Today, among the spectrum of vaccine adverse events reported in dogs and cats, feline injection-site sarcoma (FISS) ranks as the most serious. Although it occurs infrequently, the consequences of a malignant tumor developing at a vaccination site are devastating to the patient and owner.

Consider the following facts:

- Tumors linked to vaccine administration are high-grade sarcomas.
- Untreated, affected cats will die from complications associated with the tumor.
- Time from vaccination to tumor development is typically between 3 months and 4 years. A smaller number of tumors develop 5 or more years after vaccine administration.
- Radical excision (3- to 5-cm margins and 2 muscle planes deep), along with radiation therapy, is recommended for tumors arising in skin over the thorax or abdomen. Limb amputation is recommended for tumors at injection sites on a limb.
- Despite aggressive surgery, recurrence rates up to 50% are reported.¹
- Local recurrence is common when simple excision of the tumor is attempted; 86% of recurrences develop within 6 months.¹
- Pulmonary metastasis occurs in 21% of cats diagnosed with grade 3 tumors.²

**HISTORY OF INJECTION-SITE SARCOMAS**

**Association with Aluminum**

Over 20 years ago, pathologists from the University of Pennsylvania reported an alarming 61% increase in the number of injection-site fibrosarcomas among feline biopsy accessions from 1987 to 1991. This increase was epidemiologically linked to the enactment of a mandatory 1987 rabies vaccination law for pet cats residing in Pennsylvania.³ ⁴

Electron probe microanalysis of tumors identified aluminum (commonly used as an adjuvant in feline vaccines) within macrophages surrounding the sarcomas. The hypothesis was advanced, but not proven, that persistent inflammatory and immunologic reactions to aluminum adjuvants might lead to neoplastic transformation in cats.⁵

**Adjuvants Role in Pathogenesis of FISS**

In 1993, an epidemiologic study involving 345 cats with fibrosarcoma provided evidence that vaccination with feline leukemia virus (FeLV) and rabies virus vaccines could lead to tumorigenesis at the injection site, particularly when vaccination was repeatedly administered at the same site.⁶

At the time the study was conducted, all FeLV and rabies virus vaccines licensed for cats in the U.S. were inactivated, adjuvanted products. This fact raised concerns that chronic inflammation caused by adjuvant-containing vaccines, rather than one particular vaccine brand, played a role in the pathogenesis of these tumors.

Since the early days of vaccine-associated sarcoma (now known as FISS) discovery, several studies have been published that characterize tumor pathology, offer diagnostic recommendations, outline treatment options for affected cats, and assess survival rates. However, progress has been remarkably slow when it comes to:

- Understanding the pathogenesis of FISS
- Defining true prevalence
- Mitigating risk.

A brief chronology of FISS is presented in Table 1.
**TABLE 1. Chronology of Feline Injection-Site Sarcoma**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>The first FeLV vaccine (inactivated, aluminum adjuvanted) is introduced (Leukocell, Norden Laboratories).</td>
</tr>
<tr>
<td>1985</td>
<td>Attenuated rabies virus vaccines sold in the U.S. are replaced with inactivated, adjuvanted rabies virus vaccines.</td>
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<tr>
<td>1987</td>
<td>Pennsylvania mandates administration of rabies virus vaccine to pet cats (at that time, all rabies vaccines sold in the U.S. were inactivated and adjuvanted).</td>
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<tr>
<td>1991</td>
<td>Letter from University of Pennsylvania, Surgical Pathology Laboratory, published in JAVMA cites significant increase in sarcoma occurrence at injection sites in cats, suggesting correlation between rabies vaccination and tumor formation.</td>
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<tr>
<td>1992</td>
<td>Hypothesis linking tumor development in cats and inflammatory response to aluminum (adjuvant) at vaccine injection sites is advanced, but unproven; aluminum found inside macrophages around injection-site tumors.</td>
</tr>
<tr>
<td>1993</td>
<td>Evidence links (inactivated) FeLV and rabies virus vaccine administration with tumorigenesis.</td>
</tr>
<tr>
<td>1996</td>
<td>AVMA and AAHA jointly sponsor a meeting, leading to formation of the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) to fund and plan research and promote education and awareness.</td>
</tr>
<tr>
<td>1997</td>
<td>Vaccination-site guidelines recommend administration of rabies in distal portion of right hindlimb, FeLV in distal portion of left hindlimb, and all other vaccines in right shoulder region.</td>
</tr>
<tr>
<td>1999</td>
<td>VAFSTF, in conjunction with Veterinary Cancer Society, recommends “3-2-1 Rule” (see Table 2) regarding diagnosis of suspected sarcomas.</td>
</tr>
<tr>
<td>2001</td>
<td>Government report (UK) on vaccine adverse reactions cites FISS were 5× more likely to develop in cats receiving aluminum adjuvanted (FeLV) vaccines than those receiving nonadjuvanted vaccines. (NOTE: The UK is rabies free and dogs/cats are not vaccinated against rabies).</td>
</tr>
<tr>
<td>2004</td>
<td>VAFSTF discontinued; roundtable discussion published, highlighting the controversies surrounding FISS risk management.</td>
</tr>
<tr>
<td>2009</td>
<td>Study published citing changes in characteristics of FISS (392 cases) subsequent to VAFSTF vaccination-site recommendations: FISS decreased at interscapular sites, but more than doubled in pelvic limbs.</td>
</tr>
<tr>
<td>2012</td>
<td>Study cites cats with FISS were significantly less likely to receive recombinant vaccines than inactivated (adjuvanted) vaccines; study also concluded that no vaccine is risk-free.</td>
</tr>
</tbody>
</table>

**ISSUES & CONTROVERSIES**

Today, the profession still struggles with ambiguous recommendations and controversy over FISS risk management.

**Other Causes of Sarcomas**

Most authors agree that vaccines are not exclusively responsible for inducing sarcomas in cats; implicated causes include:
- Repository corticosteroids
- Long-acting penicillin
- Nylon suture left in the skin for extended periods
- Skin trauma

These observations support the fact that chronic inflammation, due to a variety of causes, may lead to oncogenesis in some cats.

**Roles of Genetics & Adjuvants**

All cats do not share equal risk for vaccine-associated tumorigenesis, which supports a role for genetics in determining FISS risk. Several authors suggest that the adjuvants currently present in all inactivated feline vaccines licensed in the U.S. cause chronic inflammation, which may provoke tumor formation in genetically predisposed cats.

**Vaccine Selection Challenges**

Recommendations to avoid use of inactivated (adjuvanted) vaccines in cats have been met with resistance from the industry. This is not surprising considering the fact that the majority of rabies vaccines sold and administered in the U.S. are inactivated 1-year and 3-year vaccines.

In addition, in the U.S., there is only 1 nonadjuvanted (recombinant) vaccine each for FeLV and rabies virus (only available as a 1-year vaccine). These vaccines are priced higher per dose than adjuvanted (killed) FeLV and rabies virus vaccines, a factor that influences purchasing decisions.

**WHAT IS STILL UNKNOWN**

**Prevalence of FISS**

Published estimates on the prevalence of FISS vary significantly, depending on the study design, numbers of cats in the study, geographic location of the cats, and the fact that injections other than vaccines are known to induce sarcomas.

Prevalence estimates from 1 in 10,000 cats to as many as 1 in 1000 cats have been cited. Studies reporting risk according to doses of vaccine administered/sold also vary (from 1 to as many as 36 cases per 10,000 doses).

Reliably tracking and reporting prevalence, or the proportion of cats in the population that develop tumors subsequent to vaccination, are critical in learning whether...
recommendations to reduce or eliminate risk are effective over time. Tracking prevalence of FISS has proven challenging due to several reasons, including low/inconsistent reporting of FISS, lack of a centralized database, and genetic influence.

Pathogenesis of FISS

Several sophisticated studies have addressed cellular and subcellular changes associated with FISS. Proposed mechanisms tend to center around:

- Chronic inflammation
- Up-regulation of platelet-derived growth factor and subsequent proliferation of fibroblasts
- Mutations in TP53 (so-called “tumor suppressor gene”).

While there is little agreement on the actual role these factors play in the pathogenesis of FISS, it is agreed that the events leading to tumor formation in cats following vaccine administration involve the complex interaction of:

- **Intrinsic factors**, such as individual genetics and nature and degree of inflammatory response following injection
- **Extrinsic factors**, such as type of vaccine administered, frequency of administration, and number of vaccines administered at a site.

What isn’t known is how these factors interact in the individual cat, leading to tumorigenesis.

Predicting FISS

Predicting cancer is an important, emerging field in human and veterinary medicine. The ability to detect mutations in the BRCA1 and BRCA2 genes, for example, allows physicians to identify women at significant risk for developing hereditary breast and ovarian cancer.

Mutations in the TP53 gene of some cats with FISS have been detected in studies conducted at the University of Minnesota. Although these studies suggested potential for assessing genetic predisposition for FISS, there is no commercially available test that will reliably predict which cats will develop tumors.

**Nonsurgical Treatment Options**

If FISS is confirmed, current recommendations consistently cite the role of radical surgery with radiation therapy to prolong survival. It’s the degree of “radical” that obviously impacts the patient’s recovery, postsurgical quality of life, and cost (emotional and financial) to the owner.

Due to the fact that injections other than vaccines can induce tumors in cats, it becomes reasonable to seek nonsurgical treatment and management options to limit the consequences of surgery. At this time, medical treatment of FISS offers limited value to the individual patient, even when combined with radiation therapy.

**MITIGATING RISK FOR FISS**

After over 20 years of causing, diagnosing, and treating injection-site sarcomas in cats, the question that is reasonably asked is: What can a veterinarian do to mitigate the risk for, or limit the consequences of, FISS?

Note that the following succinct review of recommendations has appeared in the literature and been presented at national conferences over the past several years; however, the recommendations have not consistently been subjected to scientific scrutiny and often represent expert opinion rather than results of published studies.

**Only administer vaccines when reasonable risk of pathogen exposure is apparent.**

There is widespread agreement that limiting the number of vaccines administered to an individual over time may reduce the risk for tumor development. For this reason, veterinarians are strongly encouraged to follow current vaccination guidelines for cats.

Among adult household cats that have completed the initial vaccination series, core vaccines (feline parvovirus-herpesvirus 1-calicivirus) should be administered at 3-year intervals. Rabies vaccine should be administered according to state or local statutes and at an interval consistent with the product label. Only administer noncore vaccines to cats with realistic exposure risk.

**Only administer parenteral vaccines by subcutaneous route.**

Intramuscular administration of vaccines does not reduce the risk for FISS. Furthermore, a tumor that develops in skeletal muscle (deep) may be detected later than a tumor that develops in skin (superficial).

**Administer vaccines in accordance with current vaccination site recommendations.**

Current vaccination site recommendations need to be reassessed. Although most veterinarians seem to follow recommendations published by the VAFSTF in 1996 (rabies,
right rear; FeLV, left rear), FISS continue to be diagnosed at the interscapular region. Furthermore, it appears that most veterinarians prefer to administer vaccines to cats at sites above the stifle, not below, and over the right shoulder, rather than below the right elbow, as recommended in current feline vaccination guidelines (Figure, page 54).

Obviously, the recommendation to inject vaccines at distal limb sites is intended to facilitate complete removal of the tumor and minimize the risk of local recurrence, following amputation of the affected limb.

- However, tumors can, and have, developed simultaneously in 2 limbs in the same patient.
- In addition, consistently administering vaccines into distal limb sites results in the administration of subsequent vaccine doses into the same site, which may increase risk for tumor development.
- Concern has also been expressed over the fact that efficacy of licensed rabies vaccines has never been validated in cats inoculated below the stifle.

Educate clientele about reporting postvaccination lumps.

To promote early diagnosis of FISS, advise owners to:

- Observe (by touching or petting) their cats for the development of lumps at injection sites and contact the practice if any lump increases in size or persists beyond 1 month postvaccination.

Manage postvaccination lumps in accordance with the 3-2-1 Rule (Table 2).

When performing a biopsy of an injection-site lump, an incisional rather than excisional biopsy is recommended for at least 2 reasons:

1. Simply excising a small lump (lumpectomy) may complicate efforts to define the original site in the event sarcoma is diagnosed and the owner delays definitive treatment as the incision heals and hair regrows.

2. Most postvaccination lumps are benign. However, if the assumption is made that the lump is malignant and no biopsy is performed, the cat undergoes unnecessary surgery and excessive tissue removal for a lesion that would resolve spontaneously.

Perform routine thoracic radiographs in cats confirmed to have FISS.

High rates of pulmonary metastases in cats with FISS justify obtaining thoracic radiographs (including left and right lateral views) prior to committing the patient and owner to a definitive treatment protocol.

Avoid the use of adjuvanted (inactivated) vaccines whenever feasible.

Adjuvant is a chemical, microbial constituent, or mammalian protein commonly added to an inactivated (killed) viral or bacterial vaccine to enhance the immune response against a selected pathogen. Adjuvants are known to cause local reactions characterized by inflammation, granulomas and, occasionally, sterile abscess formation. Current ly, all inactivated (killed) feline vaccines sold in the U.S. and Canada are adjuvanted. Modified-live and recombinant feline vaccines are not.

The hypothesis linking adjuvant-induced chronic inflammation to sarcoma formation has been suggested by several authors beginning in the early 1990s. Controversy over the role of adjuvant in sarcoma pathogenesis intensified with the publication of a limited number of studies suggesting there was no significant difference in FISS risk posed by adjuvanted versus nonadjuvanted vaccines. No studies have been published that suggest an adjuvanted vaccine is safer than a nonadjuvanted vaccine, with respect to FISS risk.

The controversy surrounding safety of administering nonadjuvanted vaccines over adjuvanted vaccines is likely to continue. The scientific evidence simply isn't available currently to support unambiguous conclusions. The consequence is that cats will continue to be diagnosed with FISS attributed to routine vaccination.

Despite continuing controversy, the fact—that sarcoma diagnoses in cats became more common as the use of adjuvanted vaccines became more prevalent—remains a critical and undeniable piece of information that highlights a potential role for adjuvant in the pathogenesis of FISS. The recommendation to avoid adjuvanted vaccine in cats whenever feasible is justified.

References


(continued on page 26)

TABLE 2. 3-2-1 Rule for Biopsy Diagnosis of Suspected Injection-Site Sarcomas

If a mass meets 1 or more of the following criteria, an incisional (not excisional) biopsy of the mass lesion is recommended.

3: Mass is known to persist for 3 months or longer.
2: Mass is, or becomes, larger than 2 cm in diameter.
1: Mass continues to increase in size 1 month following an injection.