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THE MERIAL MONITOR

E-NEWSLETTER ON INFECTIOUS DISEASE AND PREVENTIVE MEDICINE

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Vaccine Update

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Top 10 Questions
The Transdermal Recombinant Feline Leukemia Vaccine*

Late in 2004, a nonadjuvanted, recombinant feline leukemia virus (FeLV) vaccine (PureVax® Recombinant Leukemia—Merial Limited) was introduced in the United States. This vaccine is the first companion animal biological administered transdermally, without the use of a needle. To date, there is considerable interest in the vaccine's technology and administration. Following are the 10 most prevalent questions concerning this novel vaccine.

1 How is the recombinant canarypox-vectored vaccine different from other FeLV vaccines on the market?

In the United States, there are currently four licensed FeLV vaccines on the market. Two of these vaccines are killed, whole virus vaccines; one is a subunit vaccine that contains selected viral proteins of FeLV. The newest FeLV vaccine is a recombinant canarypox-vectored vaccine. The two killed-virus vaccines and the subunit vaccine are administered parenterally and contain an adjuvant. The recombinant canarypox-vectored vaccine is administered transdermally and doesn't contain an adjuvant.

Both of the killed FeLV vaccines and the subunit vaccine require administering a 1-ml dose subcutaneously or intramuscularly. The recombinant canarypox-vectored vaccine is unique in that the entire vaccine dose is only 0.25 ml.

The canarypox virus used in the recombinant FeLV vaccine is the same vector used in the recombinant feline rabies vaccine (PUREVAX Feline Rabies—Merial Limited) and in the recombinant HIV vaccine still in clinical trials. The recombinant FeLV vaccine uses two key genes of the FeLV subgroup A virus to induce a humoral immune response and a cell-mediated immune response. The canarypox virus transports the FeLV subgroup A *env* and *gag* genes of the FeLV genome into the patient. The recombinant vaccine doesn't contain whole FeLV. The *env* and *gag* genes code for the envelope glycoprotein (gp70) and the capsidal protein (p27), respectively.[1] The robust immune response to the selected genes protected 100% of kittens against a virulent virus challenge. The recombinant vaccine is unique among FeLV vaccines because it induces a cell-mediated immune response as well as neutralizing antibody. With cell-mediated immunity, cytotoxic T lymphocytes destroy FeLV-infected cells, which is critical in protecting cats against the consequences of FeLV infection.[2]

2 Why is it important that the recombinant vaccine is nonadjuvanted?

The recombinant FeLV vaccine is currently the only nonadjuvanted FeLV vaccine available in the United States. This is important because of concerns about the relationship between postvaccinal inflammation associated with adjuvanted, killed vaccines and the risk of tumor development.[3–5]

For more than 10 years, we've known that vaccines, particularly killed, adjuvanted FeLV and rabies vaccines, will cause cancer—especially fibrosarcoma—in some cats.[6] Since 1993, estimates indicate that between one in 10,000 and one in 1,000 vaccinates suffer from vaccine-associated sarcomas. There is no evidence to suggest that the prevalence of vaccine-associated sarcomas in cats has declined in the past decade.

A predominant hypothesis today links adjuvant-induced inflammation to tumorigenesis. In fact, the dramatic and well-documented increase in the occur-

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rence of feline fibrosarcoma coincided with the introduction and widespread use of two killed, adjuvanted vaccines—rabies and FeLV—during the mid-1980s. Although specific vaccine brands have never been linked to tumor formation, studies have revealed components of vaccine adjuvant within tumor development sites and postvaccinal granulomas.[7] Inflammation from other causes, such as skin trauma, suture (nylon) left in the skin for extended periods, and repository drugs, has also been linked to fibrosarcoma development.[8,9]

The ability to reduce or eliminate the postvaccinal inflammatory response may be an important step in mitigating the risk of vaccine-associated sarcomas in cats. Current published recommendations for the prevention of vaccine-associated sarcomas include using only nonadjuvanted vaccines in cats.[5]

One study compared postvaccinal inflammatory responses to various killed, adjuvanted rabies and FeLV vaccines with responses to a nonadjuvanted FeLV vaccine and saline.[3] Adjuvanted vaccines containing aluminum produced local inflammation most consistently. Nonadjuvanted (recombinant) vaccines, which were comparable to saline, produced no postvaccinal inflammatory response.[3,10]

3 Does the recombinant FeLV vaccine stimulate a better immune response than a killed vaccine?

To date, there are no studies comparing the immune response induced by the killed FeLV vaccines with that of the recombinant, transdermal FeLV vaccine. While we can't state that one vaccine is better than another, the immune responses induced by these two vaccine types are different.

Killed, whole virus vaccines produce neutralizing antibody to protect against FeLV infection. This humoral immune response will neutralize circulating virus but isn't effective against virus integrated into host cells. Killed FeLV vaccines aren't known to induce protective cell-mediated immunity.

To survive, all retroviruses, including FeLV and feline immunodeficiency virus, must fuse with the cell membrane of the selected cells, especially lymphoid bone marrow stem cells, and deposit viral RNA into the cytoplasm.

Once a cell is infected, the FeLV viral genome enters the cell nucleus, where it integrates into the host's DNA. This process represents the most intimate form of parasitism known. Once integrated into host DNA, the virus transcribes, or codes for, new viral RNA. The newly formed viral RNA leaves the cell, incorporating proteins from the cell wall, making new FeLV. After leaving the cell, the newly formed FeLV is free to find new cells to infect.

In short, the humoral immunity, or antibody, is effective against circulating FeLV. But antibody isn't effective against virus-infected cells. Cell-mediated immunity, on the other hand, is effective.

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The recombinant FeLV vaccine induces both humoral and cell-mediated immune responses. The activation of cytotoxic T lymphocytes—fundamental to cell-mediated immunity—is especially important in achieving a comprehensive postvaccinal immune response to FeLV infection.

4 Does the recombinant vaccine offer a longer duration of immunity?

For all of the commercially available FeLV vaccines, including the recombinant vaccine, manufacturers recommend annual boosters in cats that have received the initial two-dose series. Durations of immunity for FeLV vaccines haven't been shown to extend significantly beyond 1 year. Additionally, FeLV vaccine manufacturers and the American Association of Feline Practitioners (AAFP)–Academy of Feline Medicine (AFM) Advisory Panel on Feline Vaccines do not stipulate a duration of immunity for any FeLV vaccine longer than 1 year.

5 Why do I need to administer the recombinant FeLV vaccine by the transdermal route versus conventional needle and syringe?

For more than 3 years, a recombinant FeLV vaccine (Eurifel® FeLV—Merial Limited) has been used in Europe and the United Kingdom as a parenteral vaccine—a 1-ml dose administered subcutaneously. However, there are some important advantages to administering the vaccine transdermally.

One advantage is the volume per dose. When administered transdermally, a 0.25-ml volume per dose stimulates an immune response that is the same as, or better than, the response from vaccine deposited under the skin or into muscle.

Second, and perhaps more important, the transdermal injection system actually disperses the recombinant FeLV vaccine into the skin, subcutaneous tissue, and muscle. The immunologic impact of this stems from the ability to consistently deliver vaccine antigen into the skin—the location where antigen processing is known to be particularly effective.

Some readers may recall the introduction of the human diploid cell vaccine for rabies. Initially, two administration routes were offered: 1 ml intramuscularly or 0.1 ml intradermally. One-tenth of the same vaccine, effectively administered by the intradermal route, induced a protective immune response. (The 0.1-ml intradermal route was discontinued after studies showed significant inconsistency in technique when administering an intradermal vaccine with a needle and syringe.) Using the transdermal administration system offers precise, consistent delivery.

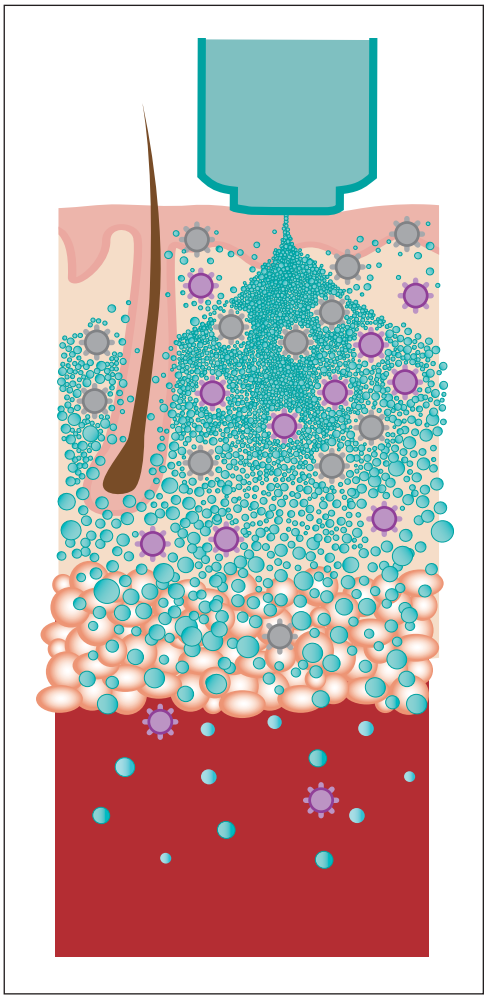

Figure 1. *Transdermal administration disperses vaccine through immune-cell–rich tissue.*

Intradermal administration enhances the immune response because the skin is unique in its ability to process antigen. Dendritic cells, also called antigen-presenting cells (APCs), are abundant in skin as well as lymph nodes and mucosal surfaces. Dendritic cells form a lattice-like network within the skin, where they increase antigen trapping efficiency and maximize contact between dendritic cells and lymphocytes. Excellent reviews of antigen (vaccine) processing by dendritic cells have recently been published.[11,12]

6 How does the transdermal administration system work? Is it like the air gun the military used several years ago?

While the general concept is similar, the transdermal administration system is much improved over the earlier air-pressure injection systems the military used for mass inoculation programs. Those earlier devices, in fact, are no longer used.

The current transdermal administration system (Vet Jet™—Merial Limited) has been engineered specifically for cat skin, considering such factors as skin thickness and haircoat. Once the 0.25-ml volume of vaccine is loaded into the transdermal vaccination system, a nozzle/piston assembly delivers the vaccine through an orifice equivalent to a 36-gauge needle, about the diameter of a human hair. The dose is administered in less than 0.3 second. The transdermal vaccination system's life span is about 3,000 doses. At the end of the device's life span, the vaccination system is designed to lock so it can't deliver vaccine.

Note: There is a short learning curve to use the transdermal vaccination system correctly. It's not complicated, just different. Veterinarians and veterinary technicians must learn proper loading and injection techniques before vaccinating patients.

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7 Do the current recommendations to administer rabies vaccinations on the right and FeLV vaccinations on the left, as low on the leg as practical, still apply?

Yes, but not entirely. The Vaccine-Associated Feline Sarcoma Task Force published recommendations regarding vaccination sites in cats.[13,14] They state that no vaccine should be given in the interscapular space. Rabies vaccines should be administered subcutaneously in the distal right rear leg. FeLV vaccines should be administered subcutaneously in the distal left rear leg, and all other vaccines should be administered subcutaneously in the right shoulder.

Note that these are task force recommendations only and there is no legal precedent that mandates compliance. In fact, in the author's opinion, these recommendations need immediate revision for at least two reasons:

- One study assessed the effect of administering multiple vaccinations simultaneously at the same site.[6] It found that vaccine reactions were additive, and the likelihood of fibrosarcoma development increased with the number of vaccines given simultaneously in the same site. While vaccines aren't typically given simultaneously in the right or left rear legs, this study raises the concern over repeated vaccinations in the same site, even if administered annually. Obviously, it isn't possible to rotate vaccination sites when injecting in the distal rear leg. There simply isn't sufficient surface area to work with year after year.
- The recombinant transdermal FeLV vaccine should not be administered as low on the leg as possible because this may elicit a painful response (see question 8). Instead, administer the vaccine over the middle of the lateral left thigh at a point behind, not directly over, the femur. With this change, I recommend following the task force guidelines.

8 How do cats typically respond when the recombinant FeLV vaccine is administered transdermally?

Observations from veterinarians across the United States suggest three types of responses:

No response. The injection port is extremely small—equivalent to a 36-gauge needle—and the volume per dose is small—0.25 ml. That, and the quick administration time of about 0.3 second, may explain why transdermal FeLV administration is well-tolerated.

An alerting response. The needle-free injection device elicits an audible noise described as a click when properly loaded and activated. Some cats will turn their heads, some may jump, and some may try to move away. The noise may be loud enough to startle some cats and is likely responsible for the alerting response during inoculation. Veterinarians have successfully employed creative distraction techniques to prevent these responses, including a diversionary noise or a visual distraction, such as a feather. Note: Some veterinarians report that the activation noise occasionally startles owners. I recommend informing owners of the click before activating the transdermal system.

Pain. Veterinarians occasionally report a painful response at the injection site. This response is immediate and associated with the vaccine penetrating the skin. Such responses are not sustained. While some sensation can be expected at the inoculation site, a properly administered vaccination shouldn't be extremely painful. Further examination into the cause of pain has revealed some possible explanations:

- Not holding the injector firmly against the skin.
- Administering the vaccine over the distal femur or stifle. The transdermal FeLV vaccine wasn't intended to be administered close to the distal femur or stifle. Because the injection is intended to penetrate skin, subcutaneous tissue, and muscle, positioning the transdermal device over bone will likely cause the vaccine to impact the periosteum. While this isn't dangerous, it may be painful.
- Incompletely filling the injection nozzle and administering vaccine with air. Once the 0.25-ml volume is drawn up, the nozzle should be carefully examined for air. Drawing vaccine into the nozzle while holding the injection device horizontally may introduce air into the nozzle, causing a painful response when injected. Holding the injection device vertically when drawing a vaccine dose into the nozzle substantially reduces the chances of incorporating air into the nozzle.

Drawing and administering the vaccine properly will eliminate the possibility of painful injection.

9 Can I use other vaccines with the transdermal injection system? And can I use a needle or syringe to administer the recombinant FeLV vaccine?

No to both questions. At this time, the recombinant canarypox-vectored FeLV vaccine is the only vaccine that has received USDA licensure for transdermal administration. While additional vaccines may eventually be licensed for transdermal administration, the immunogenicity of any other vaccine administered by this route can't be assured.

Likewise, administration of the recombinant FeLV vaccine with conventional needle and syringe isn't approved. Doing so may result in a suboptimal immune response. Although a similar vaccine used in Europe and the United Kingdom is administered parenterally, the viral concentration in the U.S. product is different than the concentration in the European FeLV vaccine.

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10 What's the recommended protocol for administering the recombinant FeLV vaccine, and should it be considered core or noncore?

The manufacturer recommends an initial two-dose series at 9 and 12 weeks of age. Thereafter, an annual booster is recommended.

The AAFP–AFM Advisory Panel on Feline Vaccines hasn't convened since 2000, when the latest feline vaccination recommendations were published. Recommendations from the advisory panel regarding the recombinant FeLV are not available. However, it's reasonable to assume that the recombinant FeLV vaccine will be recommended as a noncore vaccine, similar to all other FeLV vaccines currently on the market.

Discussions with practicing veterinarians suggest that because kitten susceptibility to FeLV is so much greater than that of adults, the FeLV vaccination may reasonably be regarded as core in kittens. An initial two-dose FeLV vaccine would be administered to all kittens (a single dose at 9 and 12 weeks) followed by a booster 1 year later. A kitten that will not have contact with other cats (assuming this can be verified) has virtually no risk of infection and will not benefit from vaccination.

Vaccination of adult cats (older than 1 year of age) would then be recommended as noncore, or optional. In this case, annual boosters would be recommended for cats spending unsupervised time outside as well as for cats known to have close contact, especially through bites, with other cats.

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