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) in May 2020 and published by Hartmann et al. in Viruses 2023, 15, 1708. This update was drafted by Herman Egberink.

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), including feline injection-site sarcomas (FISSs) can occur (Day, 2006; Day et al., 2016; Hartmann et al., 2023). Although these are believed to be rare, understanding their potential occurrence is an important part of informed consent for owners when deciding about vaccination (Day et al., 2016; Stone et al., 2020). The greatest difficulty is to obtain data on those VAAEs that manifest months or years after vaccination. In contrast, those VAAEs that occur soon after vaccination (e.g., within days) and/or at injection sites are more easily recognized. Despite VAAEs are being likely underreported in all animal species, VAAEs were more often reported in dogs and cats than in other animals (Gaskell et al., 2002; Zaugg and Ottiger, 2021).

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 the vaccination process. However, a cause-effect relationship is often 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 VAAEs (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) (Gaskell et al., 2002), as many reactions may not be reported by the veterinarian or owner of the animal. However, in human medicine, substantial case capture, at least for clinically severe VAAEs, has been demonstrated (Miller et al., 2020). Underreporting makes it difficult to obtain reliable data on the nature and true incidence of VAAEs in the field.

With one exception, namely the development of subcutaneous sarcomas at the injection site (feline injection site sarcomas – FISS), the number of published studies on VAAEs in cats are limited. 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 is the subject of a separate guideline written by the ABCD (Hartmann et al., 2015; Hartmann et al., 2023; ABCD Guideline for Feline Injection Site Sarcoma) and will not be further discussed in this paper.

In the UK, surveillance work carried out by the Veterinary Medicines Directorate (VMD), including pharmacovigilance reports on VAAEs after drug use in animals, are published regularly (Davis et al., 2016, 2015, 2013; Dyer et al., 2007, 2008, 2009, 2010, 2011, 2012) and the pharmacovigilance reporting system in the UK continues to provide an excellent example of practical and effective arrangements for collecting this important information (Davis et al., 2016). However, such reporting systems on adverse effects, including VAAEs, do not provide proof of a causal relationship between drug application (e.g., vaccination) and adverse events (e.g., VAAEs) (Day, 2006; Moore and HogenEsch, 2010) although 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 are used to support the cause-effect relationship. Unfortunately, few studies have been published addressing the incidence of vaccine-associated adverse events (VAAEs) in cats. In one substantial survey in the USA, many cases of VAAEs were recorded in cats that were presented to the Banfield Pet Hospitals between 2002 and 2005 (Moore et al., 2007). More than 1.25 million doses of various vaccines were administered to nearly 500,000 cats and VAAEs within 30 days of vaccination were reported at a rate of 0.52% in the vaccinated cats. The most commonly reported VAAEs were lethargy, anorexia, and fever for

three days after vaccination, or local inflammation at the site of injection. 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 as the total volume of vaccine and number of vaccines administered concurrently increased (Moore et al., 2007). 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 VAAEs reported to the UK VMD 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 VAAEs of 0.61 per 10,000 doses sold for the years 1995-1999 was found. In 2020, 130 reports on VAAEs were received in Switzerland of which 25% (33/130) concerned cats. Many of the reports in cats involved the application of vaccines against feline herpesvirus (FHV), feline calicivirus (FCV), and feline panleukopenia virus (FPV), and some *Chlamydia felis*, in combination with feline leukaemia virus (FeLV). Causality assessment between vaccination and the reaction described was considered as being “probable” in 27% and as being “possible” in 44% of all reported cases (all species), demonstrating that the confirmation of a causal relationship is difficult (Zaugg and Ottiger, 2021); moreover, demonstration of true causality would need prospective studies with a very high number of participants. Although observational 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 that VAAEs are rare in veterinary practice (Zaugg and Ottiger, 2021).

Types of adverse reactions

1. Local reaction at the injection site

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, especially in inactivated vaccines. 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. However, as cats are prone to develop FISSs, all lumps should be closely monitored (Hartmann et al., 2023). 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; Jas et al., 2021; Hartmann et al., 2023). Use of a recently introduced non-adjuvanted vaccine against FHV, FCV, FPV, and FeLV formulated in a reduced volume (0.5 mL) with the same antigen content as the conventional 1 mL presentation caused fewer local events, while keeping the same immunogenicity as the corresponding 1 mL vaccine, and thus, might help to reduce the incidence of VAAEs (Jas et al., 2021), although further prospective work is needed to confirm this.

2. Non-specific systemic reactions

The nonspecific innate response can induce mild systemic signs such as fever and lethargy and these are the most common adverse reactions observed after vaccination. One prospective study did investigate the incidence of VAAEs in cats following vaccination against FPV, FHV, and FCV. Only 9.8% (11/112) of the cats developed a mildly reduced general condition for a few days that was, however, positively correlated with an antibody response to FPV vaccination; no severe VAAEs were noted (Bergmann et al., 2018). These signs are indicative of the vaccine stimulating the immune system (Bergmann et al., 2018; Moore et al., 2007).

Although these reactions are signs of immune activation it is preferable that they should have minimal impact on the health of the animal.

A significant association between VAAEs, including non-specific systemic reactions (e.g., lethargy with or without fever), and the number of concurrently administered vaccines or the total vaccine volume administered was found. Unfortunately, the number of agents vaccinated for and the number of separate vaccine injections per visit were not stated in that paper (Moore et al., 2007). In an older study from 1993, significantly more reactions (e.g., lethargy and inappetence) were detected in cats vaccinated with a multivalent vaccine (at that time a new vaccine against FPV, FHV, FCV, and “*Chlamydia psittaci*”) when this vaccine was used concurrently with an FeLV and rabies vaccine, than without FeLV and rabies (Starr, 1993).

3. Disease induced by the vaccine organism or contamination

The vaccine organism in 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, it has been suggested that immunization of pregnant cats with an attenuated FPV vaccine may lead to cerebellar hypoplasia in the foetus (Truyen et al., 2009), although confirmatory testing was not carried out in the described cases. Generally, modified live FPV 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 might

be shedding the vaccine virus, is best avoided and live attenuated vaccines should not be administered to kittens younger than four weeks of age. MLV FCV vaccines could have been the cause of FCV outbreaks in cat colonies (Ohe et al., 2007; Radford et al., 2000, 2001), but this rarely seems to be the case.

Mucosal intranasal vaccination against respiratory pathogens (e.g. *Bordetella bronchiseptica* vaccine) might evoke mild upper respiratory tract signs. Additionally, if viruses (especially FHV and 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 or during injection. In one study, RT-PCR was used to amplify a 235 bp hypervariable region of the FCV genome obtained from vaccinated cats with clinical signs of FCV infection and the sequences were compared to the sequences from three attenuated vaccine viruses. The sequences derived from the vaccine failure cats fell into two categories. Most were distinct (21.33–38.00% distant) from vaccine virus sequences and thus were likely field viruses. However, in some cases, sequences were sufficiently similar to vaccine sequences (0.00–5.33% distant) to suggest that the isolate might have originated from the vaccine strain. However, it was unproven that these cases occurred due to improper administration of the vaccine (Radford et al., 1997). Transient shifting lameness due to polyarthritis, which is sometimes seen following FCV infection, in some cases might be due to replication of the vaccine virus with an immune response in the affected joints (Bennett et al., 1989; Dawson et al., 1994).

In rare cases, contamination of the vaccines can lead to severe vaccination-associated diseases. MLV vaccines are considered more susceptible to contamination than inactivated vaccines, especially when vaccines are produced in large numbers and in different production lines. Infected calf serum (Povey and Carman, 1997; Erickson et al., 1991) or infected cell cultures (Wellemans and Van Opdenbosch, 1987; Bolin et al., 1994a, 1994b) can also pose a risk for contamination. However, generally, compliance with good manufacturing practice guidelines can significantly reduce the risk of contamination (Luff and Soulebot, 1997a, 1997b).

4. Hypersensitivity reactions

Vaccination can lead to different types of hypersensitivity reactions, although these are rare in cats (Moore et al., 2007).

4.1. Type 1 hypersensitivity reactions

Type I hypersensitivity reactions are the most common and occur when allergens cross-link immunoglobulin E (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 (Day and Schultz, 2014; Tizard, 2018). 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, respiratory distress and anaphylactic shock (Davis-Wurzler, 2006; Moore and HogenEsch, 2010). Data from the UK VPC indicate that anaphylaxis occurs in one of 555,000 vaccinated cats (Day, 2006; Meyer, 2001). Such reactions would normally be expected to occur within minutes (20-30 minutes) of vaccination (Brooks, 1991; Meyer 2001). Vaccines can 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 dogs, bovine serum albumin (BSA), which is included as a vaccine excipient, is responsible for many of these acute reactions (Ohmori et al., 2005a, 2005b) and thus manufacturers have worked to reduce the content of BSA in canine vaccines; BSA might also cause acute reactions in cats. Indeed, in Japan, severe VAAEs after vaccination in cats were examined from 316 cases reported to the authorities during a 15-year period, with 130 cats (41%) showing anaphylaxis, and in 99/130 cats (76%) anaphylaxis resulted in death; it was suggested that high levels of BSA in the commercially available feline vaccines indicated insufficient purification (Yoshida et al., 2022).

Such reactions might occur on the occasion of first vaccination of a kitten; however, an animal that developed a hypersensitivity reaction to a vaccine does not necessarily develop a reaction to the next vaccine (Brooks, 1991). 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 whenever possible; a greater risk of developing adverse reactions has been associated with a higher number of applied vaccines (Moore et al., 2007). If appropriate, non-adjuvanted modified live (MLV) vaccines should be used instead of inactivated (killed) adjuvanted products because the latter are more likely to be associated with hypersensitivity reactions (Gershwin, 2018). If possible, a different vaccine formulation (or product from a different manufacturer) is recommended instead of 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 (up to 30) minutes prior to vaccination. After vaccination, predisposed animals should be kept under observation in the clinic for a few hours and watched then at home by the owners (Moore and HogenEsch, 2010; Richards et al., 2006; Sykes, 2022).

4.2. Type II hypersensitivity reactions

Type II hypersensitivity is considered an autoimmune reaction and is the result of binding of antibodies to host cells. Cell-bound antibodies can 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 (Gershwin, 2018). 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 FPV, FHV, and FCV 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). Since vaccine strains are commonly produced in CRFK cells cellular antigens might be included in the vaccine. Antibodies recognizing CRFK cells were shown to also react with feline renal extracts. However, neither clinical signs nor abnormalities in urinalysis or biochemical blood parameters were observed in any cat (Lappin et al., 2005). In one study, frequent or annual vaccination was identified as one of two risk factors 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.

4.3. Type III hypersensitivity reactions

Type III hypersensitivity reactions are rarely documented in cats in association with vaccination (Moore et al., 2007). Type III reactions are characterized by antigen-antibody complexes that induce an acute inflammatory response after deposition in the capillary beds of certain tissues (Day and Schultz, 2014). Polyarthritis after FCV infection, which is characterized by lameness and fever, and sometimes after vaccination has been suggested to represent a type III reaction. However, co-infection with FCV field virus or, rarely, vaccine virus, seem to be the main causes of this syndrome (Bennett et al., 1989; Dawson et al., 1994).

4.4. Tpe IV hypersensitivity reactions

Type IV hypersensitivity reactions (delayed-type hypersensitivity) are also rarely documented in cats in association with vaccination (Moore et al., 2007). They are considered to result primarily from cell-mediated, cytotoxic immune responses, rather than from an antibody response to a specific antigen. Thus, type IV hypersensitivity reactions differ fundamentally from type I, type II, and type III hypersensitivity reactions (Day, 2006; Day et al., 2007). Upon exposition to a sensitizing antigen, memory Th1 cells are produced; re-exposure leads to the reactivation of these cells and an inflammatory response (typically after 24 to 72 h) by the release of proinflammatory cytokines (Day et al., 2007). Granuloma formation might occur (Day and Schultz, 2014), characterized by accumulations of immune cells, which is the hallmark of type IV hypersensitivity (Mak and Saunders, 2006). Granulomatous inflammation after vaccination has also been demonstrated in cats (Day et al., 2007).

5. 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. It has been suggested that 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 FPV vaccine: although not proven, mild immunosuppression induced by vaccination could have facilitated the development of fatal salmonellosis in kittens carrying the pathogen (Foley et al., 1999).

6. Lack of efficacy

Under some circumstances, lack of efficacy is also considered a VAAE. The majority of these are likely to reflect inappropriate storage and administration of the vaccine which is considered poor ‘vaccine husbandry’ (Day et al., 2016; Luff and Solebout, 1997a, 1997b), 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

In cats, VAAEs appear to rarely occur. However, limited information on the type and prevalence of VAAEs in cats is available, with the exception of the induction of FISS. Lethargy, with or without fever, is the most commonly diagnosed VAAE (Gaskell et al., 2002; Moore et al., 2007). Some risk factors have been identified (Moore et al., 2007). The risk for VAAEs was found to be greater in neutered *versus* entire cats, female *versus* male cats of the same neuter status and in cats up to one year of age. The factor associated with the greatest increase in risk was the number of concurrently administered vaccine antigens or the total vaccine volume administered. 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.

Practices to ensure maximum vaccine efficacy and precautions to eliminate unwanted adverse effects are also described in the ABCD Guideline for Good Vaccination Practices.

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