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The use of vaccines in veterinary medicine has progressed from an experimental adventure to a routine and relatively safe practice. The common and aggressive use of efficacious vaccines has been, in large part, responsible for control and eradication of several diseases. However, despite progress in research technologies, diagnostic capabilities, and manufacturing methods, there remain many infectious diseases for which no effective vaccines exist. Global availability, field compliance, effectiveness, and safety are also significant concerns. This review addresses the history, current practices, and potential future improvements of vaccine use in veterinary medicine.

THE HISTORY OF VACCINES IN MEDICINE: VARIOLATION, VACCINATION, AND IMMUNIZATION

The development of vaccines and vaccination programs has been evolving for centuries. The observation that persons that had recovered from smallpox infections were immune to reinfection has been recorded throughout history by several societies. Many Eastern cultures practiced different forms of variolation for several centuries.1 By the sixteenth century the practice of variolation (inoculating partially attenuated variola virus to prevent smallpox) was common in Europe.2 This practice originated more or less simultaneously with the practice of inoculating lambs with sheep pox. In the latter years of the eighteenth century, cross-protective properties of the vaccinia virus (cow pox) allowed for the more socially acceptable practice of “vaccination” to
become a routine component of medicine. Problems with consistent potency, available supply, purity, and safety were common. Nevertheless, both the effectiveness and imperfections of vaccination lead to the eventual global eradication of smallpox, and was the inspiration for development of the products and programs for immunization against several diseases in humans and animals.

Louis Pasteur first used the term vaccine in 1881 for immunogens directed at other diseases besides smallpox. Pasteur directed many investigations that demonstrated the feasibility of attenuating or inactivating microbes. Studies with fowl cholera and anthrax led to the concepts of chemical inactivation as a means to reduce the virulence of microorganisms. Studies with erysipelas and rabies explored serial passage in animals (lapinization or passage through rabbits) or other animal derived tissues as an alternative strategy to reduce or eliminate virulence. Thus, the virulence of infectious microbes could be completely or partially reduced. These studies have led to the eventual successful control of anthrax and rabies in particular. The work of Salmon and Smith (1886) clearly demonstrated that some microbes could be completely inactivated (killed). These developments eventually led to successful immunization programs against typhoid fever, tuberculosis, rinderpest, and foot and mouth disease (FMD). Attenuation and inactivation principles were extended to microbial toxins by the work of Gaston Ramon at the Pasteur Institute. A tetanus toxoid was developed in 1924 through heat and formalin inactivation of the toxin to form an “ana-toxin.” Also, enhanced efficacy was provided by absorbing the toxoid to an aluminum hydroxide, providing an adjuvant effect. These process and formulation improvements were developed and refined in the early twentieth century, first through production of equine sera with antidiphtheria and antitetanus toxin-neutralizing antibody for prophylactic use. In the modern era of vaccine use, these same basic technologies are still the mainstays of vaccine production. However, new generations of recombinant, nucleic acid and subunit vaccines have become available. It is remarkable that the principles of developmental research, registration, and manufacture still follow the techniques of the grand heritage.

During the early years of the modern era of vaccine production, infected tissues were often used as a source of microbial antigens through grinding, inactivation (typically with formaldehyde solutions), and subsequent filtration or clarification. More often than not these vaccines were produced in regional research institutions. Industrialization of the processes began in the 1930s and 1940s when large-scale, controlled processes were used to produce FMD antigens in Germany by Waldmann and colleagues. The development of first primary and subsequently clean cell lines occurred in the 1950s and 1960s. Development of high-volume roller bottle methods and later large-scale bioreactors has made possible the production of millions of doses of vaccines. Further, production has been maintained in secure, closed systems, enhancing the security for the environment as well as the technical staff. In like manner, improvements in inactivation technologies (cyclized binary ethylene-imines), purification and concentration of antigens, storage of bulk antigens, improved aluminum gels, and oil suspension adjuvants in the formulation of polyvalent antigens have been critical achievements in the steady advancements in vaccinology.

As these technical advances were employed in the industry, independent and collaborative efforts by numerous governmental authorities created regulatory frameworks that have established regulations and guidelines for registration of new biologicals as well as consistent manufacture of pure, safe, and potent vaccines. Under these regulations all released lots of vaccines are tested to ensure consistent formulation characteristics and potency (immunologic strength), safety, and purity (sterility and freedom from contamination with extraneous biologic agents). Development of
Good Manufacturing Practices guidelines and master seed and master cell stock concepts has further ensured consistent manufacture of vaccines that will provide consistent immunogenicity and efficacy. A veterinary clinician therefore may use with confidence any approved vaccine as recommended by the manufacturer to achieve the anticipated clinical outcome of protection.

VACCINES IN CLINICAL PRACTICE IN VETERINARY MEDICINE

As the vaccine manufacturing processes improved with regard to consistency of biologic activity, robustness, and efficiency, routine clinical use of vaccines became more practical and economical. There is no doubt that widespread use of efficacious vaccines has been associated with the global eradication of smallpox in humans and the regional control of FMD and rabies. The routine use of processed immunoglobulins (usually in the form of processed horse serum) preceded the use of vaccines. Although passive protection by the immunoglobulins is still employed (particularly for rabies and tetanus post exposure prophylaxis), the advantages of active immunity (immunologic memory and reduced risk of infection) have significantly reduced the use of passive immunity.

In the mid-1950s, veterinarians were commonly using rabies vaccines of brain tissue origin in dogs. The principal biologic products used in practice at that time were rabies vaccines, “viabilized” canine distemper/hepatitis virus vaccine and antisera, hog cholera and erysipelas vaccines and antisera, leptospirosis bacterins, and clostridial toxoids (Fig. 1). As the development and manufacturing capacity increased with time, vaccination of companion animals expanded to include rabies for cats, feline herpesvirus, parvovirus in cats and dogs, and feline calicivirus. Table 1 describes the types of vaccines currently available to companion animal practitioners in most regions of the world (http://www.aphis.usda.gov/animal_health/vet_biologics/vbLicensedProducts.shtml) These vaccines include very traditional inactivated antigen formulations, multiple attenuated agents, and new technologies such as poxvectored vaccines, defined subunit vaccines, and nucleic acid vaccines (see Table 1). The term vaccine is now used to describe many therapeutic or prophylactic formulations and products that stimulate active immunity in the vaccinated animal. This discussion focuses on vaccinations associated with infectious diseases.

Routine clinical use of these vaccines usually includes immunization of puppies and kittens at approximately 3-week intervals after maternal-derived antibody decreases to noninterfering titers. These immunization series are usually administered between the fourth and 16th weeks of life. Puppies and kittens associated with unusual risk may be vaccinated at younger ages or at more frequent intervals. Rabies vaccination is usually first given at 4 months of age. It is a common and efficacious practice to provide booster doses at 1 year of age for most vaccines. These immunization practices will provide a solid duration of immunity of at least 5 to 7 years and longer in some cases. General recommendations (World Small Animal Veterinary Association) are to vaccinate every third year after the initial immunization series, and these recommendations are consistent with product label guidelines. These initial immunization guidelines are derived from the initial registration immunogenicity and efficacy studies for any individual vaccine product. The efficacy studies define the minimum immunologic strength for the vaccine (the potency that must be present when the vaccine lot goes out of date). These same types of studies also define the minimum age of animals that can be successfully immunized as well as the specifics of the initial and booster immunization regimens (part 9, Code of Federal Regulations). It has
become very clear that many vaccines provide effective and long-term immunity for an extended period of time. Over the past 3 decades, cumulative evidence for extended duration of immunity has been provided to support the 3-year booster intervals for most vaccines in dogs and cats. However, as described in Table 1, the relative efficacy of some vaccines is less than ideal.
VACCINE EFFICACY AND EFFECTIVENESS

“Ideal” immunity would be not only protection from clinical disease (morbidity and mortality) but also blocking the infection/replication/spread or progression of infectious agents. Some vaccines do achieve this degree of protection. Some, however, may only reduce morbidity and/or mortality without generating a sterilizing immunity. Based on clinical and microbiological outcomes of an efficacy study challenge of immunity, various degrees of protection may be achieved and therefore claimed. The United States Department of Agriculture (USDA) has recognized these differences through a hierarchy of efficacy claims that may be allowed for a vaccine based on the outcomes of efficacy studies (Box 1).

The degree of efficacy and claim structures are usually derived from direct investigations of efficacy and challenge of immunity studies in their respective host animal species. Vaccinated and nonvaccinated animals are challenged with fully virulent organisms, and the degree of protection (efficacy) is determined under controlled settings. These classic studies are adequate to establish the efficacy of the vaccine but are not always sufficient to estimate the field effectiveness of a vaccine, or, in other words, the ability of a vaccine to control disease in the field. Effective control of infectious disease should result in reduced incidence and prevalence.15,16 This would be true of not only clinical disease but also of infection and spread of the infectious agent. It is very clear that use of efficacious products has reduced incidence of rabies, particularly in dogs. Immunization of dogs has reduced the incidence of canine rabies to essentially nil in the United States and western Europe.17 The rabies immunization programs in these countries have been so effective that most manufacturers of rabies vaccine for dogs and cats have switched to master seeds from canine street strains of virus to other types of terrestrial rabies (bat strains, for instance) to protect from the most significant current threats in these regions.

Fig. 1. (continued)
Vaccination has also greatly reduced the incidence of canine distemper, canine parvovirus, infectious canine hepatitis, feline panleukopenia, and feline herpes virus infections as well as other diseases. When these diseases do occur, there are usually issues with vaccine dose compliance, vaccination of sick or immunocompromised animals, exposure to wildlife, or problems associated with vaccine handling and/or administration. In situations where vaccines do not provide prevention of infection, concurrent infections may exist and vaccine failures are therefore more common. There are often issues with type-specific protections. For instance, it is not clear that available vaccines can protect cats against all types of calicivirus infections. Continual vigilance is required to ensure continued protection of animals in the face of potential newly evolving and emerging pathogens (eg, rabies and other lyssaviruses, canine distemper and parvoviruses, and feline calicivirus).

| Antigen                     | Strain                              | Type                           | Relative Efficacy                      |
|-----------------------------|-------------------------------------|--------------------------------|----------------------------------------|
| Canine distemper virus      | Rockborn, Snyder Hill,              | MLV/recombinant nonreplicating | High                                   |
|                             | Oondersport, canary pox             | in canary pox                  |                                        |
| Canine adenovirus           | Type 1 (historical) Type 2          | MLV                            | High                                   |
| Canine parvovirus           | Type 1 (historical) Type 2          | MLV Inactivated                | High, although some antigenic variation may exist |
| Rabies virus (canine and feline) | Bat strain (historical canine street strain virus) | Inactivated recombinant nonreplicating in canary pox (feline) | High |
| Feline panleukopenia virus  | Feline origin                       | MLV and inactivated            | High                                   |
| Feline herpesvirus          | Feline origin                       | MLV                            | Good for clinical disease              |
| Feline calicivirus          | Multiple serotypes                  | MLV                            | Moderate, strain gaps                  |
| Canine coronavirus          | Canine origin                       | MLV and inactivated            | Moderate, questionable DOI             |
| Canine parainfluenza        | Canine origin                       | MLV                            | Moderate                               |
| *Bordetella bronchiseptica* | Canine origin                       | Bacterin and inactivated       | Questionable                           |
| (canine and feline)         |                                     |                                |                                        |
| Leptospirosis bacterins, multiple serotypes | Canine origin | Inactivated | Moderate to good |
| *Borrelia burgdorferi*      | Canine origin                       | Inactivated bacterin and OspA recombinant vaccine | Moderate |

Abbreviations: DOI, duration of immunity; MLV, modified live virus.

Data from Day MJ, Horzinek MC, Schultz RD. Guidelines for the vaccination of dogs and cats. Compiled by the Vaccination Guidelines Group (VGG) of the World Small Animal Veterinary Association (WSAVA). J Small Anim Pract 2007;48:528–41; and Patel JR, Heldens JG. Review of companion animal viral diseases and immunoprophylaxis. Vaccine 2009;27:491–504.
HOW DO VACCINES WORK?

The vaccines used in veterinary medicine generally fall into 1 of 3 categories: inactivated vaccines (in which antigens are typically combined with adjuvants); attenuated, live vaccines; and recombinant technology vaccines, which may include subunit antigens or genetically engineered organisms. In practice, combination and multivalent vaccines may employ all 3 approaches. All of these technologies have been used successfully, and each approach has inherent advantages and disadvantages. The protective mechanisms associated with vaccines are also becoming clearer.

Historically, the most common correlate of immunity to derive from vaccination has been measurements of antibody responses.\textsuperscript{18,19} Antibodies have several functions including facilitating opsonization, complement-mediated cellular lysis, neutralization-blocking adherence or replication, and facilitating cytotoxic cells. However, mature, well-differentiated immune responses are the consequence of cumulative, regulated interactions between phagocytic cells, antigen-presenting cells, and both B and T lymphocytes. Therefore, a well-differentiated antibody response with isotype switching, affinity maturation to high avidity, and memory requires some effective initial stimulation involving dendritic cells and expansion of regulatory T lymphocytes.
(likely CD4+) and B lymphocytes. This stimulation phase is followed by a phase of differentiation into effector/memory T cells, B cells, and plasma cells.

With respect to the nature of pathogenesis of many infectious agents, the adaptive immune response to the vaccine often blocks or interferes with a specific segment of the infection process. For instance, antibody-mediated neutralization of rabies virus in extracellular spaces inhibits transmission to neurons and subsequent axonal progression of the virus to the central nervous system. In this case the presence of preformed, neutralizing antibody is critical for protection. A summary of protective characteristics of the immune responses to vaccines (as potential correlates of protection and disease prevention) is provided in Table 2. Although antibody responses are good correlates of protection, they do not always reflect all available protective mechanisms provided by a well-differentiated immune response. In some cases, other correlates are available. It is clear that the presence of neutralizing, vaccine-derived antibody will reduce mucosal virus replication, virus shedding, and viremia in kittens vaccinated with modified live feline herpes vaccines.20–22 However, regulated CD4+ and CD8+ cellular responses are required to control tissue damage and reactivation of disease.23 In this case, antibody may be a protective correlate of infection while cellular immunity is a protective correlate of disease. The ability of modified live vaccines to generate a very rapid onset of cytokines and interferons (and rapid antigen focusing in dendritic

| Correlate of Protection | Description | Prevent Infection? | Vaccine Characteristics |
|-------------------------|-------------|--------------------|------------------------|
| Neutralizing antibody (viral or bacterial, adhesion factors, toxins) | IgG, matching field strains or outbreak strains | Yes, potentially | MLV or inactivated, toxoids, nonreplicating viruses and particles |
| Nonneutralizing antibody (virus) | IgG, potentially interfering | Questionable | MLV or inactivated, any formulation |
| Nonneutralizing antibody (bacteria) | IgM or IgG, somatic antigens, opsonizing and complement-mediated clearance | Yes | Bacterins or attenuated vaccines |
| Mucosal surface protection | IgA, viral or bacterial, adhesion factors, toxins | Yes, if infection occurs at mucosal surface, may limit infection and shedding | Attenuated vaccines, especially intranasal or oral |
| Virus-specific, cytotoxic T cells | CD8+ T cells, MHC-restricted killing of infected cells | Yes, limit infection spread and pathology by destruction of infected cells | Primarily attenuated vaccines, but newer formulations with novel adjuvants |
| T-helper cells | CD4+ T cells | Help differentiate antibody- and cell-mediated responses, essential for memory | Attenuated and inactivated formulations with appropriate adjuvants |

Data from Rimmelzwaan GF, McElhaney JE. Correlates of protection: novel generations of influenza vaccines. Vaccine 2008;26 Suppl 4:D41–4.
cells in lymphoid tissues) is associated with a rapid onset of protection, even though antibody responses may not be detectable in serum for up to 2 weeks. Therefore, the early response of multiple cytokines and concurrent activation of the innate immune system may serve as early correlates of protection.

There are also documented cases in which functional immunity outlasts detectable circulating antibody; this is true with many herpesvirus infections. However, the presence of detectable neutralizing serum antibody is correlated with protection against recrudescent disease. In situations where vaccinated animals may be exposed to heterotypic viruses or bacteria, the presence of immune CD4+ T cells specific to conserved antigens may be very important for protection. It is possible that the effective mechanisms for development of protection associated with a vaccine may be specific to the nature of the disease and infectious process. Recent studies have provided important information regarding this phenomenon. A common hypothesis is that vaccine-induced immunity should reflect convalescent immunity following natural infection. For example, it is known that recovery from primary poxvirus infections requires robust cytokine responses, natural killer cells, and antibodies as well as T helper (CD4) and cytotoxic T (CD8) lymphocyte effector functions. However, recovery from a secondary infection requires only T- and B-lymphocyte interaction and an anamnestic antibody response. Again, neutralizing antibody will reduce infection, viremia, and spread of a virus (and may do so to the extent of blocking infection) while T-cell–mediated responses will allow survival and recovery. It seems clear that balanced antibody and cellular responses are necessary for complete protection from infection and disease as well as spread to other animals.

It should be mentioned that not all antigen-binding antibodies are protective. In some cases, such as with influenza virus, canine distemper virus, and herpesvirus vaccines, nonneutralizing antibody may be produced that does not contribute to the blocking of infection or enhancing clearance of the infectious agent. For this reason, correlates or surrogates of protection should be linked to protective mechanisms; this can be done through retrospective analysis of data from efficacy and immunogenicity studies or through associational studies in immune populations (such as with primary vaccinates in an efficacy study).

**FUTURE DEVELOPMENTS IN VACCINE TECHNOLOGY**

Veterinary vaccinology has realized significant successes that have affected human and animal well-being, and the ability to coexist. The virtual elimination of canine rabies in North America and western Europe has indirectly led to human-animal bonding at a very intimate level that was not feasible when canine rabies was relatively common. However, there remain many diseases for which no efficacious or effective vaccine exists. Many parasitic diseases as well as diseases of a chronic, intracellular nature are not covered by any available vaccine. In some cases safety profiles or efficacy characteristics of existing vaccines are not acceptable. Fortunately, there are promising technologies that may close the technical gaps for prevention of these challenging diseases.

The processes of absorption of antigens such as chemically inactivated toxoids or viruses to aluminum gels, or the creation of water-in-oil emulsions of antigen particles have been the principal methods used for veterinary vaccine formulations. In some cases compounds such as crude or purified saponins (Quil A), squalenes, or pluronic block copolymers have been added to enhance immune stimulation. Although these practices have been successful, newer technologies such as CpG DNA, defense peptides, imidazoquinolones, and polyphosphazenes may enhance both safety and
efficacy. Further, additional cholesterol and phospholipids may be combined with antigens and saponins to create immunostimulating complexes (ISCOMS) particles. Similar adjuvant particles can be generated with no antigen (ISCOMATRIX) that can be admixed directly with antigen suspensions. These advanced formulations may be used to provide very efficient adjuvants to in turn allow development of microvolume formulations as well as transdermal applications. Also, as better understanding of immune genotypes and phenotypes in animal populations emerges, individualized formulations of vaccines may be developed and produced that may enhance safety and efficacy.

Proteomic technologies may very well provide methods to identify antigen subsets from among complex organisms and infectious agents such as bacteria and protozoa. These organisms contain large, complex genomes. Antigen expression is often dependent on growth conditions, and the medium may be very complex. These conditions are difficult to reproduce and regulate in vitro. The combination of transcriptional and proteomic analysis may provide a means to identify key antigens associated with tissue or cellular persistence and potential virulence. Such analyses could provide means to simplify vaccine formulations to include only protective antigens and reduce the presence of nonprotective, potentially interfering bacterial proteins. Not only would this potentially improve efficacy, but it could also improve safety profiles by reducing the antigenic mass in a vaccine dose.

The continued use of alternative expression systems has many potential advantages. Transgenic expression of protein antigens and plant-based systems may provide access to oral vaccines as well as enhanced stability of antigens. Expression of antigens in avirulent viruses, bacteria, and yeast and insect cells may provide both manufacturing and user safety by eliminating the need to use a virulent or partially virulent microbe to provide immunity. Further development of nucleic acid vaccines may provide even greater formulation simplicity and biosecurity. Viral particles such as capsids from avirulent viruses may serve as building blocks to deliver nucleic acids, protein subunit antigens, and microadjuvants directly to secondary lymphoid tissue. Not only would these biologically engineered vaccines provide targeted immunity and eliminate the need to work with dangerous microbes, they very likely would reduce the time required for the onset of immunity, with excellent safety characteristics.

One of the most pressing problems associated with manufacturing vaccines is the requirement to rapidly modify antigen formulations as new diseases emerge or as older pathogens mutate and reemerge. Transcriptomics and proteomics combined with established recombinant or synthetic approaches could potentially provide antigens that could be rapidly formulated with approved new-generation adjuvants to produce novel and efficacious vaccines. These technologies are commonplace in experimental laboratories. Using combinations of proteomics, reverse genetics, recombinant or molecular syntheses, and stable, consistent adjuvant platforms will allow development of “first line of defense” vaccines for a rapidly emerging disease in a short time. Such a use-inspired approach to vaccines would allow the use of assembly-line techniques to manufacture vaccines. As new antigens are required they could be selected, evaluated, and produced in a short period of time, and inserted directly into an established production system. This process would greatly reduce the time required for exploratory research and early development. Classic development cycles may require 5 to 7 years and sometimes may require even longer times for unusual or new types of pathogenic microbes. A reduction of the development time by 30% to 80% may be achievable using newer research and development technologies.
It is clear that new methods to assess efficacy and definitive, direct correlates of immunity also need to be identified. It is also clear that use of the many new technical achievements and discoveries will require advances in the regulatory framework to ensure more efficient but adequate evaluation of new biologicals. Vaccine development faces many technical, political, and ethical challenges. The history of vaccine research and development as well as the continued use of immunization as the principal method to prevent infectious disease predict that the innovative experimental procedures of today will lead to common clinical applications tomorrow.

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