ABCD Guidelines on Vaccination in Immunosuppressed Cats

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Introduction

Immunosuppression (or immune suppression, synonym immunodepression or immune depression) is a reduction of the activation or efficacy of the immune system. An animal or person who is undergoing immunosuppression or whose immune system is weak for other reasons is classified as to be immunocompromised or having an immunocompromised condition. An immunosuppressant is any agent that weakens the immune system, including infectious agents, immunosuppressive drugs, and toxins. Immunodeficiency (or immune deficiency) is the state resulting from immunosuppression in which the immune system's ability to fight infectious diseases and tumours is compromised or completely absent.

Immunosuppression is a common condition in cats, especially due to wide-spread infections with immunosuppressive viruses, such as feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV), but also due to chronic non-infectious diseases leading to immunosuppression, such as tumours, diabetes mellitus, and chronic kidney disease, as well as treatment with immunosuppressive drugs, such as glucocorticoids, cyclosporine, or tumour chemotherapy.

Life expectancy in cats has been increasing in the last decades, especially in privately owned cats receiving good preventive, medical, and nutritional care, and with older age, prevalence of chronic diseases raises. Senior cats represent now a large percentage of patients in practice that probably will even increase in the future. In human medicine, specific recommendations exist on vaccination of immunocompromised people, such as the "Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence of the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 1993) or the Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for Vaccination of the Immunocompromised Host (Rubin et al., 2014). In addition, comprehensive systematic reviews and meta-analyses on specific vaccinations, such as against influenza in immunocompromised people have been published (Atashili et al., 2006; Anema et al., 2008; Beck et al., 2012). Data in cats are limited and not many controlled studies in immunocompromised cats exist so far; thus, most of the following recommendations will be based on data in humans or in dogs as well as on expert opinions.

The degree to which an individual cat is immunocompromised should be determined by the veterinarian. Severe immunosuppression can be due to a variety of conditions, including congenital immunodeficiency, FIV or FeLV infection, tumours, tumour chemotherapy or radiation, glucocorticoids, cyclosporine, or other immunosuppressive drugs. For some of these conditions, affected cats will be severely immunocompromised; for others, such as FIV infection, the spectrum of disease severity due to disease stage will determine the degree to which the immune system is compromised. As a general recommendation, cats with acute diseases or short term immunosuppressive treatment should not be vaccinated, and vaccination should be postponed until recovery or after termination of the treatment course. In some situations, postponing of vaccination would imply, however, a significant risk for the cat, such as when entering a shelter environment with high infectious pressure, and in these specific situations vaccination might be necessary despite acute illness or poor general condition. For sick cats, any decision about vaccination has to be taken for the individual cat, but when entering a shelter, vaccination is

recommended whenever and as soon as justifiable (Möstl et al., 2013). Alternatively, passive immunisation with serum containing antibodies against feline panleukopenia virus (FPV), feline herpesvirus (FHV), and feline calicivirus (FCV), as commercial compound or self-produced by the veterinarian, can be used instead of active immunisation in acutely ill cats when immediate protection (against other infectious diseases) is required.

However, some cats are immunocompromised long-term, and this guideline will concentrate on these conditions. Some important points have to be considered when vaccinating immunocompromised cats, including (1) the safety of modified-live virus vaccines and the concern that vaccines might regain their pathogenicity if the immune system is not working properly, (2) the question whether vaccines work at all in immunocompromised cats and whether duration of immunity after vaccination is shortened compared to that in healthy cats, (3) the concern that in some of these conditions, e.g., in cats with FIV infection or chronic kidney disease, vaccination and resulting immunostimulation might lead to a progression of the disease.

Cats with Congenital Immunodeficiency Disorders

Congenital (primary) immunodeficiency in cats has rarely been described (Kraft, 1996; Datz, 2010; DeBey, 2010). In human medicine, it is recommended that patients with primary immunodeficiency should receive all routine vaccines based on the Center of Disease Control annual schedule. None of the vaccines are contraindicated (Rubin et al., 2014). Due to lack of data in cats, this recommendation should be followed in cats with congenital immunodeficiency as well.

Cats with Retrovirus Infections

In domestic cats, 3 retroviruses have been identified: FIV, FeLV, and feline foamy virus (FeFV). All 3 are global and widespread but differ in their potential to cause disease (Hartmann, 2014). FeFV (previously known as feline syncytium-forming virus, FeSFV), a spumavirus, is not associated with disease, and no special management is required in cats with FeSFV infection. FIV, a lentivirus that shares many properties with human immunodeficiency virus (HIV), can cause an acquired immunodeficiency syndrome in cats leading to increased risk for opportunistic infections, neurologic diseases, and tumours. In most naturally infected cats, FIV infection does not cause a severe clinical syndrome, and with proper care FIV-infected cats can live many years (Hosie et al., 2009). FeLV, an oncornavirus, is the most pathogenic of the 3 viruses. Despite the fact that progressive FeLV infection is associated with a decrease in life expectancy, many FeLV-infected cats kept only indoors will live for many years with good quality of life (Lutz et al., 2009). Cats with FIV or FeLV infection can have long asymptomatic stages with no or only little immunosuppression, but in a later stage can be severely immunocompromised.

Cats with feline immunodeficiency virus infection

Vaccination of FIV-infected cats is much in debate as is vaccination of HIV-infected people. Most data in HIV-infected people exist on influenza vaccination, but still, meta-analyses on efficacy of influenza vaccination in HIV-infected patients (Atashili et al., 2006; Anema et al., 2008; Beck et al., 2012) concluded that evidence supporting influenza vaccination of HIV-positive individuals is limited, poorly quantified, and characterized by substantial methodological shortcomings, and that a reasonable estimate of influenza vaccination effectiveness in HIV-positive patients cannot be derived from published data. Evidence, though limited, suggested that influenza vaccines would be moderately effective in reducing the incidence of influenza in HIV-infected individuals (Tasker et al., 1999; Atashili et al., 2006; Anema et al., 2008), although studies reported an inferior antibody response of HIV-infected individuals compared with HIV-negative controls (Beck et al., 2012). No significant difference was

found in vaccine-associated adverse events (VAAEs) between HIV-positive patients and controls. Data on variables describing the effect of vaccination on HIV status, such as CD4+ cell count, HIV load, or RNA level, are inconclusive with some trials reported no significant changes in such variables when comparing baseline with post-vaccination levels, while other studies found increases in HIV RNA levels (Staprans et al., 1995; Rosok et al., 1996; Vigano et al., 1998; Gunthard et al., 2000; Banic et al., 2001) and/or decrease in the percentage of CD4+ cells (Tasker et al., 1998; Tasker et al., 1999). In conclusion, as the benefits outweigh the VAAEs, international guidelines recommend that HIV-positive patients should be vaccinated for influenza annually.

FIV infection leads to progressive disruption of normal immune function (Sellon and Hartmann, 2006; Hosie et al., 2009). Early and persistent immunologic abnormalities that occur after experimental (Ackley et al., 1990; Barlough et al., 1993) and natural (Novotney et al., 1990; Hoffmann-Fezer et al., 1992) infection include decreases in both the number and relative proportions of CD4+ cells in the peripheral blood as well as in lymphoid tissues. Ultimately, loss of CD4+ cells impairs immune responses because CD4+ cells play critical roles in promoting and maintaining both humoral and cell-mediated immunity. Over time, lymphocytes loose the ability to proliferate in response to stimulation with lymphocyte mitogens or recall antigens, and have impaired priming by immunogens *in vitro* (Hosie and Jarrett, 1990; Taniguchi et al., 1990; Barlough et al., 1991; Taniguchi et al., 1991; Torten et al., 1991; Bishop et al., 1992a; Bishop et al., 1992b; Hanlon et al., 1993). Lymphocyte function can also be impaired by reduced or altered expression of cell surface molecules, such as $CD4^{+}$, major histocompatibility complex antigens or other co-stimulatory molecules, cytokines and cytokine receptors (Willett et al., 1991; Ohno et al., 1992; Rideout et al., 1992), or even expression of abnormal molecules (Nishimura et al., 2004). Many of these molecules have a critical role in antigen presentation or amplification and control of immune responses.

It has been proposed that cats with FIV infection should solely receive inactivated vaccines, if possible. Although there is no definitive scientific proof that FIV-infected cats are at increased risk from modified-live virus vaccines, inactivated vaccines are preferred (Hosie et al., 2013), out of the concern that modified-live virus vaccines given to immunocompromised animals might regain pathogenicity. It has been reported that FIV-infected cats have developed illness with modified-live panleukopenia vaccine (Greene and Levy, 2012).

Efficacy of vaccination seems to depend on the stage of FIV infection. It has been shown that FIV-infected cats in an early stage of infection are able to mount appropriate levels of protective antibodies after vaccination (Lawrence et al., 1995), but responses can be impaired during the terminal phase of infection (Foley et al., 2003). One study investigated the effect of experimental primary-stage FIV infection on FCV vaccination and subsequent challenge. Although there was some level of protection through vaccination, clinical signs of acute FCV-associated disease were more widespread in the cats infected with FIV than in those which were not. FIV infection also prolonged shedding of FCV, with more FIV-infected cats becoming chronic carriers. There was also evidence of an impaired FCV-neutralizing antibody response in FIV-infected cats following FCV challenge (Dawson et al., 1991). In another study, 15 cats experimentally infected with FIV and 15 FIV-negative control cats received a FeLV vaccine. High antibody titres developed after vaccination in both FIV-infected and FIV-negative cats. After challenge with FeLV, FIV-infected cats were protected as well as the non-FIV-infected cats. Thus, in this study at least in the early stage of FIV infection, the immune system was not markedly suppressed, and therefore, cats were successfully immunized (Lehmann et al., 1991). In a follow-up study, long-term protection of a FeLV vaccine was determined in 30 specified pathogen-free cats for over 3 years. Half of the cats had previously been infected with FIV, the other 15 cats served as non-infected controls. There was no difference in vaccine efficacy between FIV-infected and FIV-negative cats. After 3 years of observation, the FeLV-vaccinated FIV-infected cats had significantly higher survival rates as well as better clinical and laboratory parameters than the not-FeLV-vaccinated FIV-infected cats, thus indicating, that the FeLV vaccine was effective in these FIV-

infected cats (Hofmann-Lehmann et al., 1995). In contrast, in a 5-year field study aimed to control FeLV infection by vaccination in a colony of 30 adult cats naturally exposed to FeLV, FeLV vaccination was effective in FIV-negative cats, but failed to protect FIV-infected cats against FeLV (Bandecchi et al., 2006). Although results from experimental studies cannot necessarily predict outcome in naturally infected cats, it is clear that there are major differences in the response to vaccination depending on the immune status of the individual FIV-infected cat.

In addition to concerns about efficacy, there is debate about negative effects of vaccine-induced immunostimulation in FIV-infected cats, as immunostimulation could potentially lead to progression of FIV infection by altering the balance between the immune system and the virus (Sellon and Hartmann, 2006). Although some studies even suggest that immunostimulation can help to stabilize CD4+ cell numbers (Reubel et al., 1994), vaccination of chronically infected FIV-infected cats with a synthetic peptide on the other hand was associated with a decrease in the CD4/CD8 ratio (Lehmann et al., 1992). Stimulation of FIV-infected lymphocytes is known to promote FIV production *in vitro*, and *in vivo*, lymphocyte stimulation can increase the expression of cellular FIV receptors and increase virus production, a combination that could enhance progression of infection. Thus, vaccination and antigenic stimulation might potentially be disadvantageous. In conclusion, if adult FIV-infected cats that had been vaccinated previously, are kept strictly indoors, the risk of being infected with other pathogens is likely lower than the possible harmful effect of vaccination. Ideally, antibody levels, at least against FPV, should be determined (Mende et al., 2014b) and only in cats lacking protective antibodies vaccination should be considered. If antibody measurement is not possible, booster vaccinations in adult indoor-only cats, that have received previous vaccinations in their lives, are not recommended. If potential exposure to FPV, FHV, or FCV cannot be excluded, only core vaccines should be administered, and those, when available, in an inactivated form.

Cats with feline leukaemia virus infection

Cats with progressive FeLV infection are more severely immunocompromised than cats with FIV (Lutz et al., 2009; Hartmann, 2012; Hartmann, 2014); they have suppressed cellular and humoral immunity, thus predisposing cats for just about any type of infection. Therefore, maintaining a good level of protection is considered very important. While FIV preferentially replicates in CD4+ lymphocytes and macrophages, FeLV can replicate and destroy virtually all hematopoietic cells. Lymphopenia and neutropenia are common in FeLV-infected cats. In some cats, lymphopenia is characterized by preferential loss of CD4+ helper T cells, resulting in an inverted CD4/CD8 ratio (comparable to FIV infection) (Quackenbush et al., 1990; Hoffmann-Fezer et al., 1996), but more commonly, substantial losses of both helper cells and cytotoxic suppressor cells (CD8+ cells) occur (Hoffmann-Fezer et al., 1996). Many immune function tests of naturally FeLV-infected cats are abnormal, including poor response to T-cell mitogens, prolonged allograft reaction, reduced immunoglobulin production, depressed neutrophil function, complement depletion, and altered cytokine levels (Linenberger and Deng, 1999). Finally, primary and secondary humoral responses to specific antigens are delayed and decreased in FeLV-infected cats. Those cats with FeLV-associated myelosuppression have a particularly strong immunosuppression because of the occurring pancytopenia (Hartmann, 2012).

Although it has been recommended that FeLV-infected cats should receive inactivated vaccines and not modified-live virus vaccines (when available), little evidence indicates that the cats are indeed at increased risk of VAAEs through those vaccines (Levy et al., 2008).

It has been shown that cats with progressive FeLV infection might not adequately respond to vaccination. When cats with FeLV infection were vaccinated with rabies vaccines, they were only protected for 6 months (Franchini, 1990). This has been proven for rabies but is likely also true for other vaccine components as well. Thus, for good

protection, vaccination with core vaccines (against FPV, FHV, and FCV) should be performed regularly, even if the cat is kept strictly indoors (this is different to FIV-infected cats). If an owner cannot be convinced to keep a FeLV-positive cat inside, rabies vaccinations should be given (in accordance with state and local regulations). Protection in a FeLV-infected cat after vaccination is not as complete and long-lasting as in a non-infected cat. Thus, either more frequent vaccinations (e.g., every 6 months) are recommended in FeLV-infected cats or measurement of antibody titres to assure sufficient protection, e.g., against panleukopenia virus (Mende et al., 2014b) is recommended, especially if the cat is allowed to go outside.

Cats with Tumours

Oncology patients can have immunosuppression for several reasons, including the cause of the tumour itself, e.g., if caused by FeLV infection, the debilitation, acquired disorders of antibody production and cell-mediated immunity caused by the tumour, and the drugs used to treat the tumour. Splenectomy performed to remove a splenic tumour can further compromise the patient (Schaer, 2008). Tumours can lead to immunosuppression that favours tumour progression and metastasis and evolves by constitution of an immunosuppressive network, which is mediated by several tumour-derived soluble factors, such as interleukin-10, transforming growth factor-b, and vascular endothelial growth factor, and which extends from the primary tumour site to secondary lymphoid organs and peripheral vessels (Kim et al., 2006).

Some specific tumours, such as multiple myeloma and some lymphomas, can cause acquired disorders of antibody production. This is more likely to happen when the tumour cells produce a paraprotein increasing globulin production but simultaneously interfering with the patient's normal antibody response. In cats with tumour-associated disorders of antibody production, vaccination is very unlikely to be effective. There are also neoplastic disorders that can cause neutropenia, which is amongst the most important risk factors for serious infection in the immunocompromised host. A severe neutropenia can be seen in myelophthisic disease caused by spread of the tumour to the bone marrow. Myelophthisis can occur with both lymphoma and carcinoma types of neoplasia (Schaer, 2008).

In humans, meta-analyses on efficacy of influenza vaccination in patients with tumours revealed a significantly reduced immunological response in patients with tumours compared to controls, although this was not the case in all studies. Adult human tumour patients had depressed antibody responses to immunisation even before starting chemotherapy (Lehane and Lane, 1974). On the other hand, no evidence of serious VAAEs or disease progression was identified as being related to the administration of influenza vaccine. Thus, recommendation in human medicine states that vaccination should be maintained in humans with tumours (Beck et al., 2012; Rubin et al., 2014), but in these patients no modified-live virus vaccines should be administered, because replication of the vaccine virus can be enhanced in severely immunocompromised persons (Mitus et al., 1962; Bellini et al., 1992).

A few studies in dogs demonstrated immunosuppression associated with various tumours, such as lymphoma or osteosarcoma (Walter et al., 2006) and mammary carcinoma (Mucha et al., 2016). Dogs with lymphoma or osteosarcoma had reduced T cell numbers when compared to healthy dogs (Walter et al., 2006). A recent study demonstrated the immunosuppressive network present in dogs with mammary carcinoma; while the number of various T cell subpopulations was constant during tumour development, the number of regulatory T cells was significantly higher in tumour-bearing dogs than in healthy individuals as was the number of myeloid-derived suppressor cells (Mucha et al., 2016). In one study, dogs with lymphoma or osteosarcoma were vaccinated and post-vaccination antibody titres were compared to those of a healthy control group. Although dogs with lymphoma

or osteosarcoma appeared to be relatively T cell-deficient, antibody titres after vaccination were not significantly different to those of healthy controls (Walter et al., 2006).

No studies have been performed in cats with tumours to demonstrate their ability to react to vaccination. However, a recent study assessed the prevalence of antibodies against FPV in 350 client-owned cats and identified factors that were associated with a lack of antibodies in cats. Factors, including information regarding signalment, origin, environment, lifestyle, housing conditions, health status, chronic diseases, glucocorticoid therapy, and vaccination status were analysed by a multivariable logistic regression analysis. Of the 350 cats, 103 (29.4%) had no antibodies against FPV, and among other factors, tumours were significantly associated with a lack of antibodies (Mende et al., 2014a). Thus in cats with tumours, protection rate is not comparable to those of healthy cats. Antibody measurement, at least against FPV infection, would be a good possibility to confirm that protection is present. If antibody measurement is not an option, more frequent boosters than usually recommended (such as once yearly) should be considered in these cats. In cats with tumour-associated severe neutropenia or disorders of antibody production, vaccination should be postponed until tumour chemotherapy improved the condition.

Cats with other Immunosuppressive Diseases

There are a number of other diseases that can alter the immune system, such as diabetes, chronic kidney disease, and asplenia. In humans, these conditions increase the patient's risk for certain diseases, and thus, specific vaccines, such as particularly bacterial vaccines, are recommended for such patients. Frequently, the immune response of those patients to these antigens is not as good as that of immunocompetent persons, and higher doses or more frequent boosters might be required. In humans, liver cirrhosis is also included in the guidelines as important immunosuppressive disease (Rubin et al., 2014), which is a very rare condition in cats and thus, will not be further discussed in the present guideline.

Diabetes mellitus

Diabetes mellitus can alter the body's immune defences, therefore rendering the patient predisposed to infection. The reasons for this have not been completely explained but can involve abnormalities with cell-mediated immunity and abnormal phagocyte function as well as poor blood supply to various body tissues because of diabetic vascular disease. Thus, infections in animals with diabetes are more common and severe and can involve the skin, urinary tract, and other body sites, such as the gall bladder and liver (Schaer, 2008). In diabetic cats, urinary tract infections are the most common secondary infections (Bailiff et al., 2006; Mayer-Roenne et al., 2007).

Although several *in vitro* tests of immunologic function are known to be abnormal among diabetic patients, these defects are likely of little clinical importance. In humans with longstanding diabetes, who often have cardiovascular, renal, and other end-organ dysfunctions, vaccinations, such as annual influenza vaccination are recommended. Patients receiving either insulin or oral antidiabetic agents responded normally to influenza vaccination without impairment of diabetic control (Feery et al., 1983). Also pneumococcal vaccines were safe and effective in diabetic patients and did not interfere with insulin levels or glucose control (Beam et al., 1980; Lederman et al., 1981). In a study on vaccination of elderly people, patients with diabetes showed an immune response comparable to that of other non-diabetic participants (Govaert et al., 1994). Still, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommends to vaccinate adult diabetic patients as early as possible after their diagnosis (Centers for Disease Control and Prevention, 1993).

The immune function of a diabetic patient, however, is more severely compromised as long as the patient remains uncontrollably hyperglycemic. Thus, vaccinations should never be given to a cat with poorly controlled diabetes, and control of the diabetic situation should be achieved before vaccination. In cats, infections play an important role in inducing insulin resistance and by causing diabetic decompensation because of endogenous hypersecretion of stress hormones, such as cortisol (Schaer, 2008). There are no data, however, whether vaccination could promote diabetic decompensation. Thus in conclusion, the recommendation would be to vaccinate diabetic cats according to the proposed guidelines for healthy cats, but postpone the vaccination in an uncontrolled diabetic case until control is achieved.

Chronic kidney disease

Patients with kidney disease have an increased risk of infection with a variety of pathogens (Linneman and First, 1979; Alter et al., 1986; Schwebke and Mujais, 1989; Johnson and Fleming, 1992). An association between chronic kidney disease and reduced antibody development following vaccination has been described in humans. The efficacy of pneumococcal vaccination for some of these patients, including those on dialysis, was considerably lower than for immunocompetent patients (Simberkoff et al., 1980; Cosio et al., 1981), their antibody levels might also be lower (Linneman et al., 1981), and they might require repeated vaccinations (Linneman et al., 1986; Rytel et al., 1986) or an increased dose of vaccines. It has been shown, that the stage of the kidney disease and thus, the impairment of the glomerular filtration rates predicted ability to produce antibodies (DaRoza et al., 2003), since a rise of antibody titres after vaccination became increasingly unlikely as glomerular filtration rate decreased (DaRoza et al., 2003). Malnutrition in patients with chronic kidney disease was also suspected to be associated with an impaired immune response (Lombardi et al., 1992), and chronic uremia, directly or indirectly, was shown to alter immune cell function (Pesanti, 2001). Consequently, a generalized immunosuppression and decreased antibody development are expected in chronic kidney disease patients with secondary antibody responses being less affected than primary antibody responses. Thus, immunisation strategies and especially vaccination with novel antigens should be formulated as early in the course of the chronic kidney disease as possible (Centers for Disease Control and Prevention, 1993).

No studies have been performed in cats with chronic kidney disease to demonstrate their ability to react to vaccination. However, a recent study assessed the prevalence of antibodies against FPV in cats in Southern Germany and identified factors that were associated with a lack of antibodies in 350 client-owned cats, and presence of chronic kidney diseases was significantly associated with a lack of antibodies (Mende et al., 2014a). Thus in cats with chronic kidney disease, protection rate is not comparable to those of healthy cats.

There is another concern that has to be discussed when considering vaccination in cats with chronic kidney disease. Some studies suggested a risk association between chronic kidney disease and frequent vaccination in cats. A recent risk factor analysis on the development of chronic kidney disease in cats evaluated clinical and questionnaire data to identify risk factors in 148 client-owned older cats (> 9 years) followed longitudinally for a variable time. Besides dental diseases, the only significant risk factor identified in the final multivariable Cox regression model was indeed annual/frequent vaccination suggesting an association between vaccination frequency and development of chronic kidney disease (Finch et al., 2016). Such an association has already been proposed in earlier studies that were aimed at identifying antibodies against feline kidney cells in vaccinated cats. Vaccine viruses are usually grown on Crandell-Rees feline kidney (CRFK) cells, and it was hypothesized that vaccinated cats would produce antibodies against CRFK cells, that could interact with their own kidney tissues and thus, could be a trigger for interstitial nephritis. Parenteral administration of CRFK cell lysates or FPV, FHV, and FCV vaccines grown on CRFK cells induced antibodies in cats against CRFK cells. These antibodies also

reacted with feline renal cell extracts. In contrast, control cats that had received an intranasal vaccine did not develop detectable antibodies against (Lappin et al., 2005). In a follow-up study, it was determined whether interstitial nephritis would be detected in cats that were immunologically sensitized with CRFK lysates, boosted with CRFK lysates, and then biopsied 2 weeks after the booster. Cats were immunologically sensitized against CRFK lysates 12 times in the first 50 weeks over 2 years. Half of the cats sensitized with CRFK lysate indeed developed lymphocytic-plasmacytic interstitial nephritis (Lappin et al., 2006). In another study, 44 kittens were inoculated with CRFK lysates and FPV, FHV, and FCV vaccines. Several CRFK antigens were identified in the kittens, and protein isolation and sequencing identified them as alpha-enolase, annexin A2, and macrophage capping protein (MCP). Sera from vaccinated and CRFK-inoculated kittens confirmed to recognize annexin A2 and alpha-enolase by Western blot and indirect ELISA. In humans, alpha-enolase antibodies are nephritogenic; alpha-enolase and annexin A2 antibodies have been associated with autoimmune diseases (Whittemore at al., 2010). Although these studies suggest a possible association between vaccination and chronic kidney disease in cats, there is no causative proof and further studies are required.

However, as most of the cats with chronic kidney disease are of older age and likely have received vaccinations in the past, the risk for such a cat to acquire infectious diseases is considered low, and vaccination might not be necessary. Ideally, antibody levels at least against FPV should be determined (Mende et al., 2014b) and only cats lacking protective antibodies should be vaccinated. If antibody measurement is not possible, booster vaccination is not recommended for a cat with chronic kidney disease that has been vaccinated previously and is kept strictly indoors. If potential exposure to FPV, FHV, or FCV cannot be excluded, only intranasal vaccine should be given, if available.

Asplenia

People who have anatomic or functional asplenia have an increased risk for infectious diseases, especially fulminant bacteremia associated with high mortality. Thus, in human medicine, especially bacterial vaccines, such as polyvalent pneumococcal and quadrivalent meningococcal vaccines, are considered important for all asplenic persons (Centers for Disease Control and Prevention, 1993).

Asplenia is rare in cats and mainly occurs after iatrogenic removal of the spleen. Asplenia is more common in dogs, and dogs without spleen are at increased risk to develop clinical manifestation of bacterial or parasitic infections that are usually asymptomatic, such as infections with *Mycoplasma haemocanis* (Kemming et al., 2004; Hulme-Moir et al., 2010; Pitorri et al., 2012). In addition, new bacterial or parasitic species have been detected in asplenic dogs, such as a new hemoplasma spp. *'Candidatus* Mycoplasma haematoparvum' (Sykes et al., 2005) or a new large *Babesia* spp. (Sikorski et al., 2010). In cats, studies on the outcome following laparatomic (Gordon et al., 2010; Kraus et al., 2015) or laparascopic (O'Donnell et al., 2013) splenectomy have been performed, but no increased risk for certain infections was observed in these studies. There is only one old case report of a cat that had recovered from *Cytauxzoon felis* infection following treatment with the anti-theilerial drug parvaquone, but showed an increase in piroplasm parasitemia after splenectomy (Uilenberg et al., 1987); thus, asplenic cats also might be predisposed for certain intracellular bacteria or parasites.

In conclusion, in asplenic cats protection rate might not be comparable to those of healthy cats. Antibody measurement, at least against FPV infection, would be an option to confirm if protection is present. If antibody measurement is not an option, more frequent boosters than usually recommended (such as once yearly) should be considered in these cats. When elective splenectomy is planned, vaccination should precede surgery by at least 2 weeks, if possible.

Cats Receiving Immunosuppressive Therapy

Immunosuppressive drugs, such as glucocorticoids, cyclosporine, or tumour chemotherapeutics, are commonly used in cats with various diseases. If used short-term, vaccination can be postponed until after the treatment, but some cats require long-term therapy.

Glucocorticoid treatment

Many clinical conditions require long-term glucocorticoid treatment, and the degree of immunosuppression depends on the glucocorticoid dosage used. In many immune-mediated diseases, glucocorticoids are the initial and primary drug of choice and most are started on high dosages, such as prednisolone 1-2 mg/kg given every 12 hours. The effects of such high dosages of glucocorticoids on the immune system are substantial with effects involving various components of the immune system. The effects on neutrophils include decreases in chemotaxis and margination and impaired phagocytosis and bacterial killing, thus predisposing the patient to infections that can involve many body tissues. The effects of glucocorticoids on macrophages result in impaired chemotaxis, phagocytosis, and bactericidal activity. Macrophages will also have decreased interleukin-1 production and antigen processing which will further predispose the animal to infection. Glucocorticoids will cause depressed lymphocyte proliferation, depressed T cell responses, impaired T cell cytotoxicity, depressed interleukin-2 production, and depressed lymphokine production. There is also an influence on immunoglobulin production. The patients being treated with high doses of glucocorticoids will be even further predisposed to infection if other cytotoxic or immunosuppressive drugs are used simultaneously (Schaer, 2008). In humans, organ transplant recipients receiving high dose-dose glucocorticoids are an important group of severely immunocompromised people, and there are specific recommendations on vaccinations (e.g., against influenza) for these patients (Kumar et al., 2011), but organ transplantation is still not very commonly performed in feline medicine.

The exact amount of systemic glucocorticoids and the duration of their administration needed to suppress the immune system in an otherwise healthy cat are not well defined. The immunosuppressive effects of steroid treatment vary, but many clinicians consider a dose equivalent to either 2 mg/kg prednisolone as sufficiently immunosuppressive to raise concern about the safety of immunisation with modified live-virus vaccines. Glucocorticoids used in lower (but greater than physiologic) doses also might reduce the immune response to vaccines. In human medicine, glucocorticoid therapy usually does not contraindicate administration of vaccines (not even with modified-live virus vaccines) when glucocorticoid therapy is short-term (less than 2 weeks); low to moderate dose; long-term alternate-day treatment with short-acting preparations; maintenance of physiologic doses (such as replacement therapy in patients with Addison’s disease); or administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection (Centers for Disease Control and Prevention, 1993).

One study investigated the effect of oral prednisolone on vaccination against canine distemper virus in Beagle puppies and found that doses of 1 mg/kg and 10 mg/kg over a period of 21 days had no effect on the response to vaccination (Nara et al., 1979). No studies have been performed in cats receiving glucocorticoid therapy to demonstrate their ability to react to vaccination. However, a recent study assessed the prevalence of antibodies against FPV in cats in Southern Germany and identified factors that were associated with a lack of antibodies in 350 client-owned cats. In this study, glucocorticoid treatment was significantly associated with a lack of antibodies, and cats receiving glucocorticoids for 11 weeks and longer were particularly at risk (Mende et al., 2014a).

In conclusion, if possible veterinarians should wait at least 3 months after discontinuation of glucocorticoid therapy before administering vaccines, especially modified-live virus vaccines, to cats who have received high-dose,

systemic steroids for more than 2 weeks. If continuous long-term glucocorticoid therapy is necessary, vaccinations schedules should be maintained, but inactivated vaccines should be applied, if available.

Cyclosporine treatment

Cyclosporine is used more and more commonly in cats, such as for feline hypersensitivity dermatitis or autoimmune diseases. Cyclosporine can interfere with cell-mediated immunity, thus compromising the host defence system against infectious agents, such as intracellular parasites (Schaer, 2008). It has been shown that cats with high cyclosporine blood concentrations at the time of primary *Toxoplasma gondii* infection can be at risk of developing systemic toxoplasmosis (Lappin et al., 2015), that latent *Toxoplasma gondii* infection can be reactivated during treatment (Barrs et al., 2006), and that in some cats being treated with cyclosporine, toxoplasmosis can be fatal (Last et al., 2004). Cats receiving cyclosporine are also predisposed to other infections, such as systemic *Salmonella* infection (Callegari et al., 2014). In a number of client-owned cats receiving cyclosporine to block renal transplant rejection, signs of upper respiratory tract disease from re-activated FHV infection occurred (Lappin et al., 2015).

One study investigated the immunosuppressive effect of cyclosporine on the ability of cats to mount an immune response following vaccination. Thirty-two healthy, immunocompetent adult cats (16 cats/group) were treated with either cyclosporine for 56 days at a dose of 24 mg/kg once daily (more than 3 times the therapeutic dose) or sham-dosed. Prior to treatment, cats had an adequate antibody response to primary vaccination against FPV, FHV, FCV, FeLV, and rabies. Booster vaccination against FPV, FHV, FCV, FeLV and rabies or novel vaccination against FIV were administered 28 days after initiation of treatment with cyclosporine. There were delays/reductions in antibody response to FHV, FeLV, and rabies in treated cats; however, adequate protection was achieved in response to all booster vaccinations. Following primary vaccination with FIV, however, control cats showed a response, but treated cats showed no antibody production. Thus, adult cats treated with high-dose cyclosporine were able to achieve adequate protection following booster vaccination, while in contrast, cats failed to mount a humoral response to a novel vaccination. This suggests that memory B-cell immune responses remain intact during high-dose cyclosporine administration in cats, but that primary immune responses are impaired (Roberts et al., 2015). Thus in conclusion, booster vaccination can be given to cats receiving cyclosporine, but novel vaccinations should be applied before cyclosporine treatment is initiated, if possible.

Tumour chemotherapy

Many of the cytotoxic drugs used for anti-tumour chemotherapy inhibit cell division, and when this occurs, the B and T cells are often times destroyed, thus impairing the body's ability to produce antibodies and to allow for cell-mediated immune protection. The immune system of the tumour patient will be further compromised by the concomitant use of other immunosuppressive agents, such as glucocorticoids, and any devastating effect of myelophthisic tumour behaviour (Schaer, 2008).

Administration of chemotherapeutic agents to mice and humans had variable effects on different components of the immune system. For example, lymphocyte depletion in human patients undergoing chemotherapy has been reported, but the degree of lymphocyte depletion appeared to be dependent on the particular chemotherapy protocol (Harris et al., 1976; Berge et al., 1984; Sabbioni et al., 1999; Kubota et al., 2001). Lymphocyte depletion, specifically, depletion of CD4+ T cells, can even persist long after completion of chemotherapy (Azuma et al., 1998; Sara et al., 1999). Not all chemotherapy agents are equally immunosuppressive. Alkylating agents, such as cyclophosphamide, are particularly prone to cause immunosuppression because of their affinity for destroying rapidly dividing cells, thus destroying the B and T cell response. These effects on the immune system are made

even worse by cyclophosphamides´ ability to suppress the bone marrow and cause neutropenia (Schaer, 2008). However, on the other hand, in humans, cyclophosphamide administered at low doses was shown to actually potentiate humoral immunity and decrease immunologic tolerance (Periti and Mini, 1987; Emens et al., 2001). Doxorubicin and related drugs also have different effects on adaptive immune responses, with doxorubicin being immunostimulatory and preserving cell-mediated immunity in some human studies (Roth et al., 1978; Periti and Mini, 1987; Formelli et al., 1988; Ehrke et al., 1989; Gautam et al., 1991; Fornasiero et al., 1992). The effects of chemotherapy on the humoral immune response can also be variable. In human pediatric oncology patients, pre-existing titres to tetanus, diphtheria, and poliomyelitis were preserved throughout chemotherapy in some, but not all studies (Ridgway and Wolff, 1993; Reinhardt et al., 2003; Zignol et al., 2004). In some studies, the ability of the humoral immune system to respond to vaccination was restored within 6 months of completing chemotherapy (Oldham et al., 1976; Alanko et al., 1992; Mustafa et al., 1998).

In dogs, chemotherapy has been documented to have no effect on pre-existing antibody titres. A prospective study determined the association between tumour chemotherapy and serum canine distemper virus (CDV), canine parvovirus (CPV), and rabies virus antibody titres in tumour-bearing dogs, including 21 client-owned dogs with various malignancies and 16 with lymphoma. No significant changes were detected in CDV, CPV, and rabies virus titres following chemotherapy in tumour-bearing dogs. Thus, established immunity to CDV, CPV, and rabies virus from previous vaccination was not significantly compromised by standard chemotherapy (Henry et al., 2001). Another prospective study evaluated the effects of 2 common chemotherapy protocols on T and B cell numbers and humoral immune responses to *de novo* vaccination in 21 dogs with tumours (12 with lymphoma, 9 with osteosarcoma) comparing effects of doxorubicin *versus* multi-drug chemotherapy. Doxorubicin treatment did not cause a significant decrease in T or B cell numbers, whereas treatment with combination chemotherapy caused a significant and persistent decrease in B cell numbers. Antibody titres after vaccination were not significantly different between control and chemotherapy-receiving dogs. These findings suggest that chemotherapy might have less impact on T cell numbers and ability to mount antibody responses in dogs with tumours than was previously anticipated and that administration of chemotherapy does not preclude administration of vaccines (Walter et al., 2006). Although there are no data in cats, ideally, recommendations in cats should follow recommendations in humans (Centers for Disease Control and Prevention, 1993), that suggest that when tumour chemotherapy or immunosuppressive therapy is being considered, vaccination ideally should precede the initiation of chemotherapy or immunosuppression by greater than or equal to 2 weeks. Vaccination during chemotherapy should be avoided because antibody responses are suboptimal. Patients vaccinated while on immunosuppressive therapy or in the 2 weeks before starting therapy should be considered unimmunised and should be revaccinated at least 3 months after discontinuation of chemotherapy.

Cats under General Anesthesia

Many countries regularly perform spay/neuter and release programs to control the stray cat population. Cats in such situations are commonly very difficult to handle and are released immediately after recovering from anesthesia. Some of these programs vaccinate cats while still under anesthesia for spaying/neutering due to easier handling. One prospective study determined the effects of anesthesia and surgery on antibody development after vaccination in 32 specific-pathogen-free kittens. Kittens were assigned to 1 of 4 treatment groups: neutering at 7, 8, or 9 weeks of age or no neutering. All kittens were inoculated with modified-live virus vaccines against FPV, FHV, and FCV at 8, 11, and 14 weeks of age and inactivated rabies virus at 14 weeks of age. Antibody response of kittens neutered at the time of first vaccination (8 weeks) were not different from those of kittens neutered 1 week before (7 weeks) or 1 week after (9 weeks) the first vaccination or from those of kittens that were not neutered. Anesthesia and neutering at or near the time of first vaccination with a modified-live virus

vaccine did not impair antibody responses in kittens. Thus, cats can be vaccinated in the perioperative period when necessary (Reese et al., 2008).

Geriatric cats

Ageing is a continuous and slow process that compromises the normal functioning of various organs and systems in both qualitative and quantitative terms (Malaguarnera et al., 2000), and has been defined as a complex process in which the individual suffers from a decline in physical condition, organ, sensory and mental function, as well as immune responses. Obviously, there is a great individual variation between biological and chronological age and how the body systems age in each individual, meaning that geriatric abnormalities or diseases can appear earlier in some cats and never appear in others. It has been proposed to comprise older cats in 2 categories, “senior cats” (11-14 years) and “geriatric cats” (15 years and older). Although general senior care guidelines have been published by the American Association of Feline Practitioners (AAFP) (Pittari et al., 2009) and the American Animal Hospital Association (AAHA) (Epstein et al., 2005) and implementation of senior/geriatric health care program in veterinary practice has been proposed (Fortney, 2012), so far, there are no specific vaccination recommendations for senior and geriatric cats, and there is a general lack of knowledge if geriatric cats have special vaccination needs.

Ageing and geriatric decline of body systems can lead to a decrease in immune function (immunosenescence) and also a pro-inflammatory state (inflammageing) plus the presence of degenerative, neoplastic, or inflammatory/immune-mediated diseases, which all can have an impact on susceptibility to infectious diseases and/or produce an abnormal or decreased response to vaccination. “Immunosenescence” has been defined as a multifactorial complex of changes that occur in the immune system of elderly individuals that predispose to increased morbidity and mortality to infection and age-related pathology. It has recently been suggested that immunological changes in immunosenescence resemble those observed following chronic stress or corticosteroid treatment (Bauer, 2016). Immunosenescence occurs in cats (and dogs) and can, in theory, make them more susceptible to certain infectious diseases and/or less efficient to mount an immune response after vaccine administration. “Inflammageing” has been defined as the effects of a lifetime constant antigenic challenge and associated production of inflammatory mediators that can trigger the onset of inflammatory disease in older individuals. Immunosenescence and inflammageing have also been demonstrated to occur in cats, but there is no data about their effects on post-vaccination immune response.

Several immunological differences have been demonstrated in some studies in senior and geriatric cats when compared to younger adult cats (Day, 2010), including lower number of circulating leucocytes (lymphocytes, CD4+ T cells, CD8+ T cells, B cells, CD56+ NK cells, and eosinophils); elevated concentrations of IgM and IgA; lower levels of insulin-like growth factor (which can be associated to lower numbers of CD4+ T cells); reduced blood lymphocyte blastogenic responses to stimulation with several mitogens; and increased monocyte production of pro-inflammatory cytokines (determined by mRNA levels). These data show some alteration of the immune response, but do not tackle all elements of immunosenescence as described in general in geriatric mammals, such as the innate immune response that might be unaltered or even increased (Pawelec et al., 2010); the ability to mount a primary serum antibody response to a novel antigen being unaltered despite a decrease in B cell numbers; presence of antibodies with lower affinity (Pawelec et al., 2010); quicker antibody titre decrease (HogenEsch and Thompson, 2010); the ability to adequately retain B cell memory and serum antibody concentrations, that however, less effectively respond to primary immunization; decrease in the CD4/CD8 ratio; decreased number of naive T cells (Pawelec et al., 2010); and increase in percentage of presumed memory CD4+ and CD8+ T cells.

In humans, specific guidelines for elderly people (generally > 60 years of age) exist, and increased vulnerability to infection of the elderly makes them a particularly important target population for vaccination. Most vaccines are considered less immunogenic and efficient in elderly people because of age-related changes in the immune system. Various strategies, such as the use of specifically designed vaccines for elderly people (e.g., novel adjuvants and administration routes) have been proposed. As antibody titres are generally lower in the elderly and decline faster, regular booster vaccinations are considered essential to ensure protection (Weinberger and Grubeck-Loebenstein, 2012).

In cats, so far no studies have been published on the response of senior or geriatric cats to vaccination, and the question arises if either immunosenescence or inflammageing might have an impact on immunity which should lead to changes in vaccination protocols in old cats. There are no data that would support the idea of infectious diseases being more common in senior or geriatric cats, and the incidence of infectious diseases preventable by vaccination in senior and geriatric cat is generally considered low. Old cats rarely die or present with signs of those infections if previously vaccinated (Kruse et al., 2011; Riemer et al., 2016). On the other hand, it is also not known, whether vaccine boosters could worsen a pro-inflammatory state in a senior or geriatric cat, and thus, reducing number of booster vaccinations would seem appropriate. In addition, many senior or geriatric cats are diagnosed with chronic inflammatory or immune-mediated diseases, such as chronic gingivitis or periodontal disease, chronic kidney disease, inflammatory bowel disease, inflammatory liver disease, or pancreatitis.

Although so far no studies have been performed on the response of senior or geriatric cats to vaccination, duration of immunity (DOI) studies have shown long-term immunity against FPV, FHV, and FCV (Scott and Geissinger, 1997; Scott and Geissinger, 1999; Lappin et al., 2002), and experimental studies have shown that immunity persists for years showing that immunological memory to core vaccines is adequate as well as the immunological response to boosters (Schultz et al., 2010; Day et al., 2016). Based on these experimental studies and expert opinion, healthy geriatric cats properly vaccinated should receive boosters at recommended intervals based on published guidelines and following assessment of individual risk (Hosie et al., 2013). On the other hand, there is some evidence that older cats might not respond efficiently to novel antigens that are administered for the first time. This has been shown with rabies vaccine in dogs but could be presumed for any other antigen. Older dogs vaccinated for the first time against rabies showed lower antibody levels compared to younger dogs, in general having difficulties to reach titres above 0.5 UI/ml (Kennedy et al., 2007). Thus, based on this study, if healthy senior or geriatric cats that need to be vaccinated against a novel pathogen for the first time (travelling, moving, changing life style), even if the regular vaccination schedule consists in one injection (e.g., rabies), a single dose should not be considered enough to ensure a proper immunisation, and a second dose is recommended in these animals. The current knowledge on immunosenescence and inflammageing adds more reasoning to avoid overvaccination or (indiscriminated) annual boosters of core vaccines in all cats.

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