GUIDELINE for Adverse reactions to vaccination

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These guidelines were drafted by H. Egberink et al., and are dedicated to the memory of Professor Michael Day (School of Veterinary Sciences, University of Bristol, UK), May 2020.

Introduction

Vaccination is undoubtedly one of the most effective measures for the prevention of infectious diseases. However, as with other biologicals, vaccine-associated adverse events (VAAEs) may occur. Although these are believed to be rare, understanding their potential occurrence is an important part of informed consent for owners when deciding about vaccines.

VAAEs are caused either by an aberrant innate or adaptive immune reaction, excessive local reactions to the vaccine at the inoculation site or by an error in administration (i.e. not in accordance with the Summary of Product Characteristics). Errors in manufacture could also lead to increased VAAEs, but vigorous quality control for vaccine manufacture means that these are extremely unlikely.

A range of clinical signs may follow vaccination and, in some cases, these might be associated with vaccination. However, a cause-effect relationship may be difficult to prove because of variability in the time of appearance of the clinical signs after vaccination as well as the variable clinical appearance of more chronic systemic adverse reactions (Moore and HogenEsch, 2010). In terms of quantifying reactions, adverse reactions are generally underreported to vaccine manufacturers or national regulatory authorities (where such reporting schemes exist), as many reactions may not be reported by the veterinarian or owner of the animal. This makes it difficult to obtain reliable data on the nature and true incidence of adverse effects.

With one exception, namely the development of subcutaneous sarcomas at the injection site (feline injection site sarcomas – FISS), the numbers of published studies on adverse reactions in cats are limited. These tumours were first reported in the USA from 1989 onwards and were suggested to be primarily associated with the use of adjuvanted vaccines (e.g. rabies and feline leukaemia virus vaccines). Later, it was shown that the occurrence of sarcomas was not exclusively associated with vaccines, but also with a range of other injectables. These injections, particularly when repeatedly administered to the same anatomical location, are thought to induce repeated local irritation with chronic inflammation, which may act as a precursor to local neoplastic transformation of stromal cells. In fact, it was the occurrence of FISS that increased the concern among cat owners about the safety of vaccines in general and rekindled the discussion on VAAEs in cats. FISS were recently the subject of a guideline written by the ABCD (Hartmann et al., 2015 and updated in 2019) and will not be further discussed in this paper.

The association of vaccination with the development of disease is often made if a close temporal relationship exists with the administration of the vaccine (Day, 2006; Moore and HogenEsch, 2010). Epidemiological data on the occurrence of disease related to vaccination will further support the cause-effect relationship. Unfortunately, few studies have been published addressing the incidence of vaccine-associated adverse events (VAAEs) in cats. In one study, a large veterinary practice group (the Banfield Hospital Group) database was used to characterize VAAEs in cats, recorded as occurring within 30 days of vaccination (Moore et al., 2007). Data from approximately 500,000 cats were analyzed, showing that most VAAEs were diagnosed within 3 days of vaccination. Risk was found to be greater for neutered *versus* entire cats, female *versus* male cats of the same neuter status and for cats up to one year of age. Also the risk of VAAEs increased with increasing number of vaccines administered on one occasion to the cat. The VAAE rate within 3 days of vaccination was 0.48% which was greater than the VAAE rate reported for dogs in a similar study (Moore et al., 2005). Another study was published in 2002 by the UK Veterinary Products Committee (VPC) (Gaskell et al., 2002). In this study the number of suspected adverse reactions reported to the UK Veterinary Medicine Directorate was determined and the percentage of reactions established based on the company sales data of the total number of vaccines over the same time period. A mean incidence of 0.61 per 10,000 doses sold for the years 1995-1999 was found. Although these kinds of studies have their limitations, such as likely underreporting of the true number of VAAEs and inclusion of only particular types and brand of vaccines, they support observations in veterinary practice

that adverse reactions are rare.

Types of adverse reactions

Local reaction at the injection site and non-specific systemic reactions

Mild cutaneous reactions at the injection site are not uncommon in cats (Moore et al., 2007). These include swelling, irritation, erythema, loss of hair, pain and rarely abscess formation. These reactions are more often seen with inactivated and adjuvanted vaccines (Day, 2006). An inflammatory reaction at the site of vaccination is in fact part of a desired innate immune response. It is induced by the release of cytokines and chemokines by immune cells and is required for the subsequent development of an appropriate adaptive immune response. Because cats are prone to develop FISS, lumps that persist for more than 3 months, are larger than 2 cm in diameter or continue to increase in size 1 month after vaccination (the '3-2-1 rule') should be evaluated by fine needle-aspiration or collection of incisional wedge biopsy samples (Scherk et al., 2013; Hartmann et al., 2015).

The nonspecific innate response might also induce mild systemic signs such as fever and lethargy and these are the most common adverse reactions observed after vaccination and again are indicative of the vaccine stimulating the immune system (Moore et al., 2007). Although these reactions are signs of immune activation it is preferable that they should remain subclinical or at least have minimal impact on the health of the animal. In the study of Moore et al. (2007), no significant association between these local reactions with the use of specific vaccines was found. However, the multivalent panleukopenia-rhinotracheitis-calicivirus-chlamydia vaccine was significantly associated with an increased risk of lethargy with or without fever (Starr, 1993; Moore et al., 2007).

Disease induced by the vaccine organism

The vaccine organism of a "live" attenuated vaccine needs to multiply to induce an effective immune response. Vaccine organisms are sufficiently attenuated to not induce specific clinical signs related to the organism in a healthy, immunocompetent cat. In animals with an acquired or congenital immunodeficiency, the vaccine organism might cause clinical signs of the infection for which the animal was supposed to become protected. For example, some have suggested immunization of pregnant cats with an attenuated panleukopenia vaccine may lead to cerebellar hypoplasia in the fetus (Truyen et al., 2009), although confirmatory testing was not carried out. Generally, live panleucopenia vaccines are not licensed for use in pregnant animals. Attenuated strains might also be too virulent for kittens in their first weeks of life. For this reason, contact of colostrum-deprived kittens with recently vaccinated animals that may be shedding the vaccine virus may be best avoided and live attenuated vaccines should not be administered to kittens less than 4 weeks of age. Mucosal vaccination against respiratory pathogens (e.g. *Bordetella bronchiseptica* vaccine) might evoke mild upper respiratory tract signs. Additionally, if viruses (especially herpesvirus – FHV – and calicivirus – FCV) in the parenteral respiratory vaccine inadvertently come into contact with the mucous membranes, clinical signs of upper respiratory tract disease might develop. This might occur if vaccination liquid leaks onto the skin and is licked by the cat or if the vaccine is inappropriately aerosolized during drawing up the dose from the vial. Transient shifting lameness due to polyarthritis, which is sometimes seen following FCV infection, might in some cases be due to replication of the vaccine virus with an immune response in the affected joints (Bennett et al., 1989; Dawson et al., 1994).

Hypersensitivity reactions

Vaccination can lead to different types of hypersensitivity reactions, although these are rare in the cat. Type I reactions are most common and occur when allergens cross-link IgE molecules that are bound to mast cells and basophils. Such cross-linking triggers the degranulation of these cells and the immediate release of histamines and heparin, followed by generation and release of prostaglandins and leukotrienes. This results in increased vascular permeability, tissue oedema, cutaneous pruritus and bronchial smooth muscle contraction. Clinical signs in cats associated with a type I reaction include subcutaneous oedema (often facial), pruritus, vomiting, diarrhoea (watery and/or haemorrhagic), hypersalivation and respiratory distress. Such reactions would normally be expected to occur within minutes (20-30 minutes) of vaccination. Vaccines contain several potential allergens including adjuvants, preservatives, antibiotics, culture medium proteins and additives. Usually it is not clear which vaccine component is responsible for the induction of the IgE mediated reaction, though inactivated and adjuvanted vaccines are more likely to be associated with this type of hypersensitivity (Gershwin, 2018). In the dog, bovine serum albumin (BSA) included as a vaccine excipient is responsible for many of these acute reactions (Ohmori et al., 2005). Manufacturers have worked to reduce the content of BSA in canine vaccines.

Such reactions might occur on the occasion of first vaccination of a kitten; however, an animal that developed a hypersensitivity reaction does not necessarily develop a reaction after the next vaccination. However, it is prudent to inform the owner about the risks of subsequent vaccines and to take some measures to reduce the risk of further hypersensitivity. Firstly, the need for each additional vaccination must be weighed against the risk of infection. Also the number of vaccine antigens delivered at one visit should be reduced where possible; a greater risk of developing adverse reactions was associated with a higher number of vaccines inoculated (Moore et al., 2007). If possible MLV vaccines should be used instead of inactivated adjuvanted products and, in general, a different vaccine

formulation (or product from a different manufacturer) is recommended to the one associated with the original primary reaction. Subcutaneous and not intramuscular inoculation of the vaccines will reduce the risk of direct uptake of vaccine components into the systemic circulation. Premedication with antihistamines can be administered at least 15 minutes prior to vaccination. After vaccination, animals should be kept under observation in the clinic for a few hours and then at home by the owners.

Type II hypersensitivity includes autoimmunity and is the result of binding of antibodies to host cells. Cell-bound antibodies might fix and activate the complement pathway leading to lysis of cells. Different effector cells can bind to these cell-bound antibodies via Fc receptors leading to cell-mediated damage of the host cells. In dogs, vaccination has been linked to some autoimmune disorders including immune-mediated haemolytic anaemia (IMHA) and thrombocytopenia (IMTP), polyneuritis and polyarthritis (Duval and Giger, 1996; Day, 2006). However, there are no reports suggesting such an association in cats. Cats inoculated with parenteral feline herpesvirus, feline calicivirus and panleukopenia vaccines were shown to develop antibodies against cellular antigens of the Crandell Rees feline kidney (CRFK) cells (Lappin et al., 2005; Whittemore et al., 2010). Vaccine strains are commonly produced in CRFK cells and, as a consequence, cellular antigens will be included in the vaccine. These antibodies were shown to also react with feline renal extracts. However, no clinical signs, abnormalities in urinalysis or biochemical blood parameters were observed in any cat (Lappin et al., 2005). In a recent study, frequent or annual vaccination was identified as a risk factor for development of chronic renal disease (CRD) in geriatric cats (Finch et al., 2016). These studies suggest an aetiological role of these antibodies, induced after primary and booster vaccinations in causing interstitial nephritis but definite causal proof is lacking. Apart from the type II hypersensitivity reactions, the other forms of hypersensitivity (type III and IV) are rarely documented in cats in association with vaccination. Type III reactions are characterized by antigen-antibody complexes that induce an acute inflammatory response after deposition in the capillary beds of certain tissues. The polyarthritis after FCV infection and sometimes vaccination has been suggested to represent a type III reaction. However, co-infection with field virus or rarely vaccine virus (see above) are the main causes of this syndrome characterized by lameness and pyrexia (Bennett et al., 1989; Dawson et al., 1994).

Immunosuppression

Studies on vaccine-induced immunosuppression have been performed mainly in dogs. Depression of cellular and innate immunity was demonstrated in dogs two weeks post-vaccination (Strasser et al., 2003). However, this is not a general observation in other studies. Some have suggested vaccine-induced immunosuppression may also occur in cats, but this is likely to be rare (Day, 2006). An outbreak of salmonellosis in cats was observed following the use of a high-titer modified-live panleukopenia virus vaccine: although not proven, mild immunosuppression induced by vaccination could have facilitated development of fatal salmonellosis in kittens carrying the opportunist pathogen (Foley et al., 1999).

Lack of efficacy

Under some circumstances, lack of efficacy is also considered an adverse reaction. The majority of these are likely to reflect inappropriate storage and administration of the vaccine (poor ‘vaccine husbandry’; Day et al., 2016), or use of vaccines in animals unable to respond, such as those with high levels of MDA or immunosuppression. The efficacy of batches of vaccines is strictly controlled by the manufacturer and licensing authorities.

Concluding remarks

Limited information on the type and prevalence of VAAEs in cats is available, with the exception of the induction of FISS. Reported prevalences are low, with lethargy with or without fever as the most commonly diagnosed adverse event (Gaskell et al., 2002; Moore et al., 2007). Some risk factors have been identified (Moore et al., 2007); risk was found to be greater for neutered *versus* entire cats, female *versus* male cats of the same neuter status and for cats up to one year of age. The factor associated with the greatest increase in risk was the number of concurrently administered vaccine antigens. Therefore, it is recommended to limit the number of vaccine antigens inoculated concurrently to a cat per veterinary visit to further minimize the already low risk of an adverse event. ABCD recommends that veterinary surgeons carry out a risk–benefit analysis for each vaccine in order to avoid unnecessary vaccination of cats, and to report all adverse events to the manufacturer and/or to their competent authority.

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