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Modern veterinary vaccines and the Shaman's apprentice

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Abstract

This paper is an overview and assessment of new, commercially available veterinary vaccines placed in a historical context. The authors critically evaluate the current state of the field of veterinary vaccines in both food and companion animals and the promises for future vaccine development. The authors maintain that there is considerable variability in safety and sustained efficacy among veterinary vaccines, especially those developed for companion animals. It is proposed that establishment of an international vaccine advisory committee be supported which would function to apprise the veterinary profession of the current status of vaccines and their use. © 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Veterinary; Vaccine; Food animal; Companion animal; Vaccine advisory committee

Résumé

Cet article survole en évaluant les nouveaux vaccins vétérinaires disponibles sur le marché et replacés dans leur contexte historique. Les auteurs exercent leurs critiques quant à la situation présente du secteur des vaccins vétérinaires, à la fois dans le cas des animaux de compagnie et de ferme. Ils soutiennent qu'il subsiste des variations considérables au niveau de la sécurité et de l'efficacité réelle des vaccins vétérinaires, notamment ceux destinés aux animaux de compagnie. Ils proposent l'organisation d'un comité consultatif vétérinaire international, dont le rôle serait d'informer la profession vétérinaire de la situation actuelle des vaccins et de leurs emplois. © 2003 Elsevier Science Ltd. All rights reserved.

Mots-clé: Vétérinaire; Vaccin; Animal de rente; Animal de compagnie; Comité consultatif

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1. Introduction

This paper represents a brief commentary and assessment of new, commercially available veterinary vaccines placed in a historical context. It is not meant to be comprehensive and the reader is referred to books by Paul-Pierre Pastoret and others [1,2] for a more complete treatise. The *conditio sine qua non* for vaccines is safety and sustained efficacy. However, there is considerable variability in these parameters among veterinary vaccines, especially those developed for companion animals, including equines. While the ideal vaccine should be safe as well as effective, the emphasis tends to be differentially placed if the vaccine is produced for food animals as compared to pet, or companion, animals. That is, untoward effects are more acceptable in food animals as long as the vaccine gives good herd or flock protection while untoward effects are far less acceptable in pet animals where the focus is on the health of the individual animal. This can lead to licensing of vaccines that have little efficacy in the latter group as long as they cause no harm. Such may be the result of the differential economic pressures present in the food animal field versus companion animals. In the former, a producer's livelihood depends upon the efficacy and the cost of a vaccine; if a vaccine does not perform as expected, or if the cost is judged too high (especially in industries having low profit margins, such as for poultry), the vaccine will not be used. In companion animal medicine, the economic pressure to produce an efficacious and cost-effective vaccine is not usually significant. The result of these differential economic pressures is that, while the demand for safe vaccines is somewhat equivalent in both production animal and companion animal medicine, the quality of the vaccines for the latter may vary considerably. The economic imperative has resulted in more rigorous evaluation of vaccines developed and marketed for use in production animal agriculture. However, without an effective oversight body, vaccines used in companion animals, especially dogs and cats, are often not rigorously evaluated and the data to support their efficacy claims are often incomplete or deficient. Also, the training of veterinary practitioners is frequently inadequate to permit individual critical assessment of vaccine safety and efficacy data, if they exist at all. Unfortunately, a rigorous scientific approach to the development of veterinary vaccines has too often been lacking and such development has often been empirical, as with a Shaman's therapies, which are occasionally efficacious, but developed through long histories of trial and error. In the worst case, lack of rigor has resulted in the sale of vaccines which are lacking in efficacy or are inappropriate for animals in certain locales. Although legislation and regulation has been in place to help assure safety and efficacy [3,4], they are not adequate. A recent AVMA Council recommendation approaches addressing these issues [5] but more is needed. A system for reporting vaccine adverse events, similar to that for humans, is clearly required (Ford, in 'Task Force on Immunization', AAHA J., 2002, to be published). Standardization of vaccines and vaccinal strains, and detailed knowledge of their safety, efficacy, potency and duration of immunity are needed before rational recommendations can truly be made [6]. It is proposed that an international vaccine advisory committee be established which would function to apprise the veterinary profession of the current status of vaccines and their use [7]. Support of initiatives of organizations such as the International Association for Biological Standardization would be a worthwhile step [8].

2. Background and overview

Immunization of people to protect against disease is historically traced to attempts by *Mithridates VI*, an ancient Greek king of Pontus (1st Century, BC.), to protect himself against being poisoned through the repeated consumption of small amounts of poisonous substances in honey (*theriaca*). There is no account of whether this actually protected him against any real attempt. Veterinary vaccinology is somewhat paradoxical in that efficacious vaccines exist for several animal diseases, but they cannot be used since vaccination would mitigate current protocols for surveillance (e.g. bovine tuberculosis); for others, like African swine fever, there are no effective vaccines. Since the introduction of variolation from the Near East in the early 18th century, the subsequent use of cowpox virus against *Variola* [9] and the first veterinary vaccine, Pasteur's preparation to immunize chickens against fowl cholera [10], there has been public concern about the safety and efficacy of vaccines. Changing attitudes towards animals, their value, and their health care have provoked vigorous and widespread discussion of the use of vaccines, especially in small animal practice [11–14]. In an ideal world, industry, government regulatory officials and the veterinary profession would address real or presumed problems with companion animal vaccines quickly and responsibly as soon as they are identified. Unfortunately, problems often are neglected, or avoided. This circumstance contributes to confusion and the creation of myths, which often are enhanced by differing views of 'experts' who have formed their own conclusions with limited data or biased sampling designs. Misfortunes with vaccines are well documented in Refs. [15–22]. They have often become elevated to catastrophes, especially by those of the 'Holistic Faith' (sic) who advocate a radical philosophy but ignore the benefits provided by vaccines. Concerns have occasionally led to the senseless conclusion that all vaccines are dangerous and are a direct or indirect cause of chronic illness ('vaccinosis'). 'Vaccinosis' are claimed to range from 'devastated immune systems, laziness, bowel disease, bloat, stained teeth, ulcers, chronic gastroenteritis, autoimmune hemolytic anaemia, and seizures,' to list but a few conditions that have been cited [23–27]. Questions commonly asked by dog owners/breeders and veterinarians are usually complex. They include: Are all vaccines available for dogs necessary? Are vaccines safe in very young pups? How effective are they in preventing disease—do both live and inactivated vaccines produce a sterilizing immunity so as to interrupt transmission? How soon does immunity occur after vaccination, and how long does it endure? Why do vaccines continue to be developed against diseases that are still poorly understood? Are too many agents packaged as multi-component vaccines, and what are the consequences? It has been well established that the immune system can respond normally to several different antigens—an issue that seems to persist; however, some combined vaccines which had inadequate field trial data prior to release have given rise to serious consequences in regard to safety. Unfortunately, answers to the questions above often reflect individual experiences, vested interests, or a disinclination to state that true answers are not known. It has been estimated that more than 50% of office visits to veterinarians are associated with vaccination. Several vaccines for dogs and cats have been licensed that have poor or questionable efficacy; yet they continue to be produced and promoted, e.g. *Leptospira* bacterins, *Giardia*, some canine coronavirus (CCV) vaccines and, in the recent past, several canine parvovirus (CPV-2) vaccines. New or 'improved'

vaccines are introduced almost yearly, yet even perfunctory examination reveals a sparse amount of data that often overstates claims for a particular product. On the other hand, questions posed by veterinarians, dog owners, or by those who oppose vaccination on philosophical grounds, often defy factual answers because of the paucity of published results. Questions often are based on the perception that valid data are available. Also, many individuals do not accept the reality that vaccination, as with other medical practices, sustain some risk. To a large extent, problems in standardizing veterinary vaccines resist solution because of the complexity inherent in the number of different vaccines and viral strains available for pet animals, most of which are poorly characterized. The authors share the belief that expectations for vaccines are at a turning point and hope that this paper will provide a ‘boost’ in addressing some of the important problems. In this commentary, we outline some personal views and experiences, note unsettled problems and point out the difficulties in resolving some of the commonly asked questions. Notwithstanding, the remarks will have little impact unless veterinarians act to gain a better understanding of vaccines, how they work, a realistic appreciation of the problems that may occur and, hopefully, how they might be remedied. Most veterinary vaccines continue to be developed empirically. With the technology now available, new vaccines will doubtless continue to be developed, including subunit vaccines, vectored recombinant vaccines, deletion mutants, nucleic acid (plasmid DNA) vaccines and, perhaps, even ‘recombinant nosodes’ (sic). When made available, however, their merits should be evaluated against presently used products, not merely for the sake of novelty. Some recombinant vaccines, e.g. *Vaccinia*-vectored rabies for wildlife, a recently licensed canary pox-vectored distemper vaccine and a Lyme disease vaccine, have shown merit in their utility, safety or, in some cases, superior efficacy.

With few exceptions, modified live (M-LV) vaccines are the most common products used worldwide [17,28,29]. Most vaccines comprise virus strains that were selected as spontaneous mutants which emerged from the native viral populations during repeated passage in cell cultures or other laboratory hosts. The majority of M-LV vaccines consist of viral populations that contain multiple mutations and few canine vaccinal strains have been biologically cloned so as to suppress the generation of non-immunizing mutants during laboratory passage to vaccine. Mutants that grow in the intended host, yet are replication-restricted in critical tissues, constitute vaccines with different degrees of loss of natural virulence (‘attenuated virus’). Non-immunizing mutants also may emerge during laboratory passage. Such variants may fail to grow in the natural host, yet proliferate luxuriantly in tissue cultures or chick embryos. Because ‘attenuation’ means reduction, not absolute loss of the capacity to produce disease, safety problems may not be revealed until extensive field tests have been conducted; unfortunately, this has occurred after a product has been licensed and marketed. A conspicuous example of such failure was the large number of dogs that died or suffered serious illness following the introduction of a live canine coronavirus (CCC) vaccine in 1983 [18,21]. Also, a vaccine judged harmless for one species may provoke illness in another one [17,22–28]. Because of the uncertainty of absolute safety with certain vaccines, e.g. distemper vaccinal strains propagated in canine cell cultures, live viral vaccines are not recommended for most wildlife species, pregnant animals, unweaned pups, or pups that are ill. Yet, breeders and some veterinarians continue to vaccinate pregnant dams, pups as early as 2–3 weeks of age, or use vaccines

for pet species where safety information is limited, e.g. ferrets. Efficacy problems persist with certain 'primary' vaccines, such as some canine parvovirus vaccines and certain canine distemper products [15–17,30–32]. However, the recent improvements in several canine vaccines, especially parvovirus vaccines that previously had poor or marginal efficacy have been greatly improved, and they now appear to provoke good immune responses. Whether the improvements will be sustained depends in large measure on the care taken by vaccine producers in selecting and conserving their seed stock. Selected modern approaches to vaccination are addressed in Section 3.

3. Current approaches to immunization

Following a short assessment of the status of currently employed vaccines, new approaches to immunization will be discussed. As evident, efficacious vaccines for use in animals have been created almost exclusively against bacterial and viral pathogens; parasitic diseases continue to pose an especially difficult challenge to immunologists.

3.1. Status of traditional vaccines

Currently recommended vaccines used in food animal and equine medicine and those used in companion animals represent mostly killed whole cell bacterins and inactivated virus, live attenuated bacteria and viruses, subunit and synthetic peptides, and toxoid vaccines produced by methods, or modifications of methods, that have been employed for decades. Several areas of improvement using somewhat traditional approaches with new technology are evident in chlamydial, spirochetal, and dermatophytic diseases, among others. Volp and coworkers [32] describe efficacy of immunization with a major outer membrane protein (GP8) from *Chlamydia caviae* (aka *Chlamydia psittaci*) but most chlamydial vaccines do not protect against infection but rather ameliorate symptoms; attenuated live or omfs are used [33] and plasma DNA offers some hope of success. Even so, a recent European Commission report emphasizes other strategies for chlamydiosis control [34]. Leptospirosis and Lyme disease vaccines have a history of some successes and several unfounded claims. A principal problem with leptospirosis vaccines is the large number of serovars and the efficacy of each serovar contained in a vaccine [35,36]. Lyme disease vaccines have posed a similar problem and have had a varied past; however, recent studies using multivalent vaccines are encouraging [37]. Vaccines to protect against dermatophytoses have had limited success but the recent discovery of a new group of immunostimulating antigens has opened avenues for exploration [38–40].

3.2. Vectored DNA

One encouraging technology has been the rapid development of methods for isolating virulence genes from pathogens, their insertion into appropriate viral vectors, and injection into host muscle tissue allowing for the encoding of virulence antigens and the stimulation of the host response. This is discussed in an accompanying paper by M-L Michel in this issue. One of the quandaries of veterinary vaccines for some important food animal

diseases is that effective vaccines exist, but they are not utilized because current surveillance procedures depend on detection of the host immune responses that the vaccine would induce. Bovine tuberculosis is an example. Studies by Orme and others create hope that the delayed hypersensitivity response to PPD can be separated from a protective immune response and that vectored DNA vaccines against tuberculosis can be created that protect against disease while permitting traditional skin testing to assess the prevalence of natural infections [41–43].

3.3. Bacterial and yeast carriers

An accompanying paper by Pastoret discusses the use of poxviruses as carriers of exogenous genes to stimulate protective immune responses. Over the last decade, bacterial carriers, and more recently yeasts, have been pursued in order to direct antigens to the relevant host lymphoid tissues. Exploiting the ability of certain salmonellae to target the intestinal lymphoid tissues, such as the Peyer's patches [44], Curtiss and others have successfully developed vaccines for human and animal use [45,46] which have already shown efficacy in flock and herd protection trials.

3.4. Recombinant foods

Although there are concerns, even prohibitions, against genetically-modified foods in the human food chain, Arntzen and coworkers have pioneered studies of creating transgenic plants, introducing genes encoding virulence antigens of pathogens into a number of foodstuffs [47,48]. Success with this approach would permit inexpensive oral immunization on a very large herd and flock scale such as accomplished with rabies vaccine incorporated artificially into synthetic 'food'. Current success in gene incorporation is being realized with bananas and potatoes. However, the usefulness of those carriers may be limited to animals capable of digesting the uncooked vegetables.

3.5. Anti-idiotypic vaccines

The development of monoclonal antibodies [49] presented immunologists with the opportunity of using the host immune system, whether a laboratory mouse through its spleen cells, or the definitive host through its peripheral blood lymphocytes or lymph node cells, to amplify host antibodies produced toward immunologically important virulence determinants on the pathogen. Massive amounts of identical antibodies encourage the possibility that antibody could be produced against antigen binding sites themselves (anti-idiotypes). Thus, immunization of a host with a monoclonal antibody could potentially provide the recipient with protection against virulence determinants of a pathogen without actual exposure to the agent or the virulence antigens and negate the need to identify and purify such antigens. To date, this approach has not produced any useful vaccine candidates. One reason is that reactivity against a single virulence antigen is rarely effective in protecting against disease. The need for a cocktail of monoclonals directed against several different virulence markers reduces the plausibility of this approach. However, Waldmann and his associates have demonstrated efficacy in the use of

monoclonal antibodies in graft versus host and cancer therapy which may have application to infectious diseases [50].

3.6. Subunit and multi-combination vaccines

There is ample evidence in the literature of the efficacy of multivalent vaccines (e.g. clostridial vaccines). Sometimes combination of vaccines into one, or co-administration of vaccines have resulted in enhancement or interference [51]; one antigen may have an adjuvant effect on the immune response to other antigens co-administered or have a suppressive effect. Expanded efforts to develop subunit vaccines have raised concerns of untoward effects when they are administered together, or induce autoimmune reactions to host tissues that would not have been observed if the subunit vaccines were administered singly, and temporally spaced. The large number of vaccines administered to military personnel embarking on service in the Arabian Gulf in 1991 has caused some to suggest that Gulf War illnesses resembling an autoimmune etiology may be the result of an adverse reaction to multiply administered subunit vaccines in genetically predisposed individuals. Such a low incidence reaction would probably only be observed in large populations immunized at similar times. Because autoimmune reactivity does not have an acute onset, such untoward effects in animals would be difficult to identify since most food animals have short production life spans and data on large numbers of companion animals, belonging to many different owners, would be difficult to compile. Thus, associating immunologically-based diseases in pet animals with a single vaccine preparation would be impossible without the adverse events reporting structure mentioned above. Clearly, this area of vaccinology requires thorough and controlled investigation.

3.7. Adjuvants

Industry and academic researchers are rapidly developing new means to enhance the immune response to vaccinal antigens. Two of the most promising avenues of investigation are cholera toxin (CT) and modified labile toxin B subunit (mLTB) adjuvants and the use of cytokines as adjuvants. First described by Elson and Ealding [52] as being able to break oral tolerance, the use of CT is proving to be highly efficacious in human oral vaccine trials [53–55]. Genetic modification of the native CT-B/LT-B (or binding) subunit, results in better host tolerance of the adjuvant with equivalent results [56–58]. The use of orally administered cytokines is an active area of investigation following on the findings that exogenous cytokine administration, such as Lymphotoxin α and β , modulate immune responsiveness through stimulation and expansion of mucosal lymphoid tissues [59].

4. Concluding remarks

Although this paper has been critical of the current state of evaluation of veterinary vaccines, there have been many successes, especially in canines where most of the vaccine shortcomings mentioned above exist. The most important canine viral infections are

distemper (CD) and CPV-2. Problems of variable CD vaccine safety and efficacy persist, but CD vaccines have greatly reduced the prevalence of disease and cases in vaccinated dogs are now rare. Infectious canine hepatitis (ICH, CAV-1 infection) also has been well controlled by vaccines for more than 35 years and it is now rare; the sporadic cases seen in the past decade have usually occurred in unvaccinated dogs. CAV-2 vaccines should continue to be given since they have proved to be safe and effective, and prevent hepatitis as well as adenoviral tracheobronchitis. Failure to vaccinate would likely result in an increase in cases of ICH, a serious disease, but never as significant as distemper and CPV infection. Distemper, CPV-2 and CAV-2 vaccines are considered 'core vaccines', i.e. vaccines that every dog should receive [5].

4.1. *Are we vaccinating too often?*

Although complex, the dominant opinion is 'yes' [60]. The question cannot be responded to unequivocally, however, since manufacturers employ different strains that vary in their immunizing capacity and, probably, duration of immunity. This question was frequent with distemper in the 1960s. At that time, many veterinarians tested batches of the vaccine they used by providing pre- and post-vaccinal sera to competent diagnostic laboratories. That practice appeared to benefit veterinarians and dogs, as well as, indirectly, the quality of vaccines. Unfortunately, many owners and some veterinarians seem to hold the view that infectious diseases such as parvovirus infection can be controlled by frequent vaccination alone, with less emphasis on hygiene and pup isolation. The common practice of dog breeders to vaccinate their animals several times each year is senseless. Revaccination for distemper and parvovirus infection is suggested at 1 year of age, but recommendations regarding the frequency of most vaccinations given after that time are unclear. Since most distemper and CPV-2 vaccines probably provide immunity that endures several years, vaccination at 3–5 year intervals, after the first year, seems a reasonable practice until more data on duration of immunity become available.

4.2. *Are too many kinds of vaccines being promoted for dogs?*

Distemper and parvovirus vaccines are essential; canine adenovirus vaccines are recommended since the few cases brought to our attention in recent years have been in unvaccinated dogs. Vaccination against respiratory infections is recommended for most dogs, especially those in kennels, or if they are to be boarded. Need has not been established for coronavirus vaccines; Lyme disease vaccines are useful in preventing illness in areas where the disease exists, but they are unnecessary elsewhere since dogs respond rapidly to appropriate antibiotics; several *Leptospira* bacterins are without benefit since they contain the critical serovars which fail to protect in most areas. Recombinant (OspA) vaccines are now available for Lyme disease (LD) that appear to be safe and effective for at least 1 year and they have not caused vaccine-induced post-vaccinal lameness, which has been documented with certain whole cell Lyme disease bacterins. Lyme disease vaccines should be restricted to dogs in, or entering, endemic areas where infested ticks reside. Leptospirosis vaccines are commonly reported as

a cause of anaphylaxis and, as noted above, several current vaccines do not contain the serovars prevalent in most regions. The vast majority of cases diagnosed at the New York State Diagnostic Lab at Cornell University are *grippityphosa* and *pomona* serovars and there have been no recent cases caused by *canicola* or *icterohemorrhagiae* serovars. Since leptospirosis is an important disease of dogs, there is an urgent need for more research and the development of safer vaccines that contain the prevalent serovars. In Mexico, dogs may be infected with several serovars and some canine vaccines contain 8–10 serovars. The *conditio sine qua non* is the availability of consistently good vaccines. Without standardization of vaccines, it seems difficult to formulate general vaccine recommendations. Effort should be directed to improving and standardizing the important vaccines in current use, not the development of new products, unless need is demonstrated. As mentioned in the introduction, the public is becoming increasingly aware of vaccine problems, perhaps even more so than the benefits of vaccination. The reality that all vaccines carry some risk is not fully perceived by many owners and veterinarians. Alternative veterinary medicine is now a growing reality; such practices are being taught in several veterinary colleges and questions pertaining to vaccine safety and efficacy will continue to vex veterinarians, vaccinologists and vaccine producers. They will have to be addressed. There is a need for better appreciation of the risks of adverse reactions. Finally, the issues which have been discussed, or recommendations that might be made, will have little influence unless biologics manufacturers, and regulatory officials exercise greater responsibility in controlling vaccine quality. This could be encouraged by the appointment of a committee of unbiased experts to review vaccines for each disease and provide recommendations based on available evidence. This view has been discussed at meetings on several occasions over the past 30 years, but it has been largely neglected because of considerations that involve industry interests, indifferent or overburdened government authorities, and the trust by veterinarians and animal owners in advertising. Vaccines and vaccination guidelines for physicians are supervised by the American Academy of Pediatrics' Committee on Infectious Diseases and the Advisory Committee on Immunization Practices that advise the medical profession and regulatory authorities [61]. Regular reviews of vaccine side effects, contraindications, and adverse reactions should be done similar to that by the CDC for human vaccines [62]. Until the veterinary profession insists on a responsible advisory council, concerns and questions regarding vaccines will continue to be met by conflicting opinions and open the door to such things as a Shaman's 'Nosodes' and 'Thuga'—whose benefits seem to be understood only by those who use and profit from them.

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