Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Vaccination Practices in Veterinary Medicine: Standardization versus Tailored to Needs?

SERGE MARTINOD

Pfizer Central Research, 1 Eastern Point Road, Groton, Connecticut 06340

I. Introduction
Vaccines have already achieved great success in controlling many diseases of importance to farm or companion animals or which threaten human health. Vaccines have brought eight major human diseases under various degrees of control: smallpox (complete eradication), diphtheria, tetanus, yellow fever, whooping cough, polio, measles, and rabies. More than 80% of the world's children are now being immunized against the polio virus and the annual number of cases has been cut from 400,000 in 1980 to 90,000 in the mid-1990s. Measles is another possible candidate for eradication. Veterinary vaccines also have had a profound influence in the world. They can control devastating diseases such as foot-and-mouth disease in cattle, canine distemper, feline and canine parvovirus, pseudorabies in swine, and rabies in all
species, as well as the economic losses due to many respiratory, reproductive, or enteric pathogens.

Prevention is always better than cure, to minimize the suffering of animals and losses among livestock. Vaccines, coupled with precautions such as quarantine, movement control, and sound management, can achieve this objective. However, immunization should never be seen as routine. It is important to recognize that biologicals can cause adverse reactions or that inappropriate use could promote the production of escape mutants. The animal owners and the public have a right to expect that the preparation and use of animal biologicals is reliably based on the highest standards of quality, safety, and efficacy. In this paper we review some of the issues surrounding standardization of veterinary vaccine practices.

II. Can We Standardize Vaccination Practices?

Immunization is one of the most important tools in veterinary medicine and probably the most cost effective. All animals around the world are at risk from a multitude of infectious diseases. Furthermore, many different products are available in countries around the world. Therefore, an effort to define vaccination schemes and protocols, while needed, must take into account numerous issues.

A. Standardization of Veterinary Practices

1. Label Claims

Before being administered to a patient, vaccines have to be researched, developed, field tested, licensed, produced, quality controlled, regulated, purchased, transported, stored, and delivered. Most of these activities are subject to national or international legislation. The data generated during the development phase and reviewed during the licensing process is the basis for the labeling and product information literature. Full instructions on how to use the product, details of the claim for it, dosing regimes, and contraindications are given in the label. It is the primary source of information provided by the manufacturers and authorized by government licensing agencies and should always be taken into consideration by the users.

2. Guidelines

For many species professional organizations such as the American Veterinary Medical Association (AVMA) regularly publish updated
guidelines to help the veterinarians in the design of the best vaccination practices. These recommendations are based on information from the label claims, the published scientific literature, the experience from the field, and the epizootiology of each disease.

3. International Organizations

Many international organizations are concerned with animal health worldwide: the Office International des Epizooties (OIE), the Food and Agriculture Organization (FAO), and the World Health Organization (WHO) deal with the control of animal diseases. Furthermore, regional organizations such as the Commission of the European Union or the Pan-American Health Organization are also involved in decision making and recommendations on animal health policies including vaccination based on political, economic, and technical considerations. Government policies can also make defined vaccination programs mandatory or exclude particular vaccines from use.

4. "Global" Diseases

Many viruses for example are distributed around the world: Canine distemper and parvovirus, feline parvovirus, bovine herpesvirus 1 (BHV1) or bovine viral diarrhea virus (BVDV), pseudorabies virus, and Marek's disease virus infect animals worldwide. At least in theory, global recommendations for vaccination programs could be made for these diseases.

5. Lessons from Human Vaccines

The use of pediatric vaccines has been standardized successfully by the WHO and local medical pediatric associations. These vaccines have brought major disease such as poliomyelitis under control in many countries. This could set up an example for veterinary vaccines.

With well-defined label claims, government or international legislation and guidelines, and professional association recommendations, vaccination programs could be easily standardized. However, such policies have many limitations where the biologicals are put into action to protect diverse populations against infectious agents.

B. LIMITATIONS

Generally, routine vaccination is undertaken in young animals with booster vaccinations at various intervals depending on manufacturers'
or government instructions. However, in practice, which vaccines are given and precisely when they are given varies according to many factors.

1. Multiplicity of Target Species and Husbandry Conditions

The market for veterinary vaccines is very fragmented. Very few individual vaccines can be administered to more than one species. Within a given species different disease conditions, distribution channels, or husbandry conditions in different countries contribute to further fragmentation. Customers require different products, use patterns, and administration routes (e.g., oral, intradermal, intranasal, intramuscular, in ovo, etc.) depending on the management system, housing, age of the animals, traditions, or opinions of leading vaccinologists in each country.

2. Difference in Disease Conditions

The prevalence of diseases within a given species varies from one region to the other. The epidemiology of different serotypes (e.g., Actinobacillus pleuropneumoniae) restricts the use of some products to certain geographic areas. Moreover, the disease incidence is often of a transient nature (e.g., transmissible gastroenteritis in pigs) and therefore the need for a particular vaccine may change rapidly.

3. Strain Variations and Antigenic Diversity

A certain degree of antigenic diversity is always identified among isolates of the same pathogen. This variation may concern only a few epitopes which are differentiated by a panel of monoclonal antibodies and not relevant for a vaccine formulation or it may require the development of a different vaccine strain. Foot-and-mouth disease virus (FMDV) occurs as seven serotypes, within each of which there is the potential for wide antigenic diversity. In the face of FMDV outbreak, it is critical to demonstrate that cross-protection is induced by the vaccines. Pestiviruses also exhibit wide differences. Two biotypes (cytopathic and noncytopathic), two genotypes (types I and II), and a continuous spectrum of antigenic variations can be found in BVDV isolates.

4. Lifestyle

Multiple-cat households are defined as homes with three or more cats. By nature cats are solitary creatures, comingling only at times of mating or territorial disputes. Many health problems seen in multiple-cat households result from artificial environments in which the cat must live and do not exist in single-cat households. Therefore, the
recommendations for vaccines should be different for cats living in multiple- or single-cat households.

5. Age at First Vaccination

Puppies become susceptible to viral infections as the maternal antibody titer declines to nonprotective levels. Currently, parvovirus in dogs is more commonly encountered in puppies from 6 weeks to 6 months of age. High levels of maternal antibodies can prevent some vaccines from being effective. Conversely, most adult dogs have become immune through vaccination or natural infection and are refractive to boosting with modified live vaccines.

6. Breed Susceptibility

Certain breeds are reported to be more susceptible to the development of parvovirus disease despite antibody titers considered protective in other breeds. Doberman pinschers, Labrador retrievers, and Rottweilers are reported to be more severely affected by parvoviral infections. For those breeds at high risk, it is sometimes recommended that the vaccination protocol be continued to 20 weeks instead of 12 weeks of age.

7. Economical Issues

BHV-1 is responsible for infections of the respiratory and reproductive tract. The infections are widespread. The virus causes severe clinical signs and economic losses in the United States, but the disease is mostly subclinical in most countries of the European Union. Therefore, the control of the clinical disease is critical in North America but not in Europe. However, European Union Directive 64/32/EEC allows countries to restrict trade in live animals on the basis of their health status. As a consequence, a marker vaccine strategy is being developed in Europe not only to control the disease, but to limit the virus circulation and eradicate the virus from the cattle population. The vaccine strategies are totally different between the two continents. Zoosanitary legislation may also limit the types of vaccines used in control programs to a particular strain or marker, thereby distorting competition in the marketplace.

8. Difference in Regulatory Requirements

National or regional regulatory requirements further contribute to the market complexity of veterinary vaccines. For example, the use of vaccines against clinical swine fever (CSF) is forbidden in the European Union despite a severe outbreak of the disease in 1997 in the
Netherlands. Vaccines against CSF are allowed in other parts of the world as a tool to control the disease outbreaks.

9. Influence of the Climate or Ecosystems

The geographic distribution of tick-borne diseases is highly dependent on the existence of the vectors. Pathogens, vectors, and reservoir hosts exist in ecologic assemblages and a combination of events have led to increasing human and companion animals interaction with these assemblages. For example, *Amblyomma americanum*, which transmits the agent of human ehrlichiosis, is found throughout the southeastern United States while *Ixodes dammini*, which transmits the agent of Lyme disease, is found in the northeastern and north central (Wisconsin, Minnesota) part of the country. The recommendation for the prevention of each disease will vary dramatically depending on the geographic location of the population being vaccinated.

The choice of a vaccine and a vaccination regimen should always be selected with the best interest of the animals and their owners in mind. Appropriate immunization should be given in accordance with manufacturers' guidelines, government regulations, and veterinarian recommendations. The local veterinarian is usually the best qualified to make the recommendation. Vaccination programs need to be tailored to each individual animal or livestock operation.

III. Are We Vaccinating Too Much?

A. Risks

Recently, concerns about vaccine reactions have raised questions and doubts about the best immunization practices.

1. Safety

Vaccination safety is of utmost importance. The use of biological products has become so routine that vaccination is sometimes believed to be innocuous. However, varying levels of immunity, adverse reactions, and other unexpected events are a reality with biological products. The major safety problems reported are injection site reactions, systemic reactions, allergic reactions, immunosuppression, inadequate inactivation, residual pathogenicity, genetic recombinations, and contaminations. An increased incidence of fibrosarcomas in cats has been linked to vaccination since many of the lesions occur in common sites of immunization. The yearly prevalence has been estimated at 2 cases per 10,000 vaccinated cats. Although there are still many unknowns,
the potential risk is to be taken into consideration before making the decision to vaccinate.

2. Duration of Immunity

Following primary immunization, natural exposure or virus persistence will result in a boosting of immunity in a population. However, in most situations, such natural boosting is unreliable. Booster vaccinations are often given at intervals to ensure immunologic memory for a rapid immune response to pathogens. The timing may vary depending on the targets and the vaccines. Currently, the conventional recommendation is for an annual booster for most vaccines with exceptions for, for instance, some rabies vaccines when a 3-year duration of immunity has been demonstrated.

It is known that some vaccines such as leptospirosis vaccines provide short-lived immunity. Furthermore, because mucosal memory is usually short lived, vaccines designed to replicate on mucosal surface may need to be repeated frequently. However, there may be a lack of scientific documentation to back up annual boosters of vaccines such as feline and canine parvovirus or canine distemper. Concerns about side effects should be incentive to conduct the research necessary to determine the optimal intervals between vaccinations. Animal serologic examination could also help define the proper immunization intervals for individual animals or herds, in diseases where antibody titers correlate with protection.

3. Vaccine Components

Effective vaccination of young puppies against canine parvovirus, distemper, and adenovirus 1 and 2 is critical. The benefits from canine coronavirus vaccines or from Lyme disease vaccines outside endemic areas is more controversial.

4. Cost

Cost is another disadvantage to overvaccination. The owner of the animal could be paying for something the animal does not really need. Therefore, the selection, strategic need, route, and program of administration of any vaccine, as well as care in handling and inoculating, should receive much more attention.

B. Benefits

As mentioned earlier, vaccines have played a very important role in bringing many diseases under control. Before decisions are made to
reduce the number of vaccinations, some factors should be carefully considered.

1. **Herd Immunity**

Vaccines are effective in preventing diseases not only in individuals but also in populations. This type of protection is called herd immunity. When a virus spreads from one animal to another, it requires both an infected host to spread it and a susceptible host to catch it. Herd immunity works by decreasing the number of susceptible animals. When the number of susceptible hosts drops low enough, the disease will disappear from the population because there are not enough animals to continue the infection cycle. It is therefore critical to maintain a high percentage of the host population immunized to achieve herd immunity and hence disease control.

2. **Wild Reservoirs**

Many species of wild carnivores, such as mustelids, are susceptible to canine distemper virus and therefore represent a potential source of infection for dogs. There are many examples of outbreaks of diseases occurring in dog populations without sufficient protection.

3. **Protection of Other Species**

In addition to protecting the target species, vaccination is also used to arrest the cycle within a species or interrupt transmission from one susceptible species to another or from animal to man. Human public health is dependent on the control of zoonotic diseases in animals. In some instances such as rabies, it is the only possible option for control.

4. **Drug Resistance and Residues**

The development of safe and efficacious antibiotics for the control of bacterial infections has probably limited the development of bacterial vaccines. However, with the increased frequency of bacterial resistance to drugs and an increase of the public awareness to antimicrobial residues in animal products, there is a need for greater use of antibacterial vaccines. The economic advantage for producers to offer residue free animal products without compromising the animal welfare and public health should not be underestimated.

5. **Animal Welfare**

Veterinarians have a duty to protect animal health and welfare. Successful vaccination involves much more than the administration of the product. They should also provide the customer with information,
recommend preventive health programs, understand the proper handling of products, report adverse reactions, and increase the public's awareness of food safety and zoonotic issues.

Balancing risks and benefits as well as tailoring vaccination programs to the individual patient or population should be taken into consideration by the veterinarians before administering any biological products.

IV. Consequences for the Animal Health Industry

A. Future Challenges

1. Technologies

The search for the ideal vaccine must continue. Many technologies such as biotechnology, delivery technology (slow or intermittent pulse release of antigens at appropriate sites), or immunomodulation hold great promises for the future. The mastering of these new technologies should result in the following improvements:

- Safer and more efficacious vaccines
- Vaccines with longer duration of immunity
- Vaccines that can bypass inhibitory maternal antibodies
- Vaccines for major diseases that cannot be currently prevented
- Vaccines for emerging diseases
- More convenient vaccines that are well adapted to husbandry management or animal owner lifestyles
- Less dependency on refrigeration (cold chain)

2. Design of New Vaccines

Recent discoveries in vaccinology and immunology will allow a better design for new vaccines. Factors that are irrelevant or detrimental to the protective immune response can be removed from the antigenic fractions of biologicals by recombinant DNA technology. It is likely that many microorganisms contain molecules capable of biasing the immune response in a fashion advantageous to the parasite.

Optimal antigen presentation is of key importance for successful immunization. Researchers involved in the design of new products should pay attention to the cells involved in the immune response, the surface molecules expressed by antigen-presenting cells and T cells, the cytokines and chemokines produced by the cells, and the peptides binding to MHC class I and II molecules.
Vaccines also need to induce long-lasting memory and should include multiple helper and cytotoxic T-cell epitopes. The persistence of antigens may also be important.

Infectious agents have developed multiple mechanisms for escaping the immune response, including the production of escape mutants, the interference with MHC antigen presentation, the exhaustion of cytotoxic T cells, or the mimicking of effects of cytokines. Decreasing the likelihood of escape mechanisms coming into play will be critical in the design of vaccines against viruses such as porcine reproductive and respiratory syndrome virus.

3. Epidemiological Implication of Vaccinations

The choice of a vaccine strain should be justified on the basis of epidemiologic data. Genomic and antigenic diversity among bovine viral diarrhea viruses may contribute to vaccine failure. Furthermore, the situation may be changing all the time: new strains of feline calicivirus different from the F9 strains are now isolated from the field. Likewise, serovars of leptospira not contained in current vaccines are being reported from diagnostic laboratories. An epidemiologic surveillance program must be developed rapidly. Strategies for the use of and measurement of the success of vaccination in the control of animal disease have to be considered in the context of the epidemiology of that disease.

4. Strategies for Vaccine Use

Prevention of disease can reach one of the three following goals: diminution of incidence, of prevalence, or of disease consequences. For example, a vaccine that only protects against clinical disease, but not against infection, allows propagation of the pathogen in the host population. Secondarily, reducing the severity of the symptoms could also contribute to the diminution of incidence by reducing shedding of the pathogens (for example, nasal discharge of BHV1). A clear definition of the goals of the vaccination and a good knowledge of the property of the biological product are needed before the decision to immunize an animal is taken. Vaccination should usually be used and judged in a population context. The development of national or regional policies and the development in the trade of animals and animal products will play a role in the development of vaccine prophylaxis at all levels. The strategic thinking is moving from “think globally, act locally” to “think locally, act globally.”
5. Cost

Fragmented markets, pressures on prices, development of a monopolistic competition, increasing cost for discovering, developing, registering, producing, and marketing biological products will impact the relatively small veterinary vaccine industry at a time when large investments are required.

B. Partnership for Better Vaccines

The availability of better biological products is dependent on a partnership, summarized in Fig. 1, in which there are many roles and responsibilities. Consumers, animal owners, veterinarians, the scientific community, national and international agencies, government regulatory offices, and the vaccine industry must communicate and collaborate. Because the control of animal diseases is becoming more and more complex, a formal structure to promote collaboration between parties might be needed.

![Diagram showing Partnership for Better Animal Health]

**Fig. 1.** Partnership for better animal health.
V. Summary

Significant achievements have been made during the nineteenth century to improve animal health and welfare through vaccination. Vaccination standards and practices will change significantly in the next century. Vaccination programs need to be tailored to each livestock operation or individual animal in accordance with manufacturers' instructions, government regulations, scientific standards, professional organization guidelines, and veterinarian recommendations. Vaccination should always be considered in a population context. A better use of vaccine will require a different approach and a significant investment in research. Finally, all the partners involved in animal health should consider a close collaboration to meet future animal and public health challenges.