that specifically attack the superficial villous enterocytes is largely mediated by specific IgA-mediated immunity in the gut lumen and within the villi. Examples of these type 1 organisms include transmissible gastroenteritis virus, porcine epidemic diarrhea virus, and rotaviruses. On the other hand, viruses that infect enterocytes deep within the crypts, designated type 2 organisms such as the parvoviruses, are controlled by both systemic and mucosal immunity. It follows therefore that type 2 organisms may be blocked by the use of parenteral vaccines whereas type 1 organisms will probably be best controlled by oral vaccines.

Systemic vaccination against surface infections may provide adequate immunity (as in human influenza and polio vaccines) because IgG may diffuse from serum to the mucosal surface. Indeed, many available vaccines simply work by stimulating high levels of IgG antibodies in blood. These are effective because once an invading organism causes tissue damage and triggers inflammation, the site of invasion is flooded by IgG. Nevertheless, this is not the most efficient way of providing immunity.

Ruminants present specific problems when considering oral vaccination. The presence and large capacity of the rumen mean that ruminal microorganisms may destroy antigens before they reach the intestine or be simply highly diluted. On the other hand, if antigen can be expressed in a fibrous plant such as alfalfa, then it will be carried to the oral cavity during rumination and thus presented to the nasopharyngeal mucosa. For example, cattle fed recombinant alfalfa hay engineered to express the leukotoxin of *Mannheimia haemolytica* increased their production of antileukotoxin IgA.

Orally delivered poxviruses, as used when vaccinating wild animals against rabies, are effectively targeted to the mouth rather than lower down the intestinal tract. The poxviruses presumably exploit small cuts and abrasions to establish lesions. Excipients that can prolong the time in the oral cavity or abrade the oral mucosa may help this process. Generally, these oral vaccines stimulate a strong humoral response.

Despite the obvious desirability of using mucosal vaccines, few effective ones have been developed. In humans there are only five: poliovirus, rotavirus, *Salmonella typhi*, *Vibrio cholera,* and the intranasal influenza vaccine. These vaccines in general do not promote long-lasting protection and all require boosting after two years.

Oral vaccines for animals may be administered in the feed or drinking water, as is done with *Lawsonia intracellularis* and *Erysipelothrix rhusiopathiae* vaccines in pigs and against Newcastle disease, infectious laryngotracheitis, and avian encephalomyelitis in poultry. Plague vaccine-coated candy has been fed to prairie dogs in the western United States and effectively prevents this disease (Fig. 20.3).

INTRANASAL VACCINATION

The intranasal route of administration has advantages over oral administration in that the vaccine is not significantly diluted by nasal fluids, and not exposed to a low pH or to digestive enzymes. It is also more appropriate to administer a vaccine at the site of the organism's potential invasion route (Fig. 8.6). Nasal associated lymphoid tissue is extensive. The collection of oronasal pharyngeal lymphoid tissue (Waldeyer's ring) includes all the tonsillar tissue, cervical lymph nodes, in addition to M cells and intraepithelial dendritic cells capturing antigen in the nasal mucosa. Intranasal vaccines are available for infectious bovine rhinotracheitis, parainfluenza 3, and respiratory syncytial virus of cattle; for *Streptococcus equi* infections in horses; for feline herpesvirus, *Bordetella bronchiseptica*, coronavirus, and calicivirus infections; and for canine parainfluenza and *Bordetella* infection. Intraocular vaccines used in poultry have a similar mechanism of action and stimulate antibody production in the harderian gland. Intranasal and intraocular administration requires that each animal be dealt with on an individual basis and may not be cost effective.

When animal numbers are large, other methods must be employed. Spray application of vaccines enables them to be inhaled by all the animals in a group. This technique is employed in vaccinating against canine distemper and mink enteritis on mink ranches and against diseases such as Newcastle disease in poultry (Chapter 19).

Novel Techniques

Although syringes and needles are simple and relatively economical, they have obvious disadvantages. Not only are they painful, but they also deposit vaccine antigens in the wrong place.
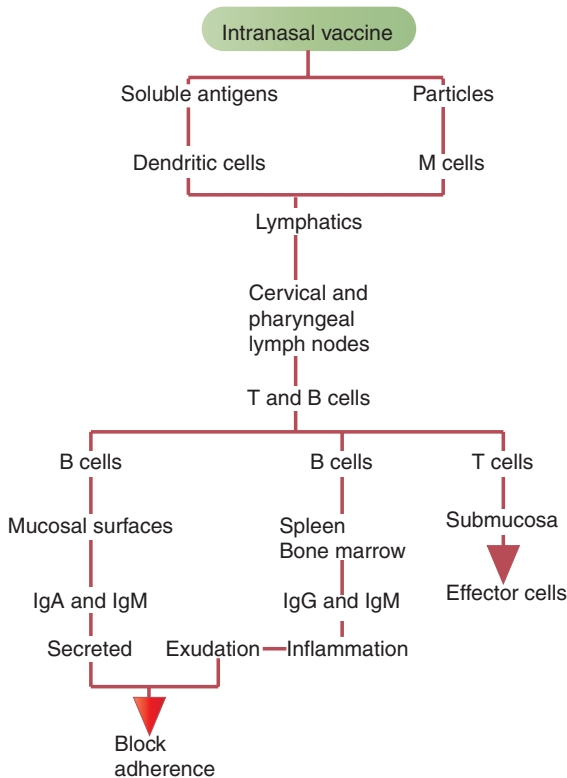
Fig. 8.6 The mechanism of action of intranasal vaccines. *Ig,* Immunoglobulin.

Antigen processing dendritic cells are relatively uncommon in the subcutis and even in skeletal muscle. The densest population of these cells is found in the dermis where there is a web of Langerhans cells and dermal dendritic cells. This means that a dose of vaccine delivered at this site will require less antigen to trigger a strong response than at other locations. Alternative methods of vaccine administration that are in development and increasingly employed in humans and animals such as pigs include intradermal vaccination using needle-free injection devices, microinjection, or topical skin application through patches or nanoparticles.

Needle-Free Injection Devices

Needle-free injection devices (transdermal jet injectors) generate a very fine stream of liquid under very high pressure. When they are held firmly against the skin the liquid stream can penetrate the epidermis. They thus deposit vaccine in the dermis and subdermis where antigen-processing dendritic cells are present in high numbers. These devices may be powered by compressed gas, batteries, or springs. Both battery and spring-powered devices are compact and relatively cheap, but exert minimal force. Gas powered units can exert much higher forces but tend to be cumbersome. They use air, nitrogen, or CO_2 cartridges attached to the injector by a tubing system. The injector is held against the skin and a stream of vaccine (with a velocity >100 meters/sec) is forced through a tiny orifice, 76 to 360 μm in diameter (about the diameter of a 36 gauge needle), and penetrates the skin in a fraction of a second (<0.3 sec). Injectors generate pressures of 130 to 1800 psi depending upon the desired depth of penetration, but

higher pressures are more painful than low pressures. The fluid is delivered in three stages. An initial high-pressure stream penetrates the skin, a second delivery stage is followed by a drop-off stage as the pressure reduces. These needle-free devices are precise and very reliable. At one time these injectors were favored for mass vaccination procedures in humans because they were very efficient and fast to use. They fell out of favor because they could cause bleeding. The blood could contaminate the injector creating the possibility of disease transmission. Cases of hepatitis B transmission by jet injectors were documented. As a result, multi-use-nozzle jet injectors are no longer used in humans in the United States. They continue to be used for mass vaccination purposes in livestock, especially pigs, but many now have disposable nozzle faces that can be easily replaced as needed. Transdermal jet injectors are also employed to administer a DNA plasmid vaccine against canine oral melanoma (Oncept, Boehringer Ingelheim). These injectors are generally much less painful than needles and thus also reduce animal fear and distress. They reduce the risks of needlestick injuries, broken needles, and improper reuse. They cause less tissue damage and fewer injection site lesions because the vaccine is distributed over a wider area, and are a reliable way of delivering the correct dose. They also deliver a consistent amount of vaccine. Because these devices deliver antigen to the dendritic cell-rich environment of the dermis they generally require a smaller volume of vaccine to generate a protective immune response. The resulting immune responses are equivalent to those caused by needle injection (Chapter 18). Despite these advantages, adoption of these devices has been slow because of the cost of purchase and maintenance, required infrastructure and complexity, and also the need for training in their use.

Microneedles

Microneedle patches are adhesive patches containing an array of micron-sized needles that can be applied by pressing the patch against the skin. The patches contain a single vaccine dose. They do not require reconstitution, simplify storage, and waste disposal, and improve vaccine immunogenicity.

Microneedles are long, thin, square, or round cones tens to hundreds of micrometers in length, and about one-hundredth of the diameter of a standard hypodermic needle. They can target dendritic cells in the dermis without causing sufficient damage and producing significant pain. Four types of microneedle have been found to work well with vaccines: solid microneedles that simply make holes through which liquid vaccines can diffuse, vaccine-coated microneedles, soluble dissolving microneedles, and hollow microneedles. Dissolvable microneedles simply dissolve in tissue fluid, so releasing the vaccine within them into the dermis. Hollow implantable dissolving microneedles contain vaccine within their core. Although microneedle applications have been investigated for many virus vaccines, including rabies, most studies have focused on influenza vaccines. In general, microneedle patches stimulate greater immunogenicity, a stronger systemic response, and a better Th1 (type 1 helper cell) response, in addition to the need for much lower doses of vaccine.

Pellets

In the United States, a Moraxella vaccine for calves is available for implantation in pellet form. Two pellets are inoculated at one time under the skin. One is designed for immediate antigen release; the other pellet rehydrates slowly and releases its antigens over a two- to three-week period.

Ballistic Vaccination

It is possible to vaccinate animals from a distance using a blowpipe. The maximum effective range for blowpipe vaccination is up to 60 feet. These are especially useful in vaccinating large exotics and the animals need not be confined. Blowpipes are virtually silent and as a result do not disturb other animals in a herd unlike the ballistic vaccines that are shot from rifles (Chapter 20).

Sources of Additional Information

Albas, A., Fontolan, O.L., Pardo, P.E., et al. (2006). Interval between the first dose and booster affected antibody production in cattle vaccinated against rabies. *J Venom Anim Toxins,* 12, 476–486.

Balakrishnan, S., Rekha, V.B. (2018). Herd immunity: An epidemiological concept to eradicate infectious diseases. *J Entomol Zool Studies,* 6, 2731–2738.

Benn, C.S., Netea, M.G., Selin, L.K., Aaby, P. (2013). A small jab—a big effect: Nonspecific immunomodulation by vaccines. *Trends Immunol*, 34, 431–439.

Bernath, S., Fabian, K., Kadar, I., et al. (2004). (2004). Optimal time interval between the first vaccination and the booster of sheep for *Clostridium perfringens* Type D. *Acta Vet Brno,* 73, 473–475.

Delamater, P.L., Street, E.J., Leslie, T.F., et al. (2019). Complexity of the basic reproduction number (R_0). *Emerging Inf Dis*, 25, 1–4.

Johnson, N., Cunningham, A.F., Fooks, A.R. (2010). The immune response to rabies virus infection and vaccination. *Vaccine*, 28, 3896–3901.

Kwon, K.M., Lim, S.M., Choi, S., Kim, D.H., Jin, H.E., Jee, G., Hong, K.J., Kim, J.Y. (2017). Microneedles: Quick and easy delivery methods of vaccines. *Clin Exp Vaccine Res,* 6, 156–159.

Logomasini, M.A., Stout, R.R., Marcinkoski, R. (2013). Jet injection devices for the needle-free administration of compounds, vaccines, and other agents. *Int J Pharm Compd,* 17, 270–280.

Nalin, D.R. (2002). Evidence-based vaccinology. *Vaccine,* 20,1624–1630.

Plotkin, S.A. (2010). Correlates of protection induced by vaccination. *Clin Vaccine Immunol,* 17, 1055–1065.

Shwiff, S.A., Kirkpatrick, K.N., Sterner, R.T. (2008). Economic evaluation of an oral rabies vaccination program for control of a domestic dog-coyote rabies epizootic: 1995–2006. *J Am Vet Med Assoc* 233, 1736–1741.

Weyer, J., Rupprech,T. C.E., Nel, L.H. (2009). Poxvirus-vectored vaccines for rabies: A review. *Vaccine*, 27, 7198–7201.

Williams, P.D., Paixao, G. (2018). On-farm storage of livestock vaccines may be a risk to vaccine efficacy: A study of the performance of on-farm refrigerators to maintain the correct storage temperature. *BMC Vet Res,* 14, 136.

Abstract: Vaccines should only be administered following a complete risk/benefit analysis by a veterinarian in conjunction with the owner. The designation of "core" or "noncore" vaccines are not absolute and will depend upon specific circumstances. Vaccines must be administered by the correct route, at the correct time, in the correct manner. Vaccination schedules must take maternal immunity into account, and revaccination must take duration of immunity data into account. Serologic tests should be employed to determine the need for revaccination. Vaccines must be stored and administered correctly. They may be administered by diverse routes, in addition to injection. Intranasal and oral vaccination, intraocular and aerosolization are all possible routes.