Adverse reactions to vaccines in cats

Vaccinationsbiverkningar hos katter

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Skara 2014

Djursjukskötarprogrammet
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Studentarbete 537, Skara 2014

G2E, 15 hp, Djursjukskötarprogrammet, självständigt arbete i djuromvårdnad, kurskod EX0702

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Nyckelord: cat, adverse reaction, vaccine, feline injection site sarcoma, adjuvant.

Serie: Studentarbete/Sveriges lantbruksuniversitet, Institutionen för husdjurens miljö och hälsa, nr. 537, ISSN 1652-280X

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| 1. Introduction |
| 2. Aim |
| 3. Materials and methods |
| 4. Results |
| 4.1 The immune system |
| 4.2 Types of vaccines |
| 4.3 Population immunity |
| 4.4 Adverse reactions |
| 4.5 Minimizing the risks of adverse reactions to vaccines |
| 4.6 Client communication |
| 5. Discussion |
| 5.1 Incidence reports and adverse reactions |
| 5.2 Change in routines |
| 5.3 Client communication |
| 5.4 Materials and methods |
| 6. Conclusion |
| 7. Populärvetenskaplig sammanfattning |
| Thanks |
| References |
Abstract

There is a debate concerning adverse reactions following vaccination of companion animals which has been ongoing for years. Every year a number of suspected vaccine-associated adverse reactions are reported to the appropriate government administrations across the world. Many of these are mild, such as lethargy and irritation at the injection site but some are more severe in nature, namely feline injection site sarcomas and anaphylactic shock. The cause of injection site sarcomas is not completely clear. However, studies have shown that they are often preceded by a severe inflammatory response in the tissue following an injection. Though this may be caused by any type of injection, vaccines containing adjuvants, specifically those containing aluminum, cause a more severe inflammatory response. Though rare, these severe reactions spread fear and doubt amongst cat owners concerning the safety and necessity of vaccines. It falls on the veterinary staff to fight these fears and doubts with facts and preventative measures. It is easy to lose sight of the dangers of a disease which, thanks to strong population immunity, is rarely seen. It is important that owners understand the benefits of vaccinations and the true risks of withholding vaccination from their pet. When fewer individuals in a population receive vaccines, the disease which was rare before may emerge again, causing suffering and death. The few risks associated with vaccinations can be avoided, if not entirely then at least in part. For example the ‘vaccine load’ on each individual animal can be decreased by individual risk assessment. In Sweden vaccinations are routinely given in the interscapular region as the incidence of fibrosarcomas are very low. If they were to become more common a change in routines may be in order as fibrosarcomas in that area are incredibly difficult to treat. Instead routines suggested by the World Small Animal Veterinary Association (WSAVA) could be implemented. These state that vaccines should be administered in the lateral abdomen region to facilitate excision of sarcomas. Also, non-adjuvanted vaccines should be chosen for cats when possible to further reduce risks of FISS developing. These changes in routines would not be able to eliminate the occurrence of adverse events but may serve to reduce the risk of the individual patient and improve the prognosis of individuals developing fibrosarcomas.
1. Introduction

Every year most of our companion pets are taken to the veterinary practice for their annual vaccinations. In most cases things go well and the patient returns home with its owner with no need of further veterinary care. However, some patients may experience adverse reactions to a vaccine and may need medical treatment.

The most common adverse reactions to vaccines are type I hypersensitivity reactions (anaphylaxis-hypersensitivity) such as vomiting and lethargy, followed by localized vaccination-site reactions (Frana et al., 2006; Moore et al., 2007; Tjälve, 2011; Tjälve et al., 2013). A rare but severe adverse reaction which mainly affects cats is Feline Injection-site Sarcoma (FISS), also called fibrosarcoma (Gobar & Kass, 2002). Unfortunately FISS is extremely hard to treat and many cats do not survive (Séguin, 2002; Martano et al., 2011) which may lead owners to choose not to vaccinate their cats for fear of them developing the disease.

Over the years there has been an increase of media coverage pertaining to adverse reactions to vaccines in human patients. During the 1990's the MMR vaccine against measles, mumps and rubella was thought to cause autism in small children. This sparked a big debate whether vaccinations were safe, or indeed needed (Yarwood, 2006). This debate has now moved over to the veterinary practice in the U.S. where laymen, owners and some veterinarians are beginning to wonder if the benefits of annual vaccinations can hold up to the risks of adverse effects. There are papers advising against vaccinating our companion animals, urging for titer-testing before vaccinations and warning pet owners about dangerous additives, mainly adjuvants, in vaccines which may harm our companion animals. Adjuvants are substances, such as aluminum hydroxide (Hammer et al., 2014), which in different ways improve or potentate the immune system’s reaction to a pathogen (Singh & O’Hagan, 2003). Though some studies have shown that specific adjuvants may be connected to an increased risk of adverse reactions (Gobar & Kass, 2002) such as Feline Injection-site Sarcoma (FISS) (Hendrick et al., 1992; Doddy et al., 1996), new research shows that this is not the case (H. von Euler, personal message, 2011 ).

Nevertheless, when there is a good overall protection against a disease we are more likely to forget the risks of the disease and instead focus on the risks of the vaccine (Yarwood, 2006; Moore et al., 2007). This may cause owners to choose not to vaccinate their companion animal (Yarwood, 2006). For vaccines to have the desired effect “herd immunity” must be achieved, where susceptible individuals are indirectly protected by the immune individuals of the population. A vaccine coverage of >70% of the population is considered necessary for reaching “herd immunity”. Coverage below this will decrease the effectiveness of vaccination on disease spread and susceptible individuals will have an increased risk of succumbing to the illness (Horzinek, 2006).

It is important that veterinary nurses who administer vaccines are aware of the fears pet owners may have so they can offer facts about vaccinations with which to calm these fears as well as informing them about the risks a loss of 'herd immunity' present.
2. Aim

The aim of this paper is to discuss which information is important for the veterinary nurse to impart on a client as well as how veterinary practitioners can minimize the risks of adverse reactions occurring. It will also aim to give the reader an increased understanding of what happens in the body following a vaccination and which, if any, risks it may entitle. The paper will provide an overview of the natural immune response to a vaccine, different vaccine types, the different adverse reactions which may occur following a vaccination and their possible causes.

The following questions will be answered:

- How does the immune system respond to a vaccine in the cat?
- Which adverse reactions may occur following a vaccination of the cat, and what is thought to be the cause?
- Which adverse reactions do we need to inform our clients about?
- How can the risks of adverse reactions be minimized?
- Which is the situation in Sweden today concerning adverse events?
3. Materials and methods

This paper was written as a literature study where the information gathered from peer-reviewed studies and review articles were compiled. All information was gathered from books and papers through the SLU library at the Swedish Agricultural University in Skara, Sweden or search engines such as ScienceDirect, Primo, PubMed and GoogleScholar. The search words used were: cat, adverse reactions, vaccine, injection-site sarcoma, benefits, communication, herd immunity. Some references were attained through referenced studies in review articles.

The search results were narrowed down by limiting the search results to journals from the veterinary field.

A total of 39 articles were found, 7 of these were discarded. Three articles were discarded as they did not refer to the veterinary field. Two articles contained outdated information and another two articles were not considered scientific as they contained no references. A total of 32 articles were used in this literature study.
4. Results

4.1 The immune system

The immune system’s primary function is to protect the animal from harmful microorganisms and foreign substances that could cause illness (Colville, 2008). It does this by releasing antibodies to fight the intruders. They detect antigens and destroy them while recognizing the difference between antigens and organisms native to the body. If something causes the immune system to collapse or be overpowered this would lead to the animal becoming ill. The immune system protects the body both by non-specific immunity and specific immunity (Colville, 2008).

Non-specific immunity does what the name indicates; it mounts a general response to an antigen (Colville, 2008). The first line of defense is the skin and mucosa which keeps foreign material out of the body. When that line of defense is breached and cells are invaded by antigens an inflammatory response is initiated and inflammatory mediators such as histamines and cytokines are released. Histamines serve as signals for white blood cells to move to the site of infection (Colville, 2008). Cytokines are released by specific T-cells called helper T-cells. The activity of other T-cells is stimulated by these cytokines. Macrophages, neutrophils and monocytes attack the infected cells, destroying them by phagocytosis or lysis (Colville, 2008). In case of viral infection the cells are destroyed by natural killer cells. During the non-specific immune response macrophages will ingest the antigen through phagocytosis and later present it to T-cells, which are part of the specific immune response (Colville, 2008).

The specific immune response is much more exact and is divided into cell-mediated immunity and humoral immunity (Colville, 2008). Cell-mediated immunity involves T-cells which attack the antigen directly. Before arriving at the site of infection T-cells are processed in the thymus where they develop one specific antigen receptor. In order for T-cells to be able to attack the antigen a macrophage must present it with the antigen after ingesting it (Colville, 2008). The T-cell will then become a sensitized T-cell which will clone itself into cytotoxic cells which attack the antigen directly. Humoral immunity involves B-cells which either become memory cells or produce antibodies that circulate in the plasma, destroying the specific antigen (Colville, 2008).

4.1.1 Passive and active immunity

There are two kinds of immunity; passive immunity and active immunity. Passive immunity is achieved by the animal receiving already formed antibodies. This means that the animal itself hasn’t created them (Colville, 2008). It occurs in utero when antibodies from the dam are passed through the placenta to the fetus, by ingestion of colostrum or by intravenous infusion of plasma rich in antibodies. In cats and dogs the ingestion of colostrum provides almost all the antibodies needed for the development of passive immunity (Hammer et al., 2014). The neonate would not survive without them as its’ own immune system is not yet fully developed. As the animals own immune system hasn’t been invoked yet, it will only be protected by its’ passive immunity for a short while (Colville, 2008; Hammer et al., 2014). This means that there are no memory cells that know which antibodies to produce and thus the animal lacks protection against infections in the future (Colville, 2008).

The effect of a vaccine on a puppy or kitten is influenced by the amount of protection it has from its passive immunity (Hammer et al., 2014). A strong passive immunity will interfere with the immune system’s reaction to a vaccine as the acquired maternal antibodies will respond before the immune system does, rendering the vaccine ineffective
(Hammer et al., 2014). The amount of colostrum ingested and absorbed, how rich in antibodies the colostrum is as well as the speed at which the antibodies degrade within the kitten, are all factors affecting the amount of protection gained from the passive immune system and is as such highly individual (Hammer et al., 2014). It is also impossible to know exactly when the passive immunity is lost (Hammer et al., 2014).

Active immunity is achieved when the animal is exposed to an antigen and memory B or T cells are produced (Colville, 2008). This means that the immune system will be able to remember which antibodies to produce in response to an antigen. The response to an infection can be slow the first time an antigen infects the animal but for the most part it is effective. The response will be quicker and more efficient the next time the same antigen infects the body and the animal often shows no signs of illness (Colville, 2008). Active immunity can be achieved either through natural exposure to an antigen (Hammer et al., 2014) or through injection of a vaccine containing either live, modified-live or killed antigens (Colville, 2008). Natural exposure often leads to the animal becoming ill before achieving immunity (Hammer et al., 2014).

Vaccines strive to create the same protection without causing disease (Terpstra & Kroese, 1996). When vaccinating the immune system responds in the same way as if the antigen infected the animal naturally. Memory cells will be produced and the animal will be protected against the antigen if it comes in contact with it again (Colville, 2008). However, most vaccines cannot stimulate an immunity as powerful as one caused by natural infection without causing illness in the animal. Thus, most vaccines may protect against clinical manifestation of disease but they cannot completely eliminate shedding and virus multiplication (Terpstra & Kroese, 1996).

Puppies and kittens are vaccinated between 6 and 12 weeks of age which is when they are thought to have a weak enough passive immunity for an active immune response to be mounted (Hammer et al., 2014). To be certain that a puppy or kitten develops an active immunity as soon as possible they often receive vaccines every 3-4 weeks until the age of 16 weeks (Hammer et al., 2014). The vaccination will enable it to develop an active immunity where the immune system produces its own antibodies against a specific antigen (Colville, 2008). In adult individuals, depending on the vaccine used, one or two injections with a vaccine are enough to stimulate an active immune response as they no longer have a passive immunity which can interfere (Hammer et al., 2014).

4.2 Types of vaccines

There are several different types of vaccines. Non-infectious vaccines contain either pathogens which have been killed or parts of pathogens. As the name indicates these vaccines do not cause an infection (Hammer et al., 2014). However, the immune response caused may not be strong enough to produce a protective immunity (Shams, 2005; Hammer et al., 2014). The onset of immunity is also slower (Hammer et al., 2014) and the duration of immunity is shorter than for infectious vaccines (Shams, 2005). To compensate for this an adjuvant is used to enhance the immune response (Singh & O’Hagan, 2003). These vaccines are more stable than infectious vaccines (Shams, 2005; Hammer et al., 2014) as well as cheaper to produce (Shams, 2005), but they are more likely to cause adverse reactions, although fairly uncommon (Hammer et al., 2014), which could be partly due to the use of adjuvants (Day et al., 2007).

In infectious vaccines the pathogens have been altered so while they are unable to cause illness, they still infect cells to stimulate an immune response (Hammer et al., 2014). Modified-live vaccines (MLV) and recombinant vaccines are different kinds of infectious vaccines. The immune response caused by infectious vaccines is similar to the one caused
by natural exposure which leads to a more effective and long-lasting immunity than the one caused by noninfectious vaccines (Hammer et al., 2014). Recombinant vaccines can contain organism which have been genetically engineered or are antigen subunits. Multivalent or combination vaccines can use any or all of these approaches (McVey & Shi, 2010).

4.2.1 Adjuvanted and non-adjuvanted vaccines

Adjuvants are substances which can boost the effect of a vaccine in different ways (Singh & O’Hagan, 2003; Hammer et al., 2014). They can speed up the immune response as well as increase the duration, enable weak antigen to provoke a stronger immune response and lower the required dose of antigen in the vaccine, thus lowering the costs of production as well as reducing competition between different antigens in combination vaccines (Singh & O’Hagan, 2003). Examples of adjuvants used in vaccine production are inorganic compounds such as aluminum hydroxide (Hammer et al., 2014) and aluminum salts (alum) (Day et al., 2007), plant based adjuvants such as Quil-A which is acquired from Quillaja saponaria, a Chilean tree (Singh & O’Hagan, 2003), and lipid-based adjuvants (Day et al., 2007) such as Freund’s adjuvant (Bokhout et al., 1981). Another adjuvant used in Sweden is Ethylene/Maleic Anhydride (EMA) (FASS Djurläkemedel, 2014).

A study by Day et al. (2007) showed that regardless if the vaccine contains an adjuvant or not an inflammation characterized by tissue edema and necrosis occurs in the vaccination site following injection. The inflammation caused by non-adjuvanted vaccines was significantly milder that the one caused by vaccines containing adjuvants. In the study a greater inflammatory response was seen when using vaccines containing a combination of Quil-A and alum as adjuvants compared to both non-adjuvanted vaccines and vaccines containing a lipid-based adjuvant. The depth of inflammation response also differed with non-adjuvanted vaccines causing an inflammation confined to the upper subcutis (Day et al., 2007). The study also showed that vaccines with a lipid-based adjuvant caused a slightly deeper inflammatory response in the subcutis. Quil-A and alum adjuvants on the other hand caused a severe necrosis which went deep into the muscle layers below. Both mentioned adjuvants were seen to accumulate inside macrophages at the injection site and remained there for as long as 62 days post vaccination (Day et al., 2007).

4.2.2 Duration of immunity (DOI)

The duration of immunity achieved by a vaccine is part of its efficacy, determining how frequently booster shots are needed (Gaskell et al., 2006). Since the DOI is determined by laboratory studies, which for economic and ethical reasons are short term, only a minimum DOI is shown in the product literature of a vaccine. Thus, for a long time, the general recommendation for booster vaccination has been set at once a year (Gaskell et al., 2006). Ideally DOI should be assessed through field studies but there are many difficulties with such an endeavor, such as owner compliance and sufficient sample size. The results of long term field studies would also be difficult to interpret as it would be impossible to anticipate the number of natural challenges which could boost immunity (Gaskell et al., 2006). DOI is often evaluated by titre testing where antibody titres in serum are measured (Day et al., 2010). This is generally not a reliable way of measuring immunity as the threshold for immunity is unknown for most feline diseases. Titre testing can be used to measure FPV antibodies and thus can determine if vaccination for FPV is needed (Day et al., 2010). However, there is no correlation between titres and protection for FCV and FHV-1 (Coyne et al., 2001). Also, titre levels may differ between different vaccine types dependent on which adjuvant is used and the quality and quantity of antigen used and therefore it is
impossible to create blanket guidelines for vaccination intervals (Coyne et al., 2001). Instead the vaccination interval recommended by the manufacturer should be followed (Department for Environment, Food & Rural Affairs, 2001).

4.3 Population immunity

The degree of protective immunity generated in the host after vaccination is called vaccine efficacy (Terpstra & Kroese, 1996). As vaccine efficacy increases the number of vaccinated animals needed to provide adequate protection decreases (Carpenter, 2001). The effectiveness of vaccination is dependent on the size of the population, the larger the population the more effective vaccination will be in protecting against infection (Carpenter, 2001).

A study by Carpenter (2001) showed that if no animals, in a population of 100, are vaccinated an epidemic can be expected where 90 of the 100 animals are infected. The study also showed that vaccination of even a small percentage of the population (20%) can lower the number of infected animals with between 10 and 53 animals depending on the vaccines efficacy and effectiveness. Thus there are indirect benefits to be gained when vaccinating a population (Carpenter, 2001). Not only are non-vaccinated or susceptible animals at a lower risk of infection as there are fewer individuals in the population who can be infected. Carpenter (2001) also stated that vaccinated individuals who are infected often have a shorter period of shedding as well as shedding a lower amount of pathogens. This means that susceptible animals are at a lower risk of infection, vaccinated or not (Carpenter, 2001).

4.4 Adverse reactions

In Swedish law adverse events are defined as a harmful and unintentional reaction to a veterinary medicinal product which appear in doses normally used in animals for prophylaxis, diagnosis, treatment of disease or to restore, correct or modify physiological functions (3§ Läkemedelsverkets föreskrifter om säkerhetsövervakning av läkemedel som används på djur. [LVFS 2012:15]).

At times concerns for adverse events subsequent to vaccine administration may be greater among owners and veterinarians than for the diseases the vaccines prevent (Moore et al., 2007).

There have been many reports during the years that determine the incidence of adverse events following vaccination in cats (Gobar & Kass, 2002; Moore et al., 2007; Tjälve, 2011; Tjälve et al., 2013). The incidence has ranged from 0.5 adverse events/ 10 000 doses (Tjälve et al., 2013) to 11.8 adverse events /10 000 doses (Gobar & Kass, 2002). Moore et al. (2007) reported an incidence of 51.6 adverse events/ 10 000 cats vaccinated within 30 days of vaccination. Most of the adverse events occurred up to three days after vaccination.

The severity of adverse reactions described in the aforenamed study range from mild (lethargy with or without fever, swelling, inflammation or soreness of the injection site and vomiting), to moderate (facial edema, generalized pruritus), or severe (anaphylaxis) (Moore et al., 2007). Of these, lethargy with or without fever was the most common followed by vaccination-site reactions and vomiting. There is an increased risk of lethargy when administering a multivalent panleukopenia-rhinotracheitis-calicivirus-chlamydia vaccine (Moore et al., 2007). Reactions commonly resolve within 30 days (Gobar & Kass, 2002).

Localized reactions more commonly occurred later in a 30 day period. The occurrence of these reactions does not seem to be related to the use of any specific vaccine (Moore et al., 2007). The diameter of localized reactions is often between 1.5 cm and 3 cm (Gobar &
Localized reactions which grow larger than 3 cm or persist for longer than 3 months should be brought to the veterinarian’s attention (H. von Euler, personal communication, 2012).

There is no clear evidence of any particular cat breeds being predisposed to develop adverse reactions to vaccines (Moore et al., 2007) although recent reports indicate that Ragdoll (Tjälve, 2011; Tjälve et al., 2013) may be slightly more sensitive. In the 2006 vaccination guidelines published by the American Association of Feline Practitioners (AAFP) Burmese and semi-longhair cats are said to develop adverse reactions more often (AAFP, 2006) The weight of the cat may play a part in adverse reactions as cats with weights of >2 kg to 4 kg were more likely to suffer from vaccine associated adverse events than cats with weights of ≤ 2 kg in a study by Moore et al. (2007).

Moore et al. (2007) also found a significant increase in vaccine associated adverse events associated with an increased number of administered vaccines per visit. The study showed that the risk was doubled with 3 and tripled with 5 vaccines simultaneously administered compared to when only 1 vaccine was administered at a single visit. This dose-response relationship was also seen in a study on dogs (Moore et al., 2005a). Reactions also occur more frequently when the vaccine contains adjuvants compared to non-adjuvanted vaccines (Gobar & Kass, 2002).

4.4.1 Anaphylaxis-hypersensitivity
Anaphylaxis-hypersensitivity is one of the most common adverse reactions to vaccines (Frana et al., 2006; Tjälve, 2011; Tjälve et al., 2013) accounting for approximately 40% of adverse reactions (Frana et al., 2006). Anaphylaxis is a type 1 hypersensitivity reaction caused by the interaction between a vaccine component and IgE antibodies (Tjälve et al., 2013) which are linked to allergic reactions (Colville, 2008). It leads to the degranulation of cells causing a release of histamine and other vasoactive amines which leads to a production of inflammatory mediators. Reactions are primarily seen in the skin, GI-tract and airways (Tjälve et al., 2013). Symptoms from the GI-tract like vomiting and diarrhea are among the most common ones seen. Rhinitis, dyspnea, edema and pruritus on the head and paws can also occur (Tjälve, 2011; Tjälve et al., 2013). Sometimes a severe form of anaphylactic reaction, anaphylactic shock, develops (Tjälve et al., 2013).

The onset of symptoms varies between a few minutes up to 2 hours post administration (Tjälve, 2011; Tjälve et al., 2013). Symptoms of anaphylaxis can persist for one to two days, thus adequate monitoring and care must be given to the patient. Repeated treatment with antihistamines, epinephrine and cortisone may be needed (Tjälve, 2011). However, most reactions resolve on their own within a few hours (Tjälve, 2011; Tjälve et al., 2013).

4.4.2 Autoimmune reactions
Lappin et al. (2005) states that Crandell-Rees feline kidney cells (CRFK) were shown to have a propagating effect in feline calicivirus (FCV), feline herpesvirus-1 (FHV-1) and feline panleukopenia virus (FPV) in the 1970’s. CRFK cell proteins are impossible to remove completely from vaccines against FPV, FCV and FHV-1 during production (Lappin et al., 2005). These cell proteins likely persist in some of the commercially available vaccines which are injected into our cats. As the proteins are derived from feline kidneys it is thought that they may cause an autoimmune reaction leading to renal disease (Lappin et al., 2005).

Lappin et al. (2005) studied the effect on antibody production and histological changes in 14 cats after injection with either CRFK cell lysates or a FVRCP vaccine, protecting against FCP, FHV-1 and FPV. The study found that while both the injection with CRFK
cell lysates and FVRCP vaccine induced a production of antibodies against CRFK cells and feline renal cell lysates, none of the cats showed any signs of a subsequent development of renal disease. Neither were any histological abnormalities nor pathological changes detected after a 56-week follow up (Lappin et al., 2005).

4.4.3 Injection-site sarcomas
Feline injection-site sarcoma (FISS) is a serious disease which is very hard to treat as these sarcomas are very aggressive (Séguin, 2002). Between 1987 and 1991 there was a significant increase in reports of fibrosarcomas in Pennsylvania, USA. They were found in common vaccination sites such as the dorsal neck and scapular region as well as the dorsolateral thorax (Hendrick et al., 1992), the interscapular region being the most frequently affected area (Doddy et al., 1996).

The incidence of vaccination-site associated fibrosarcomas was 0.63 sarcomas/10,000 cats in a study by Gobar & Kass (2002). A study conducted by Frana et al. (2006) determined that 82 cats (3.49%) developed fibrosarcomas following vaccination between the years 1999 and 2005. There were no reports of sarcomas developing in vaccination sites in Sweden during 2009, 2010 or 2012 (Tjälve, 2011; Tjälve et al., 2013).

These findings should be seen as reassurance to practitioners and the public as sarcomas are rare (Gobar & Kass, 2002). It is however obvious that of all the cats vaccinated there is a definitive number of cats who will suffer from this disease every year (Gobar & Kass, 2002).

A study by Hendrick et al. (1992) showed that although there is no conclusive evidence that certain vaccines cause fibrosarcomas in cats, a foreign material, composed of oxygen and aluminum, were found within macrophages in fibrosarcomas. One of the common feline rabies vaccines used at the time contained aluminum hydroxide as an adjuvant, possibly explaining the occurrence of aluminum inside the macrophages (Hendrick et al., 1992). Hendrick et al. (1992) argue that the aluminum found within the macrophages caused a persistent inflammation as well as immunological reaction which can cause a predisposition to the forming of neoplasia in the area. Vaccination site sarcomas are often associated with inflammation and necrosis (Hendrick et al., 1992). However, no significant difference in occurrence of sarcomas in vaccination sites compared to non-vaccination sites has been found (Doddy et al., 1996). Fibrosarcomas form in between 3 months and 3 years post vaccination (Hendrick et al., 1992).

Unfortunately, the outcome of fibrosarcoma is often death although there has been great progress in the treatment of the disease (Séguin, 2002). Despite this, treatments used today have not been shown to be effective enough against the tumors pathogenesis and infiltrating nature (Martano et al., 2011). The best prognosis is achieved with a multimodal treatment of surgery, chemotherapy and irradiation (Séguin, 2002).

4.5 Minimizing the risks of adverse reactions to vaccines
An important aspect to keep in mind is that the risk of vaccinating shouldn’t exceed the risks of the disease (Shams, 2005). Therefore an individual assessment should be made for each vaccination where a strategy is chosen based on the environment in which the animal lives as well as the potential risk of exposure to infectious diseases (Shams, 2005).

Practitioners should assess the individual risks for each patient and only administer vaccines where there is a need (Moore et al., 2007). Day et al. (2007) argue that it may be recommended not to administer a vaccine to the same site as a previous vaccine within too short a time frame as an inflammatory response may still be ongoing at the site. Thus it is important to keep this in mind when administering the second dose of vaccines to a kitten.
since there is evidence that inflammations at the injection site may persist for several weeks. Injecting at the same site may increase the inflammatory response as well as the changes caused in the tissue following the first vaccination (Day et al., 2007).

Since FISS’s have been seen in injection sites after injections with any pharmaceutical products the use of adjuvanted vaccines may not play as critical a part in the forming of fibrosarcomas as once believed (Woodward, 2011). Instead the wounding of an injection, in combination with inflammation may be a contributing factor in sarcomagenesis (Woodward, 2011). Thus, when several vaccines are needed, it may be beneficial if as few injections as possible were administered (Moore et al., 2007). One way to achieve this is to use one syringe for more than one vaccine. In a study by Brunner et al. (2006) it was determined that injecting a MLV vaccine with chlamydial components (Nobivac® Forcat) combined with a recombinant FeLV vaccine (Nobivac® FeLV) using one syringe could be done without a loss of efficacy caused by interaction between the vaccines. The occurrence of adverse effects did not increase when both vaccines were administered within one syringe. The study found no evidence of systemic reactions although there were some local inflammatory reactions seen as swelling. All of these resolved on their own within a couple of days. The swellings found in the study were no more severe than the ones seen after an injection with only FeLV vaccine. Neither did the antigenicity of the vaccines decline; in fact an increased antibody response was seen to the feline herpesvirus-1 (FHV-1), feline calicivirus (FCV) and Chlamydophila felis (C. felis) components in the vaccines due to the adjuvants used in the FeLV vaccines which have an immunostimulating effect (Brunner et al., 2006).

In 2010 The World Small Animal Veterinary Association (WSAVA) published guidelines for vaccinations in cats (Day et al., 2010) where it is recommended to administer vaccines in the lateral abdomen instead of in the scapular region. The same injection site should not be used twice in one occasion and the chosen site should be recorded with sites being rotated each time a vaccine is administered (Day et al., 2010). This would prevent the forming of fibrosarcomas in the interscapular region where removal is difficult due to the tumors infiltrating nature (Hammer et al., 2014). The guidelines state that in the event that a sarcoma forms after administration it would be easier to excise when situated in the lateral abdomen. They also suggest that non-adjuvanted vaccines be used when possible (Day et al., 2010).

The latest edition of guidelines published in 2003 by the Swedish Society of Veterinary Medicine (SVS) and the Swedish National Veterinary Institute (SVA) regarding vaccination of cats and dogs does not cover guidelines concerning the choice of vaccination site. They do however recommend that practitioners inform pet owners about the risks of sarcomas following an injection and that individual vaccination programs should be formulated based on a benefit-risk assessment (Sveriges Veterinärmedicinska Sällskap & Sveriges Veterinärmedicinska Anstalt, 2003). In 2001 similar recommendations were made by the Department for Environment, Food & Rural Affairs (DEFRA) who with the help of a Working Group on vaccine-associated sarcomas released recommendations regarding vaccinations to minimize the occurrence of feline sarcomas following vaccinations. They recommend that a warning against feline sarcomas be placed on the product information of feline vaccines. According to the guidelines it should state that while rare, these sarcomas may develop at the injection site and though any vaccine may cause them, vaccines containing aluminum adjuvants may increase the risk further. These risks should also be brought to the attention of the cat owner at the time of vaccination and should be considered when making a risk/benefit assessment (DEFRA, 2001).
4.6 Client communication

There are many different factors influencing the choice of vaccinating versus not vaccinating which is why it is important to know your audience (Yarwood, 2006). As professionals we need to be aware of what owners need to know in order to make an informed decision. Many pet owners feel strongly about their pet and want to keep them safe and do what is best for them. They want clarity, consistency, facts and openness when making their decision (Yarwood, 2006). Their own experiences, the media view of the vaccine, the owner’s social grade and attitudes as well as their knowledge of the disease and the risk of contracting it can all influence the choice. They want to know about the risks of the vaccination as well as the benefits. They also want to be able to have a dialogue with a professional whom they can trust and who makes them feel that they have been able to explore and voice their concerns (Yarwood, 2006).
5. Discussion

5.1 Incidence reports and adverse reactions

In Sweden there were no reports of sarcomas developing in vaccination sites in 2009, 2010 or 2012 (Tjälve, 2011; Tjälve et al., 2013). However, in the US there was an incidence report of 0.63 sarcomas / 10 000 cats (Gobar & Kass, 2002). Although studies have only hinted at a relationship between vaccine associated sarcomas and rabies vaccines it is likely that the increased inflammatory response caused by the aluminum adjuvant in rabies vaccines increases the risk of fibrosarcomas forming (Hendrick et al., 1996). Thus the difference in development of sarcoma in Sweden and the US may be due to the mandatory vaccination against rabies in the US. To date Sweden is a rabies free country and as such the rabies vaccine is not part of the core vaccines. However, this may change in the future as travelling to and from, as well as smuggling of dogs into, Sweden continues. This would prompt a change in vaccine policies, likely making rabies vaccines mandatory. An increased use of rabies vaccines in Sweden could increase the incidence rate of fibrosarcomas.

The most common adverse reactions were Type I hypersensitivity reactions (Frana et al., 2006; Tjälve, 2011; Tjälve et al., 2013) such as diarrhea, rhinitis, dyspnea, edema and pruritus on the head and paws. In some cases severe reactions such as vomiting and anaphylactic shock may develop. Although they often resolve on their own (Tjälve, 2011; Tjälve et al., 2013), 40% of adverse reactions are labeled as Type I reactions (Frana et al. 2006) and that should not be taken lightly as these symptoms may need treatment with cortisone or antihistamines (Tjälve, 2011).

There were no incidence reports for any auto-immune reactions. The study on auto-immune reactions to vaccines by Lappin et al. (2005) was only conducted on 14 cats during a period of 56-weeks and found no evidence of auto-immunity caused by the vaccine tested. There is a possibility that a study on a larger population would get a different result as the reaction to an injection with CRFK cell lysates on the kidney and the subsequent risk of developing renal disease may be highly individual. Though there may be a risk of auto-immunity developing in cats following administration of vaccines containing CRFK cell lysates, it seems to be incredibly small and there seems to be no need of informing owners about it at this point in time as it would only serve to worry them unnecessarily.

Incidence for less severe adverse reactions is several times higher than for fibrosarcomas which in live, infectious, vaccines could be attributed to the immune response to the antigens in the vaccine, which although not able to cause illness still simulate an immune response close to the one caused by natural infection (Hammer et al., 2014). Adverse events are also common in killed vaccines (Hammer et al., 2014), which is probably caused by adjuvants used (Day et al., 2007). Though, as adjuvants mainly cause an increased inflammatory response at the injection site (Day et al., 2007) it is likely that these vaccines are responsible for the majority of injection site reactions. Those reactions are rarely severe (Moore et al., 2007) and tend to resolve on their own within a month (Gobar & Kass, 2002). However, the inflammation caused may increase the risk of developing fibrosarcomas (Hendrick et al., 1992; Doddy et al., 1996). Thus, when possible a non-adjuvanted vaccine should be used.

The incidence reports published by Gobar & Kass (2002), Moore et al. (2007), Tjälve (2011) and Tjälve et al. (2013) all offer an indication as to which events are most common and how often they occur. Studies conducted in the US may only be based on the reports which have been made to various appropriate government administrations by veterinary
practices or owners, not the ones made to the vaccine manufacturer themselves. In 2005, veterinary practitioners in the US were not required to report adverse events by law and neither were the manufacturers if not specifically asked for a report (Moore et al., 2005b). This means that there may be an unknown number of adverse events in the studies by Gobar & Kass (2002) and Moore et al. (2007) which have not been included in these studies, and which could change the view on the occurrence of adverse events. In Sweden the law demands that any adverse events be reported to the Medical Products Agency by both the veterinarian and the company selling the vaccine (4, 13§ Läkemedelsverkets föreskrifter om säkerhetsövervakning av läkemedel som används på djur. [LVFS 2012:15]). These reports are also compiled and sent to the European database, EudraVigilance Veterinary (Medical Products Agency, 2014). Thus, the studies by Tjälve (2011) and Tjälve et al. (2013) are likely accurate.

A possible concern is the possibility that mild adverse events are not reported by owners as they are not considered severe enough. Some adverse events such as vomiting or diarrhea may also be hard to link to the administration of a vaccine. Owners should be made aware of the importance of any reactions in the cat being reported to the veterinarian, not only for the cat’s safety as it may need treatment, but also for the sake of reports being made to the Medical Products Agency.

5.2 Change in routines
In an effort to keep the occurrence of fibrosarcomas in Sweden as low as they are today, and to reduce the severity of the disease when it manifests, a change in routines may be in order. Studies have shown that the vaccine itself may not be the real cause of fibrosarcomas developing; instead it is the inflammatory response to the tissue damage caused by the needle itself, with adjuvants increasing the inflammatory response, may be at fault (Hendrick et al., 1992; Doddy et al., 1996). This would mean that any injection increases the risk of fibrosarcomas forming, regardless of the type of injected pharmaceutical. As many subcutaneous injections are administered in the interscapular region as it is, it would be good practice not to inject any vaccines in that region as well. Certainly since fibrosarcomas are notoriously hard to remove due to their infiltrative (Martano et al., 2011) and aggressive nature (Séguin et al., 2002).

Guidelines published by the WSAVA in 2010 recommend that vaccines should be administered in the lateral abdominal region. This would facilitate excision and improve the prognosis for patients with FISS (Day et al., 2010). Earlier guidelines published by the AAFP (AAFP, 2006) and the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) (Morrison et al., 2001) suggest that Rabies and FeLV vaccines should be administered in the limbs instead of interscapular due to the risks of fibrosarcomas developing. These recommendations have also been made in a recently published textbook for Veterinary Nurses (Hammer et al., 2014). However, the removal of sarcomas in the limbs may require amputation of the limb. As a practitioner one would have to consider if that is an approach which could be ethical. Excision of a sarcoma in the lateral abdomen would likely affect the cat less than the loss of a limb. Thus the WSAVA guidelines should be chosen over the ones published by the AAFP and VAFSTF. In Sweden all vaccines are administered in the interscapular region (Sveriges Veterinärmedicinska Sällskap & Sveriges Veterinärmedicinska Anstalt, 2003), possibly due to rabies vaccine not being a core vaccine, or a low incidence rate of fibrosarcomas. A change in the Swedish vaccination guidelines may be recommended regarding choice of vaccination sites if incidences were to increase. Although there has been a low incidence rate for fibrosarcomas up until this day, it is impossible to know if it will remain that way. The risk of fibrosarcomas forming
in the interscapular region, the difficulty of treatment and the expected survival rate of the 
animal need to be weighed against the possible difficulty of changing the routines of 
veterinary professionals in Sweden. Also, the question whether the threat is realistic or not 
must be asked. The author foresees no significant disadvantages with following the 
WSAVA’s guidelines in administering vaccines in the lateral abdomen. If a fibrosarcoma 
was to form it would be able to be excised without the risks involved with operating in the 
interscapular region, close to the vertebrae. Although excising the sarcoma may not be 
enough to save the life of the patient, with the fibrosarcoma situated in the lateral abdomen 
there are more options in treatments than if it were situated in the interscapular region.

In the case of an owner being very worried about the risks of fibrosarcomas forming 
non-adjuvanted vaccines could be chosen when possible as they induce a weaker 
inflammatory response at the injection site (Day et al., 2007). This approach is supported 
in the WSAVA guidelines which recommend the use of non-adjuvanted vaccines when 
possible (Day et al., 2010). This is sound advice as adjuvanted vaccines have been linked 
to a more severe inflammatory response at the vaccination site (Day et al., 2007).

Another way to reduce the inflammation at the injection site would be to combine 
several vaccines within one syringe. A study by Brunner et al. (2006) shows that Nobivac 
Forcat (FHV-1, FCV, C. felis and FPV) can safely be combined with Nobivac FeLV 
without a loss in efficacy. This should also be possible with Nobivac Ducat (FHV-1 and 
FCV) and Tricat (FHV-1, FCV and FPV) as they contain the same components as Forcat, 
only with fewer pathogens. Further studies would have to confirm this before it is put into 
practice. It would be ideal if it were possible to safely combine several different vaccines 
within one syringe without interactions between the components or loss of efficacy. This 
would allow for fewer injections, thus causing less tissue damage and its resulting 
inflammation. However, instead a greater inflammatory response could be caused at the 
injection site due to the increased number of pathogens injected. Further studies 
investigating the safety of mixing other vaccines within one syringe are needed before this 
approach should be used.

5.3 Client communication

Yarwood (2006) discusses what a pet owner may need in order to come to a decision about 
whether to vaccinate their pet or not, information being a key factor. However, it is this 
author’s opinion that if too much information is given they might become too informed. 
Many owners only have a slight grasp of their pet’s anatomy, risk of disease, how diseases 
spread and the effect of vaccination. Giving them too much or unnecessary information 
may only serve to confuse and make them unsure. While they should be informed of the 
risks of fibrosarcomas and other adverse effects, it may be best to keep the information 
simple, focus on symptoms and the importance of contacting their veterinary practice if 
any adverse reactions manifest.

It is important that owners are made aware that a veterinarian should be contacted 
immediately if their pet develops symptoms such as urticaria, vomiting, facial swelling, 
dyspnea, diarrhea or seizures (Hammer et al., 2014). Though symptoms such as diarrhea 
and vomiting may seem mild, they may become severe if left untreated. Diarrhea and 
vomiting can result in dehydration (Goddard & Phillips, 2011) which in severe cases can 
lead to hypovolemic shock (Taylor et al., 2011). The animal also loses electrolytes when 
vomiting, which can lead to electrolyte imbalances (Goddard & Phillips, 2011) such as 
hypokalaemia, causing muscle weakness and cardiac arrhythmias (Taylor et al., 2011). 
Thus, these symptoms should not be taken lightly by neither the practitioner nor the owner 
and the animal should be taken to a veterinarian immediately for examination.
It is this author’s belief that owners and practitioners should not only report severe adverse events in need of treatment, but also less severe events such as swelling or lethargy that resolve on their own. This is important in order for results to show the real incidences of different adverse events. If the owner asks for more specific information on adverse events such as fibrosarcomas, their wish should be heeded as keeping information from them could cause them to lose trust in veterinary professionals but care should be taken not to instill more fear of the disease.

Other concerns the author foresees are owners travelling with their pets as well as the transport of pets over borders for sale, practices which are becoming more common, which increase the importance of good protection against transmittable diseases. The owner of an animal must understand the importance of immunization not only for the protection of their own pet but also for the protection of others as the efficacy of a vaccine program increases as more animals are vaccinated, giving protection to susceptible individuals in the community. At least 70% of the population needs to be vaccinated for there to be a good protection against disease (Horzinek, 2006). Some may say “if everyone else vaccinates their pet, I don’t have to”. This may be true, but one should not forget the great number of stray cats living in our forests or on our streets. Certainly many of them have never received a vaccination and therefore may spread disease to our own cats. This is, of course, mainly a threat to outdoor cats that are likely to come into contact with strays. Indoor cats who rarely leave home, and then mainly when visiting a veterinarian, may not need to be vaccinated against all transmittable diseases our core vaccines protect against. But some pathogens are incredibly resistant, such as feline panleukopenia (FPV) which can survive in the environment for long periods of time and may be brought home to our indoor cats on clothing or shoes (Sveriges Veterinärmedicinska Anstalt, 2013).

5.4 Materials and methods
The aim of this review was to compile the information gathered from studies concerning vaccination and vaccine-associated adverse events and their causes. Information was gathered on the situation in Sweden, UK and the US. A literature study facilitates the compilation of results from various studies and can as such be used as a summary of our current knowledge within the field of vaccine associated adverse events in cats. However, as Sweden is currently a rabies free country, and rabies vaccines may cause more severe adverse reactions, the incidences of adverse events such as FISS may increase following an increase in rabies vaccinations. Also, a literature study may give a limited insight in the subject as studies showing different results than the ones presented in this study may have been overlooked. For example some studies found were not available to the author. It is possible that these studies would have led to a different result of this literature study. Thus this review should only be seen as an indication of the current situation. Instead of or as a complement to the literature study, a survey could have been carried out where owners would have been asked which adverse events they had experienced, if the adverse events needed treatment and if the owners reported the adverse event to either the veterinary practice or the Medical Products Agency. Such a study could give an insight into not only which adverse events owners have experienced in their pet but also into if there are adverse events which are not reported by the owner.

In the future there may also be changes in the vaccines used. Further scientific studies regarding incidences of adverse events as well as the role of specific vaccines in the development of these events will be necessary.

The question of client communication was answered largely by the author. Thus the answer to the question of client communication is highly subjective and coloured by the
authors own experiences, views and values. Furthermore, the review by Yarwood (2006) was derived from the medical field and though it gives an indication as to what owners may want to know, there are no guarantees that pet owners have the same values regarding their pet as parents have regarding their children. However, the review still offers some insight into the important aspects of information needed for owners to come to a decision and thus serves and important function. No studies on the communication with pet owners regarding vaccinations were found. Instead of using the review by Yarwood (2006) this question could have been answered through a study concerning the owner’s wishes regarding communication and information prior to vaccination. Such a study could answer the following questions: “What does the owner want to be informed about in order to make an informed choice regarding vaccination of their pet?” and “What influences the owner’s decision regarding vaccination of their pet?”

This would benefit the veterinary profession, possibly making client communication more successful.

6. Conclusion

Sometimes vaccines cause adverse reactions in animals following administration. Although adverse events do occur most are mild and resolve without treatment. Though symptoms like vomiting and diarrhea may seem like mild symptoms to owners, they can in fact become life threatening. Owners should take their pet to a veterinarian for examination immediately when symptoms are shown as treatment with fluids, antihistamines or cortisone may be required.

Severe adverse reactions such as feline injection-site sarcomas and anaphylactic shock are very rare. Thus there is no need for owners to fear vaccinating their cat.

Not all cats may need vaccination as frequently as they are receiving them today. Individual assessments should be made concerning the risk of exposure, as indoor cats have a significantly lower risk of coming into contact with infectious disease.

In Sweden vaccines are routinely administered in the interscapular region as fibrosarcomas are very rare. If incidences were to increase vaccines should instead be administered in the lateral abdomen, which makes the potential removal and treatment for fibrosarcoma more successful. To further decrease the inflammatory response at the injection site following vaccine administration, Nobivac Forcat and Nobivac FeLV can be combined in one syringe.

When an owner visits the clinic for a vaccination we need to inform them of the possible adverse reactions which may occur. We also need to stress the point that most adverse events are harmless and that the severe ones are extremely rare, but that any reaction following a vaccine should be brought to the attention of a veterinarian.
7. Populärvetenskaplig sammanfattning


Genom att vaccinera ett djur skyddas inte bara det djuret, även populationen som helhet drar fördel av det. Dels innebär vaccination att färre individer i populationen kan bli sjuka, vaccinerade individer sprider dessutom sjukdomen under kortare tid om de blir infekterade. Hur länge immuniteten varar efter vaccination varierar mellan olika vaccin och individer. Det som skrivs ut på produktinformationen är endast ett minimum och immuniteten kan hålla sig längre.

Oro för vaccinationsbiverkningar kan ofta vara större hos djurägare och veterinärer än rädsan för själva sjukdomen. Biverkningar till följd av vaccination är dock mycket ovanliga och endast mellan 0,5-11,8 per 10 000 vaccindoser orsakar en negativ reaktion. De vanligaste biverkningarna är också milda såsom slöhet, svullnad och irritation av injektionsplatsen. Allvarligare symptom som kräkningar, svullnad av ansiktet och klåda kan också förekomma. I väldigt sällsynta fall kan man se mycket allvarliga symptom så som anaafylaktisk chock eller tumörbildningar vid injektionsområdet. De allra flesta biverkningarna visar sig inom 3 dagar och går över av sig själv inom 30 dagar.

Man har sett att antalet vaccin som ges vid ett och samma tillfälle har stor betydelse för biverkningsrisken. Risken förbipassas då 3 injektioner ges samtidigt och tredubblas då 5 vaccin ges jämfört med om endast ett vaccin ges.

Vaccin-relaterade sarkom är en typ av tumör som bildas i vaccinationsområdet, oftast mellan 3 månader till 3 år efter vaccinationstillfället. Det är en väldigt ovanlig sjukdom som endast drabbar runt 0,63 katter av 10 000. I Sverige har inga rapporter om katter som drabbats av sjukdomen inkommit under 2009-2012. Information från rapporter 2011
saknas. Svullnader i vaccinationsområdet som kvarstår efter 3 veckor bör undersökas av veterinär.

Det finns inga tydliga bevis för att vaccin orsakar sjukdomen men i studier har man hittat aluminium i dessa tumörer. Det tros kunna hänga ihop med rabiesvaccinet som användes under tiden för studien då det innehöll aluminiumhydroxid som används som adjuvant. Man tror att aluminiumet kan ha lett till en kraftig inflammation som ökade risken för tumörbildning.

Tumören är mycket svårbehandlad då den växer på ett sådant sätt att den blir svår att operera bort samt är mycket aggressiv. Man kan försöka behandle genom operation, cellgiften och strålbehandling men prognosen är sällan god och avlivning är ofta nödvändig.

Vid vaccinering bör man föra en individuell bedömning gällande behovet då våra katter kan leva väldigt olika liv. En utekatt kommer ofta i kontakt med andra katter och löper därför större risk för infektion. En innekatt som endast lämnar huset för veterinärbesök kan däremot gå hela livet utan att träffa en annan katt och löper därför en mycket mindre risk och behöver kanske inte vaccineras. Ett undantag är vaccinationen mot kattpest då smittan kan överleva utomhus en längre tid och således kan följa med hem på skor eller kläder.

För att undvika biverkningar bör man vara försiktig med att vaccinera kort efter en tidigare vaccination då inflammationen i vaccinationsområdet kan kvarstå i flera veckor. Detta är viktigt att tänka på när man vaccinera kattungar då de ofta får flera injektioner på kort tid. I Sverige ger man vaccin i nackskinnet då förekomsten av sarkom är mycket låg, detta rekommenderas inte i de senaste riktlinjerna från World Small Animal Veterinary Association (WSAVA). Istället rekommenderas det att man vaccinera i flanken då det förenklar avlägsnandet av tumören. Om förekomsten av sarkom ökar i Sverige kan det vara lämpligt att ändra rutiner vid vaccinering vad gäller valet av injektionsplats.

Det är viktigt att djurägare informeras om biverkningarna som kan uppstå och att de omedelbart ska kontakta en veterinär om katten uppvisar symptom så som svullnad i ansiktet, svårighet att andas, kräkningar, diarré, utslag eller krampanfall.

**Slutsats**

Trots att biverkningar förekommer är de ofta lindriga och går över utan att behandling krävs. Allvarligare biverkningar såsom vaccin-relaterade sarkom och anafylaktisk chock är mycket sällsynta. Djurägare behöver därför inte oroa sig för att vaccinera sin katt men de bör informeras om risken. Skyddet som uppnås av en vaccination överväger risken för biverkningar. Vissa katter behöver dock inte vaccineras lika ofta som andra och en individuell bedömning bör alltid göras. Vaccineringer bör ges i flanken istället för i nackskinnet då det innebär att behandling av sarkom blir lättare om de uppstår. När djurägare kommer till kliniken för en vaccination är det viktigt att de informeras om eventuella biverkningar men att man även understryker hur sällsynta de är. Om biverkningar uppstår ska de direkt kontakta veterinären då behandling kan krävas. Om de är osäkra på om de vill vaccinera är det viktigt att man informerar dem om värdet med en vaccination såväl för djuret som för populationen samt risken man utsätter djuret för om man inte vaccinerar. Vaccineringer räddar liv!
Thanks

I want to give special thanks to Ulrika Grönlund, Agneta Gustafsson (MSD), Sara Sundbäck and Malin Carbonnier.
References


Läkemedelsverkets föreskrifter om säkerhetsövervakning av läkemedel som används på djur. (LVFS 2012:15)


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