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Vaccination: A Philosophical View

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I. Introduction

Vaccination is the most successful medical and veterinary measure: More lives have been saved by immunization, more animal production safeguarded than through all other medical and veterinary activities combined. It has been possible to eradicate a disease worldwide (human smallpox), and attempts to reach the same goal for poliomyelitis and measles are viewed with optimism. But this optimism does not apply for diseases where the causative virus has a reservoir in the wild fauna (such as in the case of distemper and parvoviruses that occur in mustellids). Against these diseases vaccination will have to continue.

Vaccines were being used long before the mechanisms of immune protection became known. Today the discipline of vaccinology has acquired proper scientific status as a interdisciplinary research area that emerged from microbiology and immunology. Because vaccines make money—for the veterinarian and as a corollary also for the pharmaceutical industry—money is being invested in vaccine research. This has resulted in impressive progress. Protection can be obtained against most animal viral diseases, and it is hoped the remaining

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conditions (e.g., feline AIDS, feline infectious peritonitis, Aleutian disease of mink) will be controlled in the near future.

For the average small animal practice in Europe, doing vaccinations provides its financial basis; between 20 and >40% of direct and indirect income is earned from vaccinations. In view of this economy-related fact, teaching of vaccinology is clearly insufficient at most veterinary colleges. While there are chairs of immunology and vaccinology at the Utrecht Faculty of Veterinary Medicine, most of the neighboring European countries lack such chairs. The paradoxical situation exists that the average veterinary practitioner knows least about his or her most lucrative activity. This is a depressing and dangerous situation, especially in view of the future developments in veterinary medicine.

II. Will There Be Vaccination in the Next Millennium?

This is a moot question, of course, but for the virologist no prophetic talent is required to answer it in the positive sense. As long as cellular organisms populate this planet, new viruses will appear at regular intervals and infect them, at times making them ill. Consequently there will always be a reason for developing new vaccines—and there are no good alternatives. One may not expect universal antiviral chemotherapeutics, irrespective of the recent successes obtained in treating AIDS patients. (*Editor's note:* HIV drug resistant strains have already appeared to threaten the sucess of treatment.)

New viral epidemics are seen time and again (from parovirus enteritis to seal distemper to swine mystery disease), the media focus the public's attention on them, people may fall ill and die (for example, after infection with "new" influenza viruses). Research has shown that "new" viruses are the result of subtle changes in the genomes of usually well-known ones, the consequence of viral evolution.

What are these new viruses? As soon as an epidemic has been identified molecular genetic research is initiated, the results of which are almost predictable: The causative agent will be a virus that is slightly different from other, well-known viruses. The virus causing the epidemic is the result of mutations followed by selection—a process we call evolution. The driving force in the evolution of RNA viruses (among which there are numerous animal pathogens) are single nucleotide changes scattered throughout the genome, but also insertions of longer pieces of genetic information cannibalized from the cell. During transcription, viruses can acquire foreign information and incorporate it into their genome by template jumps of the transcriptase, the enzyme that copies the nucleotide sequence; if that foreign information confers a selective advantage to the "parent" virus, it will be genetically perpetuated. When the mere change of a single amino acid has dramatic effects, then the uptake of entire motives (modules) of foreign information can be expected to lead to even more dramatic alterations. Thus the mutated virus could escape preexisting immunity (to the "parent" virus) in its host, thereby causing disease; on the other hand the variant could also cross the species barrier and infect a new host.

Thus viral evolution can be tracked and analyzed in molecular terms. The vaccine industry obviously follows epidemiologic developments and is eager to market a vaccine against a newly discovered virus disease as soon as possible—this contributes to its reputation and success in the marketplace. In those cases where evolutionary trends can be predicted, where mutations can be expected in certain genes (for instance, in influenza virus), this is an efficient routine procedure: Vaccines against human influenza get a yearly update.

For a company, vaccine research, development, and registration are expensive. Assessment of the return on investment may lead to compromise, especially as far as efficiency is concerned (for instance, by accepting a marginally effective antigen concentration in a killed preparation). Placebo-controlled independent field studies to evaluate the degree of protection have been performed only in a few instances, comparative studies between preparations even more rarely. Veterinarians rely on their "experience," however objective this may be. They generally stay loyal to their manufacturers, leaving them only as a consequence of a good talk by another sales representative or of "experiences" communicated by a colleague. Undoubtedly there are differences in vaccine performance between brands, but also between viruses. The notoriously bad reputation of preparations intended to protect against feline upper respiratory disease may be due to newly evolved caliciviruses in the field against which the vaccine induces less cross-protection than years ago, when they were first developed. Research has even shown annual variation between vaccines from the same manufacturer; certain lots induced poorer immunity than others.

When discussing the bad reputation of a particular vaccine one should take a sociopsychologic phenomenon into account—that of selective observation. No veterinary practitioner or breeder will mention the thousands of healthy, well-protected vaccinees, but the single animal that falls ill (after or irrespective of vaccination) gets all the attention. When the name of the preparation is mentioned in this context, a negative image may develop as a consequence. However, this is normal—also in the statistical sense of the word: No vaccine results in 100% protection and complete safety. Any biological phenomenon follows a frequency distribution of effects, and rarely—sometimes not so rarely—one may expect no effect at all. This can bias the vet's "experience" mentioned above.

III. What Is the Future of Veterinary Vaccinology?

Van Leeuwenhoek, Beijerinck, and Kluyver are famous names in microbiology; also veterinary vaccinology has its roots in the Netherlands. When Frenkel successfully cultivated foot-and-mouth disease virus in Amsterdam using suspensions of surviving bovine tongue epithelium, the basis was laid for controlled virus growth, for the industrial production of viral antigen in cell culture. The National Veterinary Institute subsequently wrote vaccinological history: It developed the herpes virus marker vaccines and the chimeric pseudorabies/hog cholera vaccine—a molecular vaccinological highlight. Protection of dogs and mink against fatal parovirus infections using a short oligopeptide made an old immunological dream come true.

Progress has been made in both the innocuity (safety) and efficacy of veterinary vaccines. Many strategies are currently being developed to arrive at maximum possible protection with minimal side effects. Veterinary medicine leads the way: Observations can be made and experience gathered in the target species, where ethical, legal, and economical reasons prevent similar approaches in the medical environment. One of the most promising developments is vaccination with DNA that carries the information for a protection-relevant protein. The immunogenic protein is not injected into the vaccinee but the genetic information for this protein that is then synthesized by the host cell itself. Although the injected DNA does not replicate, the induced immune reaction is similar to that after modified live vaccination, with respect to MHC class I antigen presentation and the induced cellular response.

Protection is not only a function of the quality of the antigen but also of correct triggering of the immune system. To improve the immunogenicity of a preparation so-called adjuvants are added to the antigen; these are minerals such as aluminum hydroxide but also water/oil emulsions, detergents, plant glycosides, etc. The antigens are immobilized at the site of injection, and during the ensuing inflammatory reaction antigen-processing cells are attracted. Chronic local inflammations may lead to malignant transformation, however, and recent observations indicate the occurrence of fibrosarcomas at injection sites of predominantly aluminum hydroxide-containing inactivated vaccines. The principle of innocuity is stringently observed by European licensing authorities—more stringently than efficacy, one is tempted to say. It is also easier to prove. An incidence of 3 fibrosarcoma cases on

10,000 cats after leukemia or rabies vaccination is only acceptable if the disease against which it must protect carries a higher risk.

Cytokines are currently the focus of attention as immunity enhancers; they are messenger molecules of the immune system that are able to direct the response. It may be expected that they will become successors of the empirically developed adjuvants.

IV. Vaccination in the Twenty-First Century

The veterinary practitioner demands a vaccination schedule that is simple, timesaving and commercially attractive. Industry met these requirements by development of polyvalent preparations that may contain seven or more components. The small animal scene gradually adopted a yearly vaccination routine and everybody appeared satisfied: the vet, the owner, the manufacturer. One visit per client per year, one injection, one vaccine—easy enough. In biological terms this is nonsense, of course. A universal scheme cannot be expected to accommodate the immunology of the carnivore, the properties of diverse infectious agents, the changing epidemiologic situation, or the age and living environment (risks of infection) of the animal.

Injection and immunization are not synonymous. The automatic yearly application of a polyvalent preparation with disregard for the vaccinee's individual life circumstances is the dangerous development alluded to above. It may be damaging for the profession.

There is nothing wrong, in principle, with combined vaccines, if immunogenicity and protective potency have been proven for each component. Studies have shown, however, that, for example, parvo/distemper virus combinations may lead to encephalitis caused by the latter; though sporadic, these cases have received much attention and led to a more critical appraisal of combination products.

There is something wrong, however, with the unreflected yearly injection of *all* the components present in a polyvalent preparation. For some diseases this is too much, for others too little. Immunity against measles is lifelong, and I do not know of any vet who requests a yearly measles booster from her or his physician. But most small animal practitioners in Europe revaccinate dogs against distemper, which is in essence canine measles, annually. Experimentally, distemper protection has been proven for 3 years, and it may last longer. In interepidemic intervals, and this is most of the time, less frequent immunizations can therefore be defended.

The other side of the coin is vaccination against, for example, feline herpesvirus, which may be too infrequent when given once a year in a shelter situation. Crowding, immunosuppression as a consequence, infection pressure, and the notoriously poor antigenicity of herpesvirus preparations all argue in favor of more frequent applications. Experimentally, protection did not last for more than 4–6 months.

In addition to the pediatric indication—the protection of pups and kittens—there may be a geriatric indication for vaccination in the face of an aging immune system. In veterinary medicine, this is unexplored territory. In medicine, influenza vaccination has a geriatric indication.

V. Outlook

The following conclusions may be drawn from the above considerations:

- The vaccine industry should consider developing and marketing mono- and oligovalent preparations—booster vaccines containing essential immunogens and lacking superfluous ones.
- The veterinarian should continuously monitor the epidemiologic situation and adjust the booster vaccination schedule accordingly. Pups and kittens should get their first shots at the breeder's. This has a twofold advantage: the animal is immunized in its own premises, and the vet can get an idea about the management of the kennel or cattery.
- The owner should be more involved in the vaccination schedule and strategy. After all, the veterinarian is responsible for the health of a family member and should therefore be informed about familial activities and changes (vacation, birth of a baby, change of residence, acquisition of another dog or cat, etc.) to implement a made-to-measure vaccination program.
- The disciplines of veterinary microbiology should become more involved in the epidemiologic surveillance of the companion animal scene, since there is no "Veterinary Communicable Diseases Center" for the dog and cat. The appearance of new viruses, new antigenic variants, zoonotic risks, and vaccine failures need to be identified and communicated to the small animal practitioner at large, but also to the vaccine industry.

The age of empirism in vaccinology is past. To vaccinate successfully is not as easy as it seems; it requires veterinary knowledge and immunologic and microbiologic insight. It was the French poet Léon-Paul Fargue (1876–1947) who wrote: "Il n'y a pas de simplicité véritable; il n'y a que des simplifications." ("There is no real simplicity, there are only simplifications.")