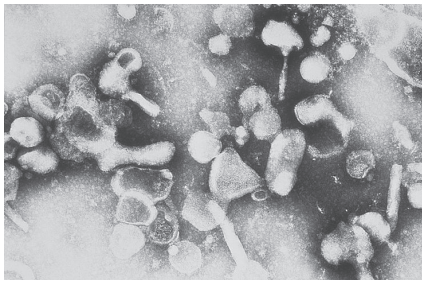
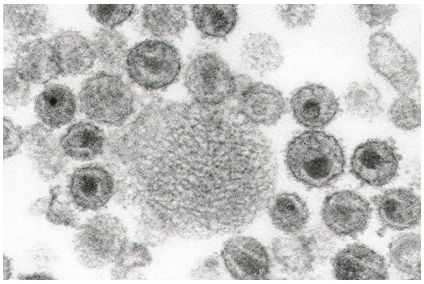
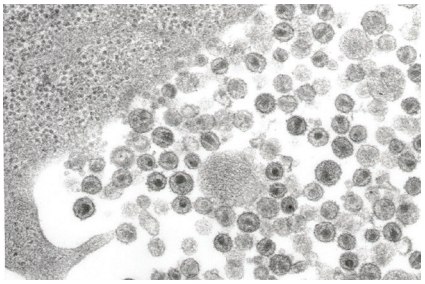
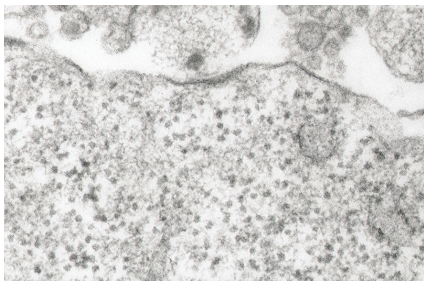
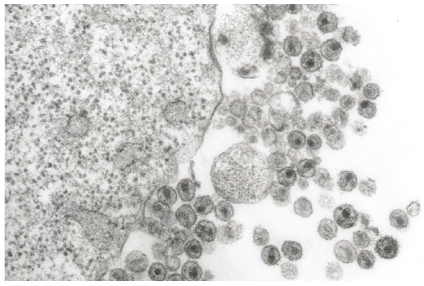
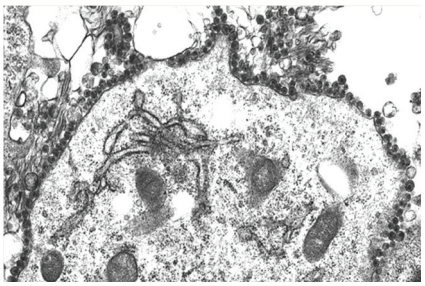
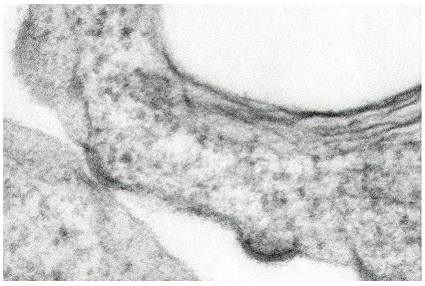
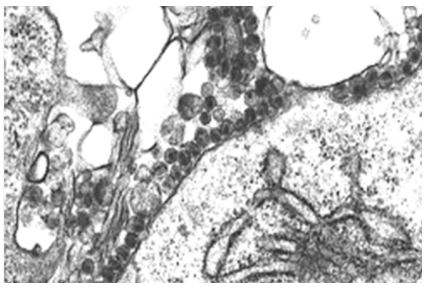
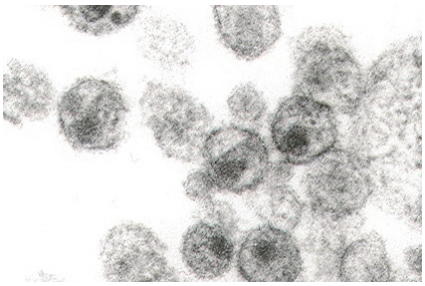
PRACTITIONER'S UPDATE
FELINE RETROVIRUS DISEASE

PRACTITIONER'S UPDATE
FELINE RETROVIRUS DISEASE

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are two of the most important infectious diseases. Information on retrovirus infection in various cat populations shows a prevalence of 2.3-3.3% for FeLV and 2.5-3.4% for FIV in Canada and the United States.[1-4] Studies have highlighted an increased prevalence of retrovirus disease in ill cats, and in cats presenting with bite wounds or oral disease.

Our first issue of **Practitioner's Update**, a series of educational journals for veterinarians, focuses on feline retrovirus disease. Well-respected experts share their expertise by providing up-to-date information on disease management and patient wellness strategies.

This journal provides practical information on feline wellness, client education and retrovirus disease prevention. Our noted contributors offer an in-depth look at evolving perspectives on FIV vaccines, and present the findings of a 2009 study on the seroprevalence of FeLV and FIV infections in Canada. In addition, current retrovirus testing and management guidelines are presented, and a global perspective on feline retrovirus disease is offered, with a report on FeLV and FIV prevalence and disease management in Australia.

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Feline wellness and client education

A discussion with Gary D. Norsworthy, DVM, DABVP (feline)

Annual or semi-annual wellness examinations, annual rabies vaccinations, and client education are all important components in the maintenance of good feline health. The annual vaccine provides an opportunity to see patients on a regular basis, so that any medical problems can be detected early on. Regular visits also help to maintain pet owner compliance with prior recommendations. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are two of the most important infectious diseases worldwide. Prevention and effective management of these retrovirus diseases is essential, particularly for cats at risk of infection such as cats that go outdoors, unsupervised, or cats that live with a FIV- or FeLV-infected cat.

During the check-up, the veterinarian has the opportunity to review the cat's medical history, assess disease risk (by considering factors such as whether or not the cat has contact with cats outdoors), evaluate the cat's oral health, and identify any potential signs of illness. Dr. Norsworthy says that during patient exams, he discusses his findings with the pet owner, while a technician enters this information into a computer. At the end of the exam he explains the cat's medical condition and provides appropriate recommendations such as tests, vaccines, or procedures. He also performs an annual ECG on his patients to screen for cardiac abnormalities.

Retrovirus disease prevention

The 2008 American Association of Feline Practitioners (AAFP) feline retrovirus management guidelines recommend that FIV vaccines be considered for cats whose lifestyle puts them at high risk of infection, such as outdoor cats that are at risk of bite wounds. FIV vaccines may also be considered for cats living with FIV-infected cats. Dr. Norsworthy says he does not generally perform annual retrovirus testing and vaccination on low-risk, indoor cats.

The guidelines highly recommend FeLV vaccination for all kittens because of potential frequent lifestyle changes. Prevention is also recommended for cats at risk, including cats permitted outdoors, those in multiple-cat households, and cats living with a FeLV-infected cat. FeLV vaccination is also highly recommended for shelter cats in grouped-house shelters or foster homes but is not generally recommended for shelter cats that are individually housed.

Addressing concern about injection-site associated sarcomas

Dr. Norsworthy says that in his practice 11,000 adjuvanted vaccines were administered over a seven-year period with no sarcomas reported. Thirty thousand modified live virus vaccines yielded only one sarcoma. Based on these findings, he says there is no difference in his mind between modified live versus adjuvanted vaccines with regard to injection-site associated sarcomas.

FIV vaccine management and compliance

For his patients, Dr. Norsworthy recommends an initial series of three FIV vaccines. To help simplify the process and thereby improve compliance, he charges the client for all three vaccines at the outset and has the technician deliver the second and third doses so that the client is in and out of the clinic quickly. With this approach he has found compliance to be around 95%. An annual FIV booster is recommended after the three initial vaccines.

Testing kittens for FIV and FeLV

Dr. Norsworthy recommends feline retrovirus testing for all kittens regardless of where they were obtained. Kittens that have incurred bite wounds, and all outdoor cats, should be tested for FIV periodically throughout their lives if they are not FIV vaccinated. They should also be tested before FIV vaccination. If a cat or kitten with an unknown vaccination status tests FIV antibody positive, it should immediately be tested with the new IDEXX PCR-FIV test for confirmation. Newborn kittens infected via FeLV-positive queens may not test positive for weeks to months after birth. If a queen or any one of her litter of kittens tests FeLV-positive, all should be considered potentially infected and isolated, with follow-up testing performed. Kittens with any chronic disease are at high risk, as are outdoor cats with illness or fever.

Signs of illness

Illnesses that are often associated with FeLV infection in cats include hematologic disease, lymphoma, and anemia. Common illnesses associated with FIV infection include stomatitis, neoplasia, ocular disease, central and peripheral neurological disease, hematological disease, chronic diarrhea, and renal disease.

Other signs of retroviral infection may include chronic inflammatory conditions, susceptibility to secondary infections, susceptibility to opportunistic infections, skin infections, and oral inflammation.

Preventing transmission in the veterinary clinic

Generally, thorough hand washing, routine disinfection, careful handling of infected bodily fluids, and separate feeding dishes is sufficient to prevent the spread of retrovirus infection within the veterinary hospital. Retrovirus-infected cats should be housed individually to prevent disease transmission, advises Dr. Norsworthy, but they do not need to be isolated in a separate hospital ward. Blood donors should be screened and confirmed negative for retrovirus disease.

Client education

The importance of regular annual exams to identify changes in health should be impressed upon cat owners. Owners should be advised to feed cats a high quality commercial diet and to avoid feeding raw meat and eggs, and unpasteurized milk. Owners should be advised to confine retrovirus-infected cats indoors to prevent the spread of disease to other cats and spay or neuter should be recommended for infected intact cats.

Since FeLV is spread by close intimate contact, often amongst friendly cats, vaccination of any FeLV-negative cats that are in contact with an infected cat is recommended. Although FIV is primarily spread by bite wounds and transmission is less likely in a household where cats are socially friendly, Dr. Norsworthy still recommends vaccination of FIV-negative cats in contact with an infected cat.

Dr. Norsworthy asks owners of infected cats to monitor them closely for potential signs of illness such as changes in social interactions with people or other pets, changes in activity level and sleeping habits, changes in food or water consumption, unexpected weight loss or weight gain, or breath odour. Owners are advised to bring the infected cat to the clinic promptly if any of these potential signs of illness are observed. Finally, Dr. Norsworthy makes FeLV and FIV hand-outs available in his veterinary clinic to help cat owners understand feline retrovirus diseases.

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EVOLVING PERSPECTIVES ON FIV VACCINES

JANET K. YAMAMOTO, PH.D.

Background

Feline immunodeficiency virus (FIV) causes infection in domestic cats resulting in acquired immunodeficiency syndrome (AIDS) which resembles immunodeficiency virus (HIV) infection in humans. Both natural and experimental FIV infections cause a major loss of CD3+CD4+ T-cells that precedes a protracted asymptomatic phase followed by a symptomatic phase consisting of immunodeficiency-associated diseases and death.

FIV was first discovered in 1986 from a stray cat cattery, which annually had a high mortality rate caused by immunodeficiency-related diseases. The worldwide prevalence of FIV infection in domestic cats is reported to be 1%-26% in high risk cats and 0.7%-16% in healthy, low-risk cats. Thus, finding an effective FIV vaccine has an important impact in veterinary medicine as well as being a small animal AIDS model for humans.

FIV vaccine development

Work on an FIV vaccine has been underway since the disease was first reported in 1987. One of the central problems facing researchers is the vaccine efficacy against diverse populations, or subtypes, of FIV isolates found worldwide. Although several vaccine approaches have succeeded in protecting against homologous virus, it has been difficult to achieve vaccine protection against strains from different subtypes.

FIV has been classified into five subtypes, and all FIV subtypes have been identified throughout the world, with subtypes B, A, and C having the most global spread and predominance.[1] In contrast, HIV-1 is classified into nine subtypes with over 20 global inter-subtype recombinants or circulating recombinant forms (CRF). Similar to HIV-1, circulating inter-subtype recombinants of FIV have been reported throughout the world with the most frequently described recombinants consisting of A/B, A/C, and B/C combinations. Hence, an effective FIV vaccine should protect cats against predominant circulating FIV subtypes A, B, and C as well as circulating recombinant inter-subtypes of FIV CRF-A/B, CRF-A/C, and CRF-B/C.

Overall, FIV infected cats have a shorter life-span and are prone to recurrent secondary infections, which become resistant to conventional treatments with time. Antiretroviral drugs for HIV-1 such as nucleoside analogs (AZT, 3TC, PMEA) had some effect against FIV in both in vivo and in vitro studies[2,3], while new HIV-1 protease inhibitors and integrase inhibitors have been reported to inhibit FIV infection in culture. Since these drugs are targeted for the use against HIV-1, the majority of these drugs are less efficacious against FIV when compared to those observed against HIV-1. Even after 23 years since the discovery of FIV, there has been no therapeutic antiviral drug specifically produced and targeted as a therapy for containing and eliminating FIV infection in infected cats. In contrast, efforts toward the development of a prophylactic vaccine has advanced much more rapidly by international collaborations and sharing of information through the International Feline Retrovirus Research Symposium. Such international efforts have lead to the development and the commercial release of the first generation dual-subtype FIV vaccine in 2002.

Prototype and commercial dual-subtype FIV vaccines

The effort to develop a prophylactic FIV vaccine began in 1989[4] after the confirmation of FIV pathogenesis in laboratory cats and the characterization of FIV genetic diversity by a number of key feline retrovirus laboratories. Both FIV pathogenesis and genetic analyses have established the similarities of the FIV virology and immunopathogenesis to those of HIV. The production of the FIV strains in established feline cell lines laid the foundation for the vaccine cell lines and the vaccine viruses needed for the inactivated conventional vaccines.

Between 1990-1997, the first FIV vaccine approaches to be tested were the inactivated whole-virus (IWV) and inactivated infected whole-cell (IWC) followed by FIV vaccines consisting of recombinant p24, recombinant gp100, Env variable region-3 (V3)-peptides, recombinant V3-fusion proteins, adenovirus serotype-5 vectored FIV *env*, and feline herpes vectored FIV *env*.[4,5] Single subtype FIV vaccines have been shown to be effective against the same subtype viruses but not against different subtype viruses. As

Fel-O-Vax® RV vaccine and prototype dual-subtype vaccine

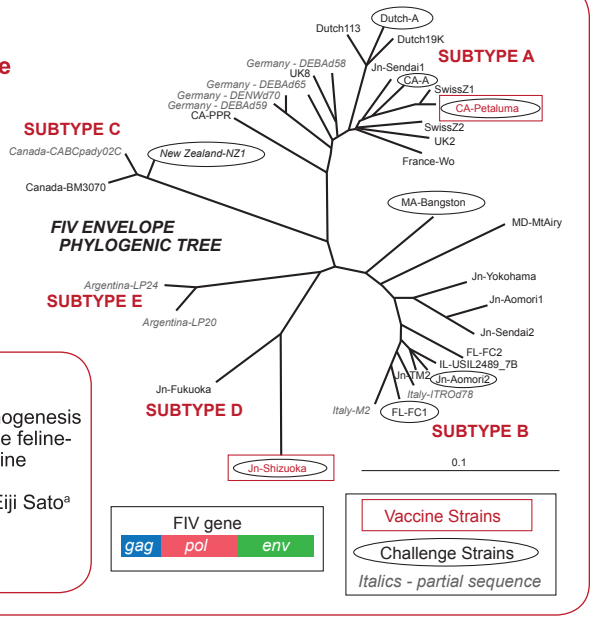
- Fel-O-Vax FIV® Vaccine (FDAH)
  $2x10^7$ FIV-infected cells plus
  50 µg FIV
  (Inactivated Whole-Virus, IWV)
- Prototype FIV Vaccine
  400-500 µg FIV (IWV)

Editorial Review

Feline immunodeficiency virus pathogenesis and development of a dual-subtype feline-immunodeficiency-virus vaccine

Janet K. Yamamoto[a], Ruiyu Pu[a], Eiji Sato[a] and Tsutomu Hohdatsu[b]

AIDS 2007, 21:547-563



well, not all strains were effective as a vaccine virus when used against the same viral strain.

In 1991, work was undertaken to combine single-strain vaccines from different subtypes into dual-subtype and triple-subtype FIV vaccines.[6] Dual-subtype FIV vaccine demonstrated the strongest immunity against homologous-subtype strains and subtype A/B recombinant. The best efficacy was achieved with dual-subtype FIV vaccine consisting of FIV strains isolated from long-term survivor FIV-infected cats. The vaccines containing pathogenic strains were less effective than those containing only non-pathogenic strains, findings which are in line with studies using single-strain vaccines. These observations are supported by the findings of broad antiviral immunity in long-term survivors of less pathogenic HIV-1 infection.

The main challenge that researchers face is developing a vaccine that works against all FIV subtypes. While the FIV genome sequence is related to HIV-1, HIV-2, and simian immunodeficiency virus, its genomic organization and the presence of regulatory genes are similar to AIDS viruses. As with HIV infection in humans, FIV in domestic cats consists of CD4+ T-cell loss which leads to immunosuppression and secondary infections. FIV infects many types of cells, including B cells and CD8+ T-cells, as well as co-receptor cells similar to those reported for HIV-1. The diverse cell tropisms of FIV have made the development of FIV vaccines as difficult as the development of HIV vaccines.

Efficacy trials with commercial and prototype vaccines

The findings from FIV vaccine research have provided insights into the development of effective vaccines for HIV-1 and HIV-2 vaccines. The dual-subtype IWV FIV vaccine is the prototype of the USDA-approved dual-subtype FIV vaccine (Fel-O-Vax FIV® vaccine) released for veterinary use. It was released in Canada in 2003, Australia and New Zealand in 2004, and Japan in 2008. This vaccine consists of inactivated whole-viruses of subtypes A plus D. It differs from prototype IWV vaccine by inducing higher levels of virus-neutralizing antibodies to homologous strains and closely related strains than the prototype vaccine.[7] Vaccine trials undertaken to determine whether the Fel-O-Vax FIV® vaccine is effective against a subtype B FIV isolate demonstrated it to be effective

Table 1. Summary of the prophylactic efficacy for prototype and commercial dual-subtype FIV vaccines

Trial Set	Vaccine(s)	Challenge Virus Strain (Subtype)	Origin	Challenge Inoculum Dose[b]	Route[b]	Protection Rate of Vaccinate (%)	Protection Rate of Control (%)	% Preventable Fraction[a] (p-value)	Reference
Short-Duration Trials									
1	Fel-O-Vax; IWV	Pet (A)	California	20, 50	IV	11 / 11 (100%)	0 / 14 (0%)	100% (<0.001)	8
2	Fel-O-Vax; IWV	Bang (A/B)	Massachusetts	10, 25, 100	IV	14 / 19 (74%)	0 / 19 (0%)	60.7% (<0.001)	8
3	Fel-O-Vax; IWV	FC1 (B)	Florida	15	IV	19 / 21 (90%)	0 / 16 (0%)	90.5% (<0.001)	8
4	Fel-O-Vax+IWV	Pet (A)	California	25	Vaginal	5 / 6 (83%)	0 / 7 (0%)	83.3% (0.008)	8
5	Fel-O-Vax; IWV	NZ1 (F'/C)	New Zealand	50	IV	4 / 9 (44%)	0 / 6 (0%)	44.4% [0.080]	11
6	IWV	UK8 (A)	Glasgow	10	IV	6 / 15 (40%)	0 / 15 (0%)	40.0% [0.065]	11
Long-Duration Contact Trial (boost 1-year [y])									
7A/1y	Fel-O-Vax	Ao2 (B)	Japan	contact cats	contact exposure	6 / 6 (100%)	5 / 8 (62%)	100% [0.282]	10
7B/1.5y	Fel-O-Vax	Ao2 (B)	Japan	contact cats	contact exposure	6 / 6 (100%)	4 / 8 (50%)	100% [0.142]	
Long-Duration Challenge Trials for USDA (no 1-year boost)									
8	Fel-O-Vax	FD/US (A)	CA-USA	1.47[c]	IM	18 / 27 (67%)	9 / 34 (26%)	54.7% (0.009)	19
9	Fel-O-Vax	FD/US (A)	CA-USA	1.79[c]	IM	21 / 25 (84%)	2 / 19 (10%)	82.1% (<0.001)	5
10	Fel-O-Vax	FD/DutA (A)	Netherland	1.73[c]	IM	21 / 24 (87%)	2 / 15 (13%)	85.6% (<0.001)	11
					Trials 1-10 combined results:	125 / 163 (77%)	17 / 153 (11%)	74.1%	

Summary of the efficacy based on % preventable fraction: [a] 74.1% Combined Average

CA-USA Pet (A) - Japan Ao2 (B) > FL-USA FC1 (B) > Netherland FD (A) > CA-USA FD (A) > MA-USA Bang (A/B) > New Zealand NZ1 (F'/C) > Glasgow UK8 (A)

100% 90.5% 85.6% 82.1%[d] (Trial 9) 73.7% 44.4% 40.0%

[a] Percent preventable fraction is defined as [(% infected control - % infected vaccinate) ÷ % infected control] x 100.
[b] Challenge dose shown in mean cat infectious dose, CID_{50}. Challenge routes are intravenous (IV), vaginal, and intramuscular (IM).
[c] The challenge dose was derived from the infection rate of the control group.
[d] % preventable fraction of the CA-USA of FDAH is from Trial 9.

against a subtype B virus (Table 1)[8-10], a subtype reported to be the most common in the United States. It is thought that humoral immunity consisting of virus-neutralizing antibodies may be involved in IWC and IWV vaccine protection against homologous challenge and closely related strains. However, both commercial and prototype dual-subtype FIV vaccines induced little to no virus neutralizing antibodies to distinctly heterologous strains from different subtypes.[7,11] The majority of protected cats had no virus neutralizing antibody titres to the challenge viruses. Therefore, protection against heterologous subtype challenges occurred in the absence or minimal presence of virus neutralizing antibodies, suggesting that such vaccine protection was likely mediated by antiviral cellular immunity. Prototype dual-subtype FIV vaccine was reported to induce strong virus-specific cellular immunity.[12] Recent preliminary studies suggest that commercial FIV vaccine also induces strong cellular immunity.[11] Since both prototype and commercial FIV vaccines contained FD-1 adjuvant, these results demonstrated that FD-1 adjuvant was an important component for eliciting strong FIV-specific cellular immunity. This observation was supported by the findings that prototype FIV immunogen formulated in Ribi adjuvant induced neither high VNA titers nor significant cellular immunity when compared to those formulated in FD-1 adjuvant.[11]

Vaccine effective against natural challenge dose

Varied efficacy to different global subtype viruses (Table 1) may be due to the diversity of the challenge doses used. No vaccines can protect animals against challenge inocula that are significantly higher than the natural exposure dose. For this reason, it is important to identify the transmission dose for natural infection. The closest studies to determine the natural transmission dose were performed by Bendinelli's and Hohdatsu's groups using contact exposure to FIV-infected cats[10,13] (Table 2). Bendinelli's study in Italy used uninfected shelter cats (9 females and 5 males) in a free-roaming facility.[13] This free-roaming shelter facility had naturally infected cats mixed with uninfected cats at a FIV prevalence rate of 52% (FIV incidence rate of 17%). Hohdatsu's study in Japan used unvaccinated laboratory male cats housed in a single room with FIV-infected laboratory male cats. In another small study performed in the United States, three laboratory female cats were housed in a single room with four naturally FIV-infected male cats from California and Hawaii. The infection rate in one year ranged from 14-37% (Table 2), and by 1.5-1.8 years of exposure, 36-67% of cats were infected. The free-roaming facility had a lower transmission rate, which was most likely due to the free-roaming facility providing less contact exposure than the single room system. These results suggested that the natural transmission dose was about 0.29-0.75 mean cat infectious dose (CID_{50}) in one year of contact exposure or an average of 0.48 CID_{50} in one year (Table 2). Roughly 1 in 4 cats, in one year, was infected in a closed housing system. Thus, the challenge doses used in FDAH vaccine trials 8-10 (Table 1) are clearly higher than the natural transmission dose. It is also important to note that the extremely high challenge doses used in the vaccine trials against FIV_{UK8}, FIV_{NZ1}, and FIV_{Bang} (Table 1) could have lowered the efficacy of the prototype and commercial FIV vaccines. Thus, both commercial and prototype vaccines should be effective if the vaccinated cats are exposed to these viruses during natural encounters.

Both Bendinelli's and Hohdatsu's studies also included a group of cats vaccinated with FIV vaccine and commingled with infected cats. Bendinelli's study consisted of 12 cats immunized with inactivated subtype-B FIV_{M2}-infected cell vaccine. In this study none of the vaccinated cats became infected during the 1.8 years of contact exposure. Hence, Bendinelli's study was the first to demonstrate the inactivated infected-cell vaccine approach conferring protection against natural exposure. In Hohdatsu's study (Table 1, trial 7), the efficacy of the Fel-O-Vax® vaccine was tested by exposing both vaccinated and unvaccinated control animals with cats infected with another subtype-B strain, a subtype prevalent in many regions of the world. After one year of commingling, each cat in the vaccinated group was given a booster dose. FIV infection was confirmed as described above in four of the eight animals in the unvaccinated control group by the 29th week in the second year of commingling. In contrast, all of the animals were negative in the vaccinated group. These findings confirmed the efficacy of this vaccine against heterologous strains classified as subtype B, and suggested that the vaccine exhibits broad efficacy against genetically diverse FIV.

Table 2. Deciphering the natural challenge dose

Trial/Study[a]	Years of Contact Exposure	Numbers of Infected Cats (%)	Dose (CID_{50})	FIV Strain(s)
Italy 2000[b]	1	2 / 14 (14%)	0.29	Subtype-B
	1.5-1.8	5 / 14 (36%)	0.72	
Japan 2005[c]	1	3 / 8 (37%)	0.75	Subtype-B
	1.5	4 / 8 (50%)	1.00	(Aomori2)
USA 1988[d]	1	1 / 3 (33%)	0.67	Subtype A
	1.75	2 / 3 (67%)	1.33	& Subtype B
	2.5	3 / 3 (100%)	2.00	
Combined Trials[e]	1	6 / 25 (24%)	0.48	Subtype A
	1.5-1.8	11 / 25 (44%)	0.88	& Subtype B
	2.5	3 / 3 (100%)	2.00	

[a] Contact exposure trials from three countries are shown with either the publication date or the starting date of the trial.
[b] Reference 13.
[c] Reference 10.
[d] Three SPF female cats were housed in a room with four naturally FIV-infected male cats from California and Hawaii starting in 1988 (Yamamoto, unpublished finding).
[e] The data from Italy, Japan, and USA were combined to provide average values for respective years of contact exposure.

Recent studies by an UK group indicated that Fel-O-Vax® vaccine conferred no sterilizing protection against FIV_{UK8}.[14,15] However, the virus load in the vaccinated group was lower than the control group when challenged by intraperitoneal route but not by the intramuscular route.[14] This may be due to the high challenge dose used and the source of the challenge inoculum, which was not described[14,15], but later studies by this group used an in vitro derived cloned FIV_{UK8} inoculum.[16] The use of in vitro-derived inoculum has been reported to alter the virus[17], and consequently the use of cloned virus may also create an artificial scenario. Trial 6 in Table 1 used in vivo-derived inoculum (infected plasma), and the prototype vaccine afforded protection rate of 40% preventable fraction. Thus, at a lower challenge dose (e.g., at least 2x natural transmission dose) and in a contact exposure study or using an in vivo-derived FIV_{UK8}, the commercial Fel-O-Vax FIV vaccine should be effective even against this virus.

Mechanisms of FIV vaccine protection

Both commercial and prototype FIV vaccines induce high levels of virus-neutralizing antibodies to homologous strains and closely related strains. Serum from single-strain IWV FIV_{Pet}-vaccinated cats protected unvaccinated naïve cats against homologous FIV_{Pet} challenge. A preliminary study demonstrated passive protection with serum from commercial dual-subtype vaccinated cats.[11] As well, both single-subtype (FIV_{Pet}) and dual-subtype (FIV_{Pet} + FIV_{Shi}) vaccines induced strong virus-specific cellular immunity, consisting of T-cell immunity. The transfer of whole blood cells from IWV FIV_{Pet}-vaccinated cats conferred protection against homologous FIV_{Pet} challenge in major histocompatability complex-matched recipients, but the transfer from unvaccinated cats did not protect either matched or unmatched recipients.[18] Recent studies demonstrate that the protection against homologous virus challenge as well as subtype-B challenge was conferred by adoptive transfer of B-cell-depleted, T-cell enriched population from major histocompatability complex-matched, dual-subtype vaccinated donors.[1,8] It is believed that dual-subtype vaccine protection against homologous FIV_{Pet} challenge most likely involves both virus-neutralizing antibody immunity and antiviral T-cell immunity. However, vaccine protection against heterologous subtype viruses is most likely the result of antiviral T-cell immunity without virus neutralizing antibody immunity.

Looking forward

The two most important factors in the early development of a commercial FIV vaccine in comparison to HIV vaccines are the availability of the domestic cats for vaccine-challenge trials and the willingness of researchers to use the inactivated vaccine approach for retroviral vaccines. It is important to note that in the last 20 years, there have been no known cases of accidental infection due to improper vaccination of the vaccine virus reported with FIV vaccines. Similarly, since the release of Fel-O-Vax FIV® vaccine in 2002, there has been neither vaccine breakthroughs nor accidental infection caused by the vaccine viruses reported for Fel-O-Vax FIV® vaccine. Currently, the dual-subtype FIV vaccines are being tested in FIV-positive cats to evaluate whether IWV/IWC vaccines are therapeutic. These studies may eventually help to identify the most effective viral antigens for an HIV-1 vaccine.

"It is believed that dual-subtype vaccine protection against homologous FIV_{Pet} challenge most likely involves both virus-neutralizing antibody immunity and antiviral T-cell immunity. However, vaccine protection against heterologous subtype viruses is most likely the result of antiviral T-cell immunity without virus neutralizing antibody immunity."

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Seroprevalence of FeLV and FIV infection in Canada

Susan Little, DVM, DABVP (Feline)

Despite the availability of testing for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), and the availability of vaccines against FeLV and FIV, retroviral infections remain common in Canada and in the United States. Worldwide, FeLV and FIV represent two of the most common and important infectious diseases among cats. The American Association of Feline Practitioners (AAFP) recommends that the retrovirus status of all cats should be known and has published guidelines for retrovirus testing and management.[1] While several studies have evaluated the seroprevalence of FeLV and FIV infection in various populations of North American cats, most of the data is for the U.S.

2009 Canadian study[2]

In order to learn more about the seroprevalence of FeLV and FIV infections in cats in Canada, and to better define ways to prevent these retroviral infections, Susan Little, DVM, DABVP (Feline) and co-authors analyzed signalment, lifestyle factors, and test results for FeLV antigen and FIV antibody for 11,444 cats from the 10 Canadian provinces. They aimed to determine the seroprevalence of retrovirus infection among cats in Canada and to identify risk factors for seropositivity.

The study involved 343 veterinary clinics and 13 animal shelters or rescue organizations. Complete FeLV and FIV test results were received for 11,144 cats, the majority being from veterinary clinics.

In total, 4.31% of cats were seropositive for FIV antibody and 3.44% tested positive for FeLV antigen. Fifty-eight cats (0.52%) were seropositive for both viruses. Significant regional differences were observed. Seroprevalence for FeLV infection was significantly higher in Quebec than in British Columbia and Ontario (6.56%, 2.23%, and 2.57% respectively). Seroprevalence for FIV infection was significantly higher in Quebec than in Nova Scotia (9.32% vs. 2.49%).

Risk factors associated with FeLV and FIV seropositivity included older age and current illness. Adult cats were more likely to be seropositive compared to juvenile cats (4.43% vs 1.69% FeLV; 5.86% vs. 1.56% FIV). Cats with a current illness had a higher probability of testing seropositive than healthy cats (6.61% vs. 1.99% FeLV; 6.67% vs. 3.22% FIV). The probability of a positive test result for FIV was 3.4 times higher in outdoor versus indoor cats; this was 1.4 times higher for FeLV. Finally, the probability of a positive test result for FIV was highest in intact males

2009 CANADIAN STUDY RESULTS

	FeLV	FIV	FeLV + FIV
Seropositive	3.44%	4.31%	0.52%
Older age vs. juvenile	4.43% vs. 1.69%	5.86% vs. 1.56%	
Sick vs. healthy	6.61% vs. 1.99%	6.67% vs. 3.22%	
Outdoor vs. indoor	1.4 x higher	3.4 x higher	
Intact vs. neutered	7.29% intact females; 7.08 intact males	7.43% intact males	

FIV AND FELV PREVALENCE BY PROVINCE

	# of samples	FIV prevalence	FeLV prevalence
Alberta	829	6.43 (n=100)	2.70 (n=42)
British Columbia	1388	2.81 (n=39)	2.23 (n=31)
Manitoba	656	2.90 (n=19)	5.95 (n=39)
New Brunswick	120	0.83 (n=1)	0.00 (n=0)
Newfoundland	300	5.00 (n=15)	4.33 (n=13)
Nova Scotia	603	2.49 (n=15)	6.63 (n=40)
Ontario	5613	3.85 (n=216)	2.57 (n=144)
Prince Edward Island	187	3.74 (n=7)	4.28 (n=8)
Quebec	1266	9.32 (n=118)	6.56 (n=83)
Saskatchewan	182	7.14 (n=13)	2.20 (n=4)

(7.43%), and for FeLV was highest in intact females (7.29%) and intact males (7.08%).

The findings with regard to the seroprevalence for both FeLV and FIV being higher in outdoor versus indoor cats, intact versus neutered cats, adult versus juvenile cats, and in sick versus healthy cats, are in line with similar North American retrovirus seroprevalence studies.[3,4] Bite wounds are an efficient mode of transmission, and are more common in intact cats than in neutered cats, and in cats with outdoor access. Both FeLV and FIV cause immunosuppression and are associated with many feline diseases; it is reasonable that they are more prevalent in sick cats than in healthy cats.

In this study, the seroprevalence of FIV and FeLV was higher compared to a recent similar U.S. study[3] (4.3% vs. 2.5% FIV; 3.4% vs. 2.3% FeLV). In the U.S. study, samples from 325 Canadian cats were included, with a prevalence of 3.1% for FIV and 2.5% for FeLV. The prevalence of co-infected cats was similar in both studies. The difference in seroprevalence may be due to participant recruitment methods; in Canada recruitment focused on centres already known to use retrovirus testing whereas in the U.S. the participants were recruited from a wider pool.

Other aspects of the results must be interpreted with caution, including possible variations in assay sensitivity. Positive results for FeLV antigen and/or FIV antibody obtained by enzyme-linked immunosorbent assay (ELISA) testing should be confirmed with a second test methodology; in the case of FeLV by immunofluorescent antibody test or polymerase chain reaction (PCR) assay and by a Western Blot assay for FIV. Newer PCR tests (e.g., FIV RealPCR™, IDEXX Laboratories) may have a role to play in confirmation of FIV diagnosis in cats that have been FIV-vaccinated or in cats with unknown vaccination history (see page 10). However, these tests require independent validation before the clinical utility is fully known. In this study, positive test results were not confirmed using an alternate assay, so it may be that false positive test results were included in the analysis. Further, FIV antibodies may be detected in uninfected cats that have been vaccinated against FIV[5] and in kittens with passively acquired immunity from an infected or vaccinated queen.[6] FIV vaccination status was not known for cats in this study. However, since veterinarians would be unlikely to test cats for FIV if they were known to be vaccinated, and the population of cats tested by animal shelters/rescue organizations is unlikely to have a high rate of FIV vaccination, the researchers conclude that it seems likely that bias of FIV prevalence caused by vaccination was minimal.

In addition, unadjusted seroprevalence data may be inconsistent due to differing criteria used for selection of cats for testing, despite the existence of testing guidelines. Although veterinarians may recommend testing for all cats, the individual cat owner will ultimately decide whether or not their cat is tested. Although seroprevalence for both FeLV and FIV infection was higher in sick cats than healthy cats, similar to findings in other studies, it may well be that sick cats are simply more likely to be tested than healthy cats. Thus, it may be possible that the rates reported in this study are artificially higher due to selection bias.

"Positive results for FeLV antigen and/or FIV antibody obtained by enzyme-linked immunosorbent assay (ELISA) testing should be confirmed with a second test methodology; in the case of FeLV by immunofluorescent antibody test or polymerase chain reaction (PCR) assay and by a Western Blot assay for FIV."

As well, risk factors for FeLV and FIV seroprevalence should be interpreted with caution because the study participants were not randomly selected. Only owned cats that received veterinary care or stray cats being cared for by a shelter or rescue facility were included. Thus, the findings cannot be extrapolated to the entire Canadian cat population. However, the identification of significant risk factors for FeLV and FIV seropositivity such as age, gender, health status, and lifestyle, are consistent with other studies. These important findings can be used to help counsel cat owners on prevention of disease transmission by, for example, limiting access to the outdoors and neutering.

In Canada and the U.S. testing for FeLV and FIV has been widely available, and vaccines against FeLV have been used for many years. In this recently published Canadian study results suggest, however, that cats in Canada are at risk of retrovirus infection and support current recommendations that the retrovirus status of all cats should be known. In order to improve testing and vaccination rates, veterinarians, animal shelters, rescue organizations, and pet owners need greater awareness of seroprevalence data. In Canada, adoption of the currently available AAFP guidelines for feline retrovirus testing and management is a critical first step.

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The AAFP feline retrovirus testing guidelines can be accessed at www.catvets.org.

Feline Retrovirus Testing and Management Guidelines

Susan Little, DVM, DABVP (feline)

The American Association of Feline Practitioners (AAFP) recommends that the retrovirus status of all cats be known and has published guidelines[1] for retrovirus testing and management. Cats should be tested for both feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) under various circumstances, such as: when first acquired, when exposed to a known retrovirus-infected cat, or prior to initial retrovirus vaccination. Sick cats should be tested even if they have previously tested negative, since studies have highlighted an increased prevalence of retrovirus infection in ill cats. Cats with bite wounds should be tested since bites are a highly efficient means of retrovirus transmission.[2] Oral disease is another common presentation associated with retrovirus infection.[3] Cats at ongoing risk of infection should be tested regularly. Identification and isolation of infected cats is recommended as an effective method for preventing new infections.

Diagnosis of FIV

The detection of antibodies in peripheral blood is used to diagnose FIV. Most cats will produce antibodies to FIV within 60 days of exposure (this can be longer in some cats)[4], and will experience a persistent, life-long infection.[5]

Screening for FIV antibodies using an enzyme-linked immunosorbent assay (ELISA) is the most common method of diagnosis. Patient-side kits are commonly used. Screening for viral antigen is not possible since the amount of circulating virus is low after the acute stage of infection.

Since occasional false positive results can occur with ELISA testing, it is recommended that the Western Blot be used as a confirmatory test, especially in cats considered low-risk. A recent study showed that the sensitivity and specificity for FIV was very high for a commercially available ELISA test kit (IDEXX SNAP® FIV/FeLV Combo).[6] A small number of cats will fail to produce detectable levels of antibodies after infection; these cats will have false negative results with both ELISA and Western Blot testing.

In kittens under six months of age, positive FIV antibody tests must be interpreted carefully since kittens born to infected queens may acquire FIV antibodies in colostrum.[7] It is uncommon for kittens to become infected from the queen and most kittens that test positive are not truly infected. They will usually test negative when re-evaluated at six months of age or older.

Vaccinated cats produce antibodies that cannot be distinguished from antibodies due to natural infection.[6] The availability of the first FIV vaccine (Fel-O-Vax FIV®, Boehringer Ingelheim) has complicated diagnosis of FIV infections. Antibodies due to vaccination persist for more than one year, and are also acquired by kittens nursing on vaccinated queens.[6]

If they have not been vaccinated, cats at risk of FIV infection – such as outdoor cats – should be tested regularly throughout their lives. Cats should also be tested for FIV infection before vaccination.

It may be difficult to determine if a positive antibody test means that a cat is truly infected with FIV, is vaccinated against FIV but not infected, or is vaccinated against FIV and is also infected. IDEXX Laboratories has recently introduced a real-time PCR test for FIV infection (FIV RealPCR™). The company recommends that this test be used only in specific circumstances. Test sensitivity is too low for use as a screening tool, but the specificity as determined by the laboratory is high, making it a potentially useful confirmatory test. The FIV RealPCR™ test is best used for cats that are FIV-antibody positive on screening testing, and that are either known to be FIV-vaccinated or where vaccination history is unknown. A positive FIV RealPCR™ test result is likely to confirm FIV infection, even in a vaccinated cat. However, due to virus genetic variability, a negative FIV RealPCR™ test result cannot rule out FIV infection. As well, this test cannot be used to determine the FIV vaccination status of a cat.

A new discriminant ELISA that can detect a range of FIV-specific antibodies has been developed in Japan and validated in the U.S.[8,9] Researchers using this method were able to distinguish FIV-vaccinated cats from FIV-infected cats with a high degree of accuracy (sensitivity 97%, specificity 100%) when testing serum samples from cats in Canada and the United States. This test could be used as a confirmatory test for cats that are positive for FIV on in-clinic or Western Blot testing. If the discriminant ELISA is negative, the cat is probably vaccinated but not infected. If the test is positive, the cat is truly infected. Unfortunately, it is not commercially available at this time.

Diagnosis of FeLV

Detection of the core antigen p27 in peripheral blood is the basis for diagnosis of FeLV.[4] In-clinic ELISA test kits detect soluble circulating antigen and are recommended for routine use since they have good sensitivity and specificity, are easy to use, contain positive and negative controls, and are affordable. ELISA tests may be used with whole blood, or serum or plasma, although the test kit should be checked for manufacturer's recommendations of the sample type. Tests performed on tears and saliva are not recommended.

ELISA tests can detect FeLV infection early, during primary viremia. Most cats will test positive within one month of exposure, although detection of antigenemia may take much longer in some cats.[10] Immunofluorescent antibody (IFA) tests on smears from blood or bone marrow detect p27 antigen within infected nucleated blood cells and are recommended as confirmatory tests, especially in low-risk patients. However, IFA tests do not detect infection until secondary viremia is established, about 6-8 weeks after infection.

Kittens can be tested for FeLV at any age since passively acquired maternal antibody does not interfere with testing for viral antigen. However, newborn kittens infected via a FeLV-positive queen may not test positive for weeks to months after birth. Kittens that test negative but have a known or suspected exposure to FeLV should be retested one month or more after exposure to rule out false negative results obtained during incubation of the virus. Periodic testing of cats at ongoing risk of FeLV infection is justified and is not compromised by vaccination. Cats should be tested for FeLV before vaccination against FeLV or FIV.

Some cats may be only transiently viremic and may revert to ELISA-negative status. A small percentage of cats have well-controlled, "regressive" infections that are only detectable using PCR. However, a positive IFA test at any time on blood or bone marrow generally indicates a cat is persistently viremic.[11]

It may be difficult to determine the true FeLV status of a cat when results of ELISA and IFA testing are discordant. Most typically, this is an ELISA-positive and IFA-negative cat. The status of the cat with discordant results may eventually be determined by repeating both tests in 60 days, and yearly thereafter until the test results agree. In most cases, these cats are truly infected. Until their status is clarified, cats with discordant test results should be considered as potential sources of infection for other cats.

PCR detects viral nucleic acid instead of antigen and can be performed on blood, bone marrow, and tissues. When performed by a well-equipped and well-trained laboratory, PCR can be the most sensitive test methodology for FeLV. It can resolve cases with discordant test results and detect latent infections. However, veterinarians may not be able to ascertain the diagnostic efficacy of a test offered by a particular laboratory.

Recently, a novel PCR for detection of FeLV viral RNA in saliva has been described.[2] The diagnostic sensitivity and specificity, as well as positive and negative predictive values for the PCR, were very high when compared to conventional ELISA. This study also found that a number of cats who tested negative for FeLV antigen in plasma were positive for FeLV provirus in blood. Most of these cats did not shed viral RNA in saliva and the clinical significance of the FeLV status is unknown.

FeLV and FIV are important diseases in feline medicine. An understanding of diagnostic testing issues and potential pitfalls is essential for the determination of a patient's true retroviral status. Confirmation of retrovirus infection by itself should not be a reason for euthanasia since many retrovirus-infected cats can live good quality lives if provided with excellent health care. Vaccination against retroviruses can be part of a preventative medicine program for cats at risk.

The IDEXX Feline Immunodefiency Virus (FIV) RealPCR™ Test is the first highly specific diagnostic that detects the presence of FIV nucleic acid to confirm active infection. However, a negative FIV RealPCR Test result does not rule out infection. Rather, it can indicate one of three situations: the cat may not be infected, it may be infected but nucleic acid is below the limit of detection, or the cat may be infected with an uncommon strain not currently detected by PCR.

Additional considerations for the FIV RealPCR test

- FIV serology testing, as with the SNAP® Combo Test and the SNAP® Feline Triple™ Test, remains the first-line diagnostic because of its high sensitivity and specificity.
- FIV RealPCR Test should only be considered in serologically positive cats when vaccination history is unknown or when cats have been vaccinated for FIV but infection is still suspected.
- Although the FIV RealPCR Test is highly specific for infection, it cannot "rule out" infection or determine FIV vaccination status.
- Given the limitations of interpretation, the FIV RealPCR Test should not be used to alter decisions regarding FIV vaccination protocol.
- FIV PCR is not recommended as a screening for FIV.

Management considerations

Management of illness in retrovirus-infected cats is similar to that for uninfected cats. However, these patients especially benefit from early diagnosis, prompt identification of illness, and aggressive treatment. Retrovirus-infected cats may respond to treatment as well as uninfected cats, although in some cases, longer or more intensive courses of therapy may be needed. It is important to allow enough time for response to treatment in these patients.

Retrovirus-infected cats should have general wellness exams at least every six months; three times yearly would be preferable. In addition to a thorough physical exam with special attention paid to the lymph nodes, skin, eyes, and oral cavity, a complete blood count, serum chemistries, and urinalysis (cystocentesis collection) should be performed at least once yearly. FeLV-infected cats should have a complete blood cell count at least every six months. Fecal examinations should be performed if the patient is at risk of parasite infection or has signs of gastrointestinal disease.

While there is some debate about "routine" vaccination of healthy retrovirus-infected cats, in general, vaccine selection should be based on individual risk assessments as for any other cat, according to the feline vaccination guidelines established by the AAFP.[12] Although little evidence suggests modified live-virus vaccines are problematic, inactivated vaccines are recommended because live-virus vaccines theoretically might regain their pathogenicity in immune-suppressed animals. Healthy FIV-infected cats have immune responses to vaccination similar to uninfected cats, while some FeLV-infected cats may not adequately respond to vaccination. Vaccination of FIV-infected cats may lead to stimulation of the immune system and subsequent increased FIV replication, although the clinical significance of this observation is unknown.

Retrovirus-infected cats may live for many years in good health and may die from causes unrelated to their retrovirus infection. Retrovirus-infected cats should be confined indoors to prevent disease transmission to other cats and to protect the infected cat from trauma and infectious disease. If possible, infected cats should be isolated from all other cats. Intact cats should be spayed or neutered. Finally, infected cats should be closely monitored for potential signs of illness over their lifetime.

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Feline retrovirus disease: an Australian perspective

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Disease prevalence in Australia and New Zealand for feline retrovirus diseases like feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) are noticeably different from Europe and the United States. Disease prevalence, the availability of certain vaccines, and unavailability of others can give a different perspective to disease prevention in Australia and New Zealand compared to other regions.

Prevalence of FIV

In Australia and New Zealand, older studies indicate a high prevalence of FIV, and newer studies confirm this. From 1988 to 1997, studies demonstrate the FIV prevalence rate to be between 14.4% and 28.0% in both healthy and sick cats. In a 2007 study[1], the FIV prevalence in two feral cat populations in Sydney was 21% and 25%, and the majority of the cats were male (60%-80%). In confined cattery populations, the FIV prevalence was 0% and in pet cats 8%. There was little difference in the prevalence rates between healthy and unwell cats; all of the FIV positive cats were domestic shorthairs with outside access, and the median age was 11 years. Prevalence in male cats (12%) was three times that of female cats (4%).

Recommendations based on the 2007 study findings include the rapid development of an accurate test that is not subject to false positives due to concurrent FIV vaccination, routine screening, and indoor lifestyles.

Prevalence of FeLV

The FeLV prevalence is thought to be low in both Australia and New Zealand, much lower in fact than in the U.S., Canada, and Europe. However, in Western Australia, the prevalence is thought to be higher.

Testing for infection

Controversy surrounds using the Fel-O-Vax FIV® vaccine because vaccinated cats can test positive to conventional antibody tests after vaccination. Because of this, it is strongly advised to microchip any FIV-vaccinated cat. Currently, three polymerase chain reaction (PCR) tests are being validated, and current procedure involves sending samples for PCR confirmatory testing. The techniques and primers used and developed during previous subtype identification studies make researchers feel comfortable with the level of accuracy of PCR tests.

Impact of FIV infection on life expectancy

Prevalence studies show very high infection rates in Australia, but the rates are also significant in the U.S. and Canada. In one U.S. study, 23.9% of cats with stomatitis were positive for FIV and/or FeLV.[2] As well, 19.3% of cats with bite wounds or abscesses tested positive.[3] This might indicate that the quality of life of infected cats can be compromised. A study[2] in the U.S. indicated that life expectancy of cats infected with FeLV and FIV is significantly affected. Six years after infection, only 51% of FeLV infected cats and 65% of FIV infected cats were still alive compared to 90% of the non-infected cat population.

> "Preventing infection is crucial and it can be achieved by keeping cats indoors, testing cats before they are introduced to multi-cat households, and vaccinating them against retrovirus diseases."

Preventing infection

Preventing infection is crucial and it can be achieved by keeping cats indoors, testing cats before they are introduced to multi-cat households, and vaccinating them against retrovirus diseases. Vaccination against FIV is increasingly gaining acceptance in Australia and New Zealand where Fel-O-Vax FIV® (Boehringer Ingelheim) is the dominant feline vaccine sold (20% in Australia and 28% in NZ). To date worldwide, no vaccine breakdown has been reported. The high prevalence of FIV might be a major factor towards implementing vaccination.

Incidence and reporting of adverse reactions

In Australia, Boehringer Ingelheim is responsible for its own pharmacovigilance, and the registration of adverse reactions is reported by veterinarians and pet owners. There is yearly reporting to the Australian Pesticides and Veterinary Medicines Authority.

Approximately 80% of feline vaccines on the Australian market are killed adjuvanted vaccines. However, injection-site sarcomas do not seem to be an issue in Australia.

Recommendations

For cats that are known to have access to the outdoors, veterinarians have a responsibility to discuss vaccination with the owner. As well, it is important to discuss the availability and prevention of disease claim of Fel-O-Vax FIV® vaccine for infection along with the correct protocol for vaccine usage. The veterinarian should also discuss the advantages and disadvantages of vaccine use, and provide the owner with the option to protect their cat from a debilitating and deadly disease.

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