Fecava lecture*

Duration of vaccine-induced immunity

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SUMMARY

Changes in vaccination schedules, particularly the prolongation of the booster intervals for some vaccine components, represents a challenge for veterinarians as well as for pet owners. For many years the annual revaccination of dogs and cats was a well-established routine procedure. Some understanding of the scientific background behind these changed recommendations is helpful for veterinarians when making decisions and advising dog and cat owners. This article offers an overview of the current knowledge on the duration of vaccine-induced immunity and the recommendations for booster vaccinations published by expert groups.

Keywords: persistence of antibodies, challenge studies, vaccination, dog, cat

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Introduction

Since the 1960s routine vaccination procedures have included yearly revaccination boosters. Baker [1959; cited by Coyne et al., 2001] suggested that approximately a third of pups did not maintain protective titres to canine distemper virus (CDV) for a year after the initial vaccination, which led to the annual revaccination recommendation. However, this recommendation was rather arbitrary and the yearly interval was considered the minimum duration of immunity (DOI) as a safety measure. It was presumed that annual vaccination would not cause any harm and would probably be helpful.

Yearly boosters: necessary?

However, some investigators questioned the necessity of yearly revaccinations and initiated studies to determine the DOI for canine and feline vaccines. R. Schultz started working on the topic in the mid-1970s [Schultz, 2006]. His considerations were based on the observation that dogs and cats, which had recovered from, for example, canine distemper and parvovirus infections, respectively, were completely resistant to reinfection for many years. Additionally, in human medicine most vaccines are given in childhood, but never again. In 1978, Schultz and Scott [1978] published a recommendation for 'an ideal (but not proven) immunization schedule for dogs and cats'. They proposed revaccination every three years against canine distemper, canine adenovirus (CAV) 1 infection, rabies and parvovirus infections in dogs/cats after a series of puppy/kitten vaccinations and a revaccination at one year. During recent decades, various researchers questioned vaccination schedules asking, 'Are we vaccinating too much?' [opinions from various experts collected by Smith, 1995].

Inducing long-lasting immunity

The immunological memory involving B and T lymphocytes, which develop in response to an antigen, plays the key role in long-lasting immunity. Such memory cells are activated rapidly after a second exposure to the same antigen. Additionally, long-lived plasma cells continue to

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produce antibodies to the core vaccines (like CDV and parvovirus) for many years, without any further antigenic stimulation. Schultz [1998, 2006] called these cells 'memory effector B cells'.

The DOI depends on the immunogenic characteristics of the infectious agent, the immunizing strain, the type of vaccine (modified live or inactivated), the degree of attenuation of modified live vaccines, and the use of an adjuvant as well as on individual immune responses of the host. In general, the adaptive immunity to generalizing viruses develops quickly and is highly effective. It induces often a sterile immunity preventing not only disease, but also infection; the DOI may be lifelong. In contrast, immunity develops slowly to bacteria, fungi and parasites and persists for short time periods. Parvovirus infections of the dog (CPV) and cat (FPV), CDV and CAV-1, induce a DOI of many years (probably lifelong), whereas it is much shorter for example for *Leptospira, Bordetella* and canine parainfluenza virus [see review by Schultz, 2006]. Variation may also occur between different vaccines, as demonstrated with rabies vaccines by Kennedy et al. [2007]. These authors also described that dogs under one year of age generate a lower antibody response to rabies vaccination compared to adults with an influence of the animal's size on the antibody response and DOI. Smaller dogs elicit higher antibody levels and a longer DOI than larger breeds of dogs. A similar observation was published by Riedl et al. [2015], who described that an adequate titre increase after CPV vaccination was associated with a body weight <10 kg ($p=0.003$).

Immunosenescence and inflammageing

In older animals the level of immunity declines because of an impairment of cell-mediated immune functions with age (immunosenescence). HogenEsch et al. [2004] showed that old dogs had a significantly lower lymphocyte proliferative response, but no difference in the concentration of IgM and IgG, compared to young adult animals. Additionally, no differences in protective titres and in post-vaccination titres against CDV, CPV and rabies virus were shown. However, old dogs were shown to be less efficient in mounting primary immune responses [Day, 2010]. In 2005 Kipar et al. [2005] observed an increased activity of monocytes in older cats leading to an increased production of pro-inflammatory cytokines pointing to the process of inflammageing, which is supposed to occur following constant antigenic challenges and the associated production of inflammatory mediators, which may trigger the onset of inflammatory disease in later life [see Day, 2010].

Determining the DOI

Serology

For the determination of the DOI, serological methods (detection of antibodies in the blood) and challenge infections are used. With serology it cannot be generally assumed that a correlation exists between the antibody titre and the level of protection. While there is a good correlation for parvoviruses, CDV and CAV-1, this is not the case for herpesviruses, where a strong cellular immunity is involved. Additionally, protection against infectious agents replicating and causing damage on mucosal surfaces (like canine coronavirus and canine parainfluenza virus) is probably based on mucosal immune responses.

Also the interpretation of titres is challenging. After an active immunity is established, titres may decline with time, even becoming undetectable. Nevertheless, in cases of infection the immunological memory may be activated so rapidly that the animal is protected against disease. For various infectious agents a high titre may be used to provide evidence of protective immunity, but a low titre does not necessarily indicate susceptibility. Titres may also vary according to the test used and the laboratory performing the test. Therefore, the term 'protective titre' is not applicable (contrary to passively, usually maternally, derived antibody titres). Schultz et al. [2010] claim that the presence of antibodies (following an active immune response), regardless of the titre, demonstrates immunity.

Challenge studies

Challenge studies have the advantage of demonstrating directly whether protection is acquired or not. They require the maintenance of animals in experimental isolation to avoid any field infection for long periods of time – many years – before infecting them (besides unvaccinated, fully susceptible control animals) with virulent infectious agents. Such situations are not directly comparable to real-life environments and may not be reproducible in animals of various ages and with different types of vaccines. Additionally, the ethical concerns have to be addressed.

DOI for core components

Many studies, especially in dogs, were performed in order to obtain information about vaccine-induced DOI. Schultz [2006] described an estimated DOI for CDV and CPV of

at least 7 years. In vaccinated dogs living in a natural environment, Schultz et al. [2010] found antibodies against CDV and CAV-1 for 14 years and against CPV for 10 years. In environments free from CDV and CPV-2, vaccinated dogs remained seropositive without any antigen stimulus for at least 9 years. Following challenge infections after 9 years all animals were completely protected [Schultz et al., 2010]. For CDV, Ottiger et al. [2006] showed that antibody levels did not significantly decrease even in dogs that had received boosters 5-6 years ago. Olson et al. [1997] detected antibodies against CDV indicating immunity in 22/30 dogs which had been imported to Iceland approximately four to ten years earlier from countries where the dogs had been vaccinated against canine distemper. As Iceland was free from CDV infection and CDV vaccination was not permitted in Icelandic dogs, the authors concluded that the DOI against CDV may last much longer than one year. Schultz [2006] claimed that 'immunity to CDV, CPV-2 and CAV-1 persists for a lifetime after vaccination, similar to the persistence of immunity after natural infection'.

In cats, Scott and Geissinger [1999] demonstrated protection against virulent FPV 7.5 years after vaccination with inactivated FPV, FCV and FHV. Protection against FCV and FHV was less effective. Mouzin et al. [2004] described, based on serology, a minimum DOI against the feline core components of 48 months. Recently, Haselberger et al. [2016] found that in clinically healthy, privately owned cats that had been presented to a veterinarian more or less regularly, the time since the last vaccination (twelve days up to 15 years) was not significantly associated with the antibody levels against the core components.

Annual boosters: the cons

Despite the knowledge that the DOI for the feline and canine core components is much longer than one year, the question may arise why not be on the safe side and continue with the yearly revaccination programme. The major reasons against that are:

- that vaccination of already immune animals is not beneficial
- every vaccination entails a small risk of adverse reaction
- it is ethical to avoid medical procedures which are of no benefit.

Lack of benefit

Vaccination of already immune animals does not provide any advantage. Pre-existing antibodies may neutralise the vaccine antigen very quickly, before it can stimulate the immune system. Antibody titres have to be low to allow an immune response to occur. Ottiger et al. [2006] observed that dogs with CPV antibody levels above the cut-off value had had fewer previous vaccinations. Riedl et al. [2015] showed that a booster effect after vaccination against CPV was associated with low pre-vaccination titres. Dogs with high antibody titres (>1:1280, HI assay) did not show any rise in titre after booster vaccination. For rabies vaccination Moore et al. [2015] described that dogs with an out-of-date vaccination status had a higher median increase in titre and reached higher median titres following booster vaccination, compared to dogs with a current vaccination status. Haselberger et al. [2016] showed that cats that had been vaccinated twelve months or less before sampling had lower antibody levels against FPV with increasing age and the number of vaccinations. Therefore, 'over-vaccination' of already immune animals may even be counterproductive.

Risk of adverse events

Vaccine-associated adverse events, which are defined as any undesirable side effect or unintended effect associated with the administration of a licensed vaccine, seem to occur very rarely, although accurate data about their frequency in small animals is only available to a limited extent. In general, the available vaccines are considered very safe, but a small risk of a vaccine-associated adverse event remains with every vaccination. Such adverse events may cover a broad range of clinical signs and severity. Most of them are mild and transient without any need for therapy, many of them only local reactions. However, hypersensitivity reactions and anaphylactic shock may also occur. Special concern is seen with a potential to initiate immune-mediated diseases, for which a causative connection may be difficult to establish because of the time lag. In cats a special risk is recognised for the development of feline injection-site sarcomas (FISS). Different injections may induce FISS, and a potential risk factor may be vaccination with some higher risk for adjuvanted vaccines [Srivastav et al., 2012; Hartmann et al., 2015]. Recently, Finch et al. [2016] looked at risk factors for the development of chronic kidney disease in cats. Their results suggest independent associations for two risk factors for the development of chronic kidney disease: frequent/annual vaccination and the severity of dental disease.

Ethically undesirable

From an ethical point of view, medical procedures that are of no benefit, but are associated with even a small risk of adverse events, are unjustified and should therefore be avoided. It should also be considered that in the case of over-vaccination the pet owner is paying for something that does not result in any positive effect, but may (rarely) cause adverse reactions.

Vaccination guidelines

The current knowledge of DOI, the fact that vaccination of already immune dogs and cats does not result in any positive effect and the consideration that with every vaccination a small risk of adverse reaction remains, are considered by expert groups providing recommendations for booster vaccinations. Vaccination guidelines serve as a bridge between the official requirements and the daily use of vaccines [Thiry and Horzinek, 2007]. They are non-compulsory recommendations, based on current scientific knowledge, and are intended to assist the veterinary practitioner in using vaccines efficiently [Thiry and Horzinek, 2007]. The goal is to achieve lifelong immunity, but to avoid unjustified veterinary medical procedures. For the individual animal the 'vaccine load' should be reduced as much as possible and every vaccination requires a risk / benefit assessment. To achieve 'herd immunity', the goal should be to induce at least a basic immunity in every dog and cat.

Vaccination guidelines are available from various expert groups, such as the WSAVA Vaccination Guidelines Group [Day et al., 2016], the 'Ständige Impfkommission Vet' [Duchow et al., 2013], the ABCD European Advisory Board on Cat Diseases [Hosie et al., 2015] or the AAFP Feline Vaccination Advisory Panel [Scherk et al., 2013]. Currently three year intervals are recommended for the viral core components FPV, CPV, CDV and CAV-1 (modified live vaccines). Day et al. [2016] used an even stricter wording and recommend that 'core vaccines should not be given any more frequently than every three years after the 6 or 12-month booster injection following the puppy/kitten series, because the DOI is many years and may be up to the lifetime of the pet.' The recommendation of three-year booster intervals is already considered for various commercially available vaccines. It has to be mentioned that this recommendation and the data sheets of vaccines refer to a minimum DOI, as dogs and cats that have responded to vaccination with these modified live vaccines maintain a solid immunity for many years without any repeat vaccination. This recommendation does not generally apply to inactivated core vaccines (except for rabies) or non-core vaccines. Bacterial antigens in particular have to be boosted more frequently (e.g. *Leptospira, Bordetella*). Currently available evidence indicating that leptospirosis vaccines may have a protective effect longer than 12 months is lacking. Therefore, yearly revaccination is recommended [Schuller et al., 2015]. Older animals that have been fully vaccinated as pups or kittens do not require a specialized vaccination schedule. Their immunological memory can be boosted. In various cases antibody determination may be helpful and in special cases an individually tailored schedule may be necessary.

Annual health checks

Finally, the importance of the annual health checks for dogs and cats has to be stressed. One aspect has to be vaccination, but contrary to earlier yearly routine vaccination procedures, it should be an occasion to reassess vaccination management and administer selected vaccines depending on the patient's situation. Routine serological testing may also be included to monitor the status of immunity and decide whether revaccination is indicated.

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