

# Three-Year Duration of Immunity in Cats Following Vaccination against Feline Rhinotracheitis Virus, Feline Calicivirus, and Feline Panleukopenia Virus\*

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## CLINICAL RELEVANCE

Forty-two seronegative cats received an initial vaccination at 8 weeks of age and a booster vaccination at 12 weeks. All cats were kept in strict isolation for 3 years after the second vaccination and then were challenged with feline calicivirus (FCV) or sequentially challenged with feline rhinotracheitis virus (FRV) followed by feline panleukopenia virus (FPV). For each viral challenge, a separate group of 10 age-matched, nonvaccinated control cats was also challenged. Vaccinated cats showed a statistically significant reduction in virulent FRV-associated clinical signs ( $P = .015$ ), 100% protection against oral ulcers associated with FCV infection ( $P < .001$ ), and 100% protection against disease associated with virulent FPV challenge ( $P < .005$ ). These results demonstrated that the vaccine provided protection against virulent FRV, FCV, and FPV challenge in cats 8 weeks of age or older for a minimum of 3 years following second vaccination.

## INTRODUCTION

In recent years, traditional annual revaccination protocols for small animals have come under scrutiny.<sup>1,2</sup> Both the limited scientific data supporting annual revaccination in

adult cats and dogs and the observation of injection-site fibrosarcomas in cats have provided the impetus for this questioning of long-held traditional approaches to vaccination.<sup>3</sup> These concerns have resulted in signif-

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icant debate and thorough analysis regarding whether 1- or 3-year revaccination intervals should be the core guideline in small animal practice.

In light of this dilemma, the American Academy of Feline Practitioners (AAFP), the Academy of Feline Medicine (AFM), the American Veterinary Medical Association's Council on Biologic and Therapeutic Agents, and the American Animal Hospital Association have convened advisory panels to study this subject and related scientific evidence. These organizations have subsequently developed and published their findings and related recommendations.<sup>3,4-7</sup> The 1998 Report of the American Association of Feline Practitioners and Academy of Feline Medicine Advisory Panel on Feline Vaccines and the follow-up 2000 Report of the American Association of Feline Practitioners and Academy of Feline Medicine Advisory Panel on Feline Vaccines were published to help veterinary practitioners appropriately update their feline vaccination protocols based on the most current scientific knowledge.<sup>3,4,a</sup>

The AAFP's 2000 report defined the overall objectives of feline vaccination as to protect the largest possible number of at-risk cats, vaccinate individual cats no more frequently than necessary, and vaccinate only against infectious agents to which individual cats have a realistic

<sup>3</sup>At the time of this writing, the AAFP Feline Vaccination Panel is in the process of updating its 2000 report on feline vaccination guidelines, with publication expected in 2006. James R. Richards, DVM, director of the Cornell Feline Health Center, is the panel's chairman. In addition to providing updates regarding newly approved vaccines, duration of vaccine-induced immunity, and routes of administration, the 2006 guidelines are expected to include information on vaccination of shelter cats and feral cat colonies, as well as vaccine administration tips. Consideration will also be given to differences in European versus US vaccine approval and regulation. (Richards JR: Personal communication, 2006.)

risk of exposure and subsequent disease.<sup>4</sup> In keeping with these objectives, the report highly recommends vaccination against feline rhinotracheitis virus (FRV), feline calicivirus (FCV), and feline panleukopenia virus (FPV) based on the ubiquity and severity of the pathogens involved.<sup>4</sup>

FPV vaccines are believed to be highly effective and offer complete disease protection. In addition, FRV and FCV vaccines are highly recommended by the AAFP to prevent the development of serious respiratory disease.<sup>4</sup> The report also recommends that veterinarians perform individual patient risk assessments to determine the most appropriate antigens and vaccination intervals for each patient based on age, health status, and exposure risks.<sup>4</sup>

In further keeping with its defined vaccination program objectives, the AAFP and AFM Advisory Panel on Feline Vaccines made the pivotal move to begin recommending triennial rather than annual revaccination for these three core feline antigens (FRV, FCV, and FPV).<sup>3</sup> These new recommendations were based on the findings of Scott and Geissinger, which indicated long-lasting titers following FRV, FCV, and FPV vaccination; results of rabies vaccine studies; and information from human medicine.<sup>1,3,8</sup> However, the 1998 and 2000 Reports of the AAFP and AFM Advisory Panel on Feline Vaccines, as well as Scott and Geissinger and other leading academicians, have indicated that additional duration-of-immunity and challenge studies are needed and have encouraged the industry to routinely provide practitioners with this information on all biologics.<sup>1-4,8</sup>

The objective of this study was to use real-time challenge-of-immunity testing methodologies to demonstrate 3-year duration of immunity in cats following second vaccination with a new multivalent, modified-live FRV, FCV, and FPV vaccine.

## ■ MATERIALS AND METHODS

### Cats

Seventy-two specific pathogen-free (SPF) seronegative cats provided by a commercial supplier were used in the study. Queens of the study cats had been housed since birth in highly secure barrier-isolation (Animal Biosafety Level 2) facilities and were not vaccinated against any bacterial or viral pathogens. The offspring test cats were similarly maintained and were neither vaccinated against nor exposed to FRV, FCV, or FPV before participating in the study.

Blood samples (via jugular venipuncture) and oropharyngeal, conjunctival, and rectal swab samples were collected from each cat on the day of first vaccination to determine their

3-year study period. Cats affected with serious unrelated medical or physical issues were either removed from the study until recovery or euthanized. For the FPV challenge, an additional 10 nonvaccinated kittens (10 to 12 weeks of age) were included to demonstrate that the challenge with FPV was sufficiently severe (it was expected that 3-year-old cats would be naturally more resistant to the challenge).

### Test Vaccine

The new multivalent modified-live virus test vaccine contained modified-live *Chlamydia psittaci* as well as the three feline-origin attenuated virus components (FRV, FCV, and FPV) of Continuum Feline HCP (Intervet). None of

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## *The geometric mean antibody titers for FCV and FPV remained at high levels throughout the 36-month period.*

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susceptibility to FRV, FCV, and FPV. Cats were determined to be susceptible to FRV and FCV based on virus neutralization (VN) antibody titers less than 1:2 and by the absence of viral isolates in oropharyngeal swab samples inoculated onto monolayers of Crandell–Reese feline kidney (CRFK) cell cultures. Susceptibility of cats to FPV was determined based on VN antibody titers of less than 1:2 and by the absence of viral isolates in rectal swab samples inoculated onto monolayers of CRFK cell cultures.

The average age of the cats was 58 days at first vaccination and 87 days at second vaccination. At study inception, cats were randomly distributed via standard methods into vaccinated (42) and nonvaccinated (30) groups and maintained in isolation. Cats were fed standard growth or maintenance cat chow rations, and water was available ad libitum throughout the study. Veterinary care and treatment for non-study-related health issues were provided throughout the

the virus antigens used in the vaccine formulation were grown on CRFK cells.

The viral vaccine components were produced at maximum virus passage level from the master seed virus. At the time of each vaccination, five replicate titrations of each vaccine component were performed. For each component, the geometric mean of the five replicate titers was calculated and used to establish immunogenicity levels.

The test vaccine was formulated at minimum protective titers, lyophilized in single-dose vials, and stored at 4°C until use. This vaccine was presented in a desiccated form with 1 ml of sterile diluent used for reconstitution. The vaccine contains gentamicin as a preservative.

### Vaccination Protocol

At 8 and 12 weeks of age, the 42 seronegative cats assigned to the vaccinated group re-

ceived a 1-ml dose of the test vaccine (desiccated vaccine reconstituted with sterile diluent) via subcutaneous injection in the intrascapular region. The remaining 30 cats served as nonvaccinated controls.

### Serologic Assays

Before each vaccination and every 1 to 6 months throughout the 36-month postvaccination isolation period, blood samples from each vaccinated cat were assessed for the presence of FRV, FCV, or FPV antibodies via serum neutralization (SN) testing methodology. Geometric mean antibody titers for all vaccinates were calculated at each of these intervals.

Blood samples from all nonvaccinated control cats were similarly assayed via SN testing methodology at the time the other cats were vaccinated and at 12 and 36 months after the vaccinated cats received their second vaccination. In addition, blood samples from five to 10 control cats from each challenge control group were assessed using SN testing for presence of FRV, FCV, and FPV antibodies every 1 to 6 months after second vaccination. The 10 kitten controls used in the FPV challenge group were tested just before FPV challenge.

In addition, blood samples for serologic testing purposes were collected from all cats and kittens involved in the FPV challenge before the challenge, and the cats were monitored for 14 days after the challenge to determine individual white blood cell (WBC) counts. Three-day baseline counts were recorded for all cats before the challenge. Serum samples were drawn twice daily (12 hours apart) on postchallenge days 3 through 8. Sera were submitted to an independent laboratory for WBC analysis. As specified in 9 CFR § 113.304, leukopenia was defined as a decrease in WBC count to below 4,000/mm<sup>3</sup> or less than 25% of the normal levels established by an average of three or more WBC counts taken before the challenge.<sup>9</sup>

### Challenge Protocol

This challenge–efficacy study was performed in compliance with 9 CFR §§ 113.304, 113.314, and 113.315 specifications required to obtain a vaccine license from the USDA.<sup>9</sup> Animal husbandry and challenge procedures were performed in compliance with institutional animal health and welfare specifications.

All cats were strictly isolated for 3 years (36 months). Before the challenge, the 42 vaccinated cats were randomly divided into two subgroups using standard methods:

- Cats in the first vaccinate subgroup ( $n = 22$ ) were challenged sequentially with virulent FRV (SGE strain, intranasal challenge) and FPV (ICK strain 33, intraperitoneal challenge).
- Cats in the second subgroup ( $n = 20$ ) were challenged with virulent FCV (strain 255, oronasal challenge).

Unvaccinated control cats were randomly assigned to three subgroups of 10 cats each. Each subgroup was challenged with either FRV, FPV, or FCV.

After the 36-month postvaccination isolation period, all cats in the vaccinated and designated nonvaccinated subgroups were transferred from isolation to challenge facilities. The remaining control subgroups were kept at the isolation facilities until needed for their respective challenges.

In the vaccinate groups, FRV, FCV, and FPV challenge protocols were performed using Center for Veterinary Biologics–Laboratory viral challenge strains. All cats were anesthetized before the challenge.

For each viral challenge, 10 age-matched nonvaccinated control cats were also challenged. Control cats were not challenged sequentially.

To demonstrate the severity of the FPV challenge, an additional 10 seronegative control

**TABLE 1. Geometric Mean Titers in Cats after Second FRV, FCV, and FPV Vaccination**

<i>Virus Component (Assay)</i>	<i>Before Vaccination</i>	<i>Months after Vaccination</i>								
		<i>1</i>	<i>3</i>	<i>6</i>	<i>9</i>	<i>12</i>	<i>18</i>	<i>24</i>	<i>30</i>	<i>36</i>
FRV (SN)	<2	13	5	4	2	3	2	2	2	2
FCV (SN)	<2	≥432	≥90	≥330	≥1,730	≥548	≥231	≥1,608	≥3,124	≥2,416
FPV (SN)	<2	≥4,096	≥4,096	≥4,096	≥4,096	≥4,096	≥4,096	≥4,096	≥4,096	≥4,096

SN = serum neutralization titer test.

kittens, 10 to 12 weeks of age, were also challenged with FPV because it was expected that the 3-year-old cats would be naturally more immune to challenge.

Daily clinical examinations were performed on all study cats 3 days before each challenge and during the 2-week postchallenge observation period. Clinical signs pathognomonic for the particular virus infection were recorded daily. Cats were evaluated using the relevant clinical signs scoring system. Cats challenged with FPV were also monitored for development of leukopenia for 2 weeks after the challenge.

### Statistical Analysis

The total clinical scores for the postchallenge period were analyzed using SAS Version 8.2 (SAS Institute, Cary, NC). This analysis was used to determine significant differences between vaccinated and nonvaccinated control cats following FRV, FCV, and FPV challenges. Differences in disease incidences were tested using Fisher's exact test. Differences in the severity of clinical signs were tested using the Wilcoxon rank sum test. Disease criteria evaluated included fever, dehydration, depression, ocular and nasal discharge, sneezing, dyspnea, salivation, and oral, lingual, and nasal ulcers following FRV challenge; fever, ocular and nasal discharge, and oral, lingual, and nasal ul-

cers following FCV challenge; and leukopenia following FPV challenge. Differences in data analyzed by statistical methods were considered significant at  $P \leq .05$ .

## RESULTS

### Serologic Tests

All cats were seronegative for FRV, FCV, and FPV on the day of initial vaccination as determined by SN titer evaluation. After the second vaccination, serum antibody titers for FCV, FRV, and FPV were measured throughout the postvaccination isolation period. The geometric mean antibody titers for FCV and FPV remained at high levels throughout this 36-month period. Thirty-six months after vaccination, the geometric mean antibody titers among vaccinates was 1:2 for FRV, 1:2,416 or higher for FCV, and 1:4,096 or higher for FPV (Table 1).

Although FRV titers were low numeric values, previous studies using various FRV vaccines have demonstrated that any detectable antibody titer (1:2 or higher) is sufficient to provide substantial disease protection.<sup>1,8,10,11</sup> These previous findings were corroborated by our challenge study results, which indicated that the vaccinated cats demonstrated a statistically significant reduction in severity of clinical signs following FRV challenge for at least 3 years after the second vaccination.

**TABLE 2. Cumulative Mean Clinical Scores in Cats after FRV Challenge**

<i>Test Group</i>	<i>No. of Cats</i>	<i>Cumulative Mean Clinical Score</i>
Vaccinates	22	23.5
Controls	10	33.6 <sup>a</sup>

<sup>a</sup>Statistically significant difference ( $P = .015$ ).

**FRV Challenge Results**

After the FRV challenge, all cats exhibited clinical signs of FRV, including fever, dehydration, depression, ocular and nasal discharge, sneezing, dyspnea, salivation, and oral, lingual, and nasal ulcers. However, as seen in Table 2, the severity of clinical signs after the challenge was significantly greater in control cats than in vaccinated cats ( $P = .015$ ). This result is consistent with reports from other investigators in which FRV vaccination reduced the severity and duration of clinical signs following FRV challenge.<sup>8,10,11</sup>

**FCV Challenge Results**

Severe clinical signs of FCV, including fever, ocular and nasal discharge, and oral, lingual, and nasal ulcers, were seen in 100% of control cats on postchallenge days 5 through 10. In contrast, no oral, lingual, or nasal ulcers were observed in any of the vaccinates. A significant difference was seen between the number of vaccinates and controls exhibiting oral ulcers following challenge ( $P < .001$ ; Table 3). Two of 20 vaccinated cats developed slight ocular discharge of short duration ( $\leq 2$  days). Fifteen of 20 vaccinated cats developed mild fevers of short duration ( $\leq 2$  days) after the challenge. Other investigators have reported similar results following FCV vaccination in cats, in which the FCV vaccine reduced the severity and duration of clinical signs following challenge.<sup>8,10,11</sup>

**TABLE 3. Incidence of Oral Ulcers in Cats after FCV Challenge**

<i>Test Group</i>	<i>No. of Cats</i>	
	<i>Total</i>	<i>Ulcers</i>
Vaccinates	20	0
Controls	10	10 <sup>a</sup>

<sup>a</sup>Statistically significant difference ( $P < .001$ ).

**FPV Challenge Results**

Because older cats are naturally more resistant to challenge, two control groups including 10 age-matched cats and 10 seronegative, 10- to 12-week-old kittens were used to evaluate the severity of the FPV challenge. After intraperitoneal challenge, clinical signs of FPV were not observed in any test cat. Leukopenia, defined in accordance with 9 CFR § 113.304 as a WBC count of less than 4,000 WBC/mm<sup>3</sup> or less than 25% of the normal level as established by a 3-day prechallenge baseline,<sup>9</sup> appeared in 100% of both adult and kitten controls. In contrast, no vaccinated cat demonstrated leukopenia ( $P < .005$ ; Table 4).

**DISCUSSION**

The most important finding of this study is that the modified-live components in this new vaccine provide protection against virulent FRV, FCV, and FPV challenges in cats 8 weeks of age or older for a minimum of 3 years following second vaccination. The defining feature of this study is the fact that real-time challenge-of-immunity data are provided rather than serologic data alone. The significance of this study to practitioners results from the fact that this is the first time a 3-year real-time challenge-of-immunity study has been conducted for a multivalent FRV, FCV, and FPV vaccine. Study results led to the availability of a three-way core feline vaccine licensed in the

United States for use at triennial revaccination intervals (Continuum Feline HCP).

The significance of these study results lies in the fact that challenge data are considered the gold standard and the definitive method for establishing duration of immunity when determining vaccine efficacy. Alternatives to challenge studies, such as serologic data, are generally not acceptable for establishing vaccine efficacy.<sup>5,12,13</sup> Although recent serologic data have suggested extended vaccine-induced immunity, the role of sustained serologic titers in disease prevention has not been confirmed; therefore, real-time challenge-of-immunity studies remain the only definitive method for establishing vaccine duration of immunity.<sup>12-14</sup> Challenge data specific to a particular vaccine are preferred because similar vaccines from different suppliers may differ significantly with regard to their duration of immunity, antigen quality and quantity, degree of attenuation, adjuvant used (if any), type of vaccine virus, and manufacturing methods used.<sup>12,13</sup>

These study findings are of particular relevance to practitioners in the context of the current debate regarding feline vaccination protocols. The results bridge the gap that existed in recent years between the AAFP's latest recommendations for 3-year use of highly recommended core feline antigens and the annual USDA label claims of corresponding vaccines (with the exception of some rabies vaccines) available to US veterinary practitioners. The paucity of vaccines specifically challenge-tested in full accordance with 9 CFR standards and USDA labeled for use at extended intervals left practitioners who wished to follow AAFP recommendations for 3-year core revaccination intervals with no option but to use vaccines at off-label intervals.

The AAFP based its recommendation for extended intervals of core vaccination on their knowledge of immunity, fear of the potential

**TABLE 4. Incidence of Leukopenia in Cats after FPV Challenge**

<i>Test Group</i>	<i>No. of Cats</i>	
	<i>Total</i>	<i>Leukopenia</i>
Vaccinates	21	0
Adult controls	10	10 (100%) <sup>a</sup>
Kitten controls	10	10 (100%) <sup>a</sup>

<sup>a</sup>Statistically significant difference ( $P < .005$ ).

for injection-site reactions resulting from over-vaccination, and the findings of Scott and Geissinger.<sup>1,3,4,8</sup> Scott and Geissinger's work was pivotal in encouraging the move toward extended vaccination intervals; however, the investigators, the AAFP Advisory Panel, and other opinion leaders have expressed the need and desire for manufacturers to test their vaccines further for actual duration of immunity and provide more information on vaccine labels.<sup>1,4,5,8,12</sup>

In response to this need, the study discussed here provides scientific evidence for a specific vaccine product in the form of real-time challenge data supporting the triennial revaccination protocols recommended by the AAFP. These data allow practitioners to extend protocols in cases in which individual patient assessment indicates it appropriate with the full backing of specific gold standard scientific evidence coupled with an official corresponding label claim.

Given the widespread presence and potential severity of the core pathogens involved, providing reliable disease protection for patients is surely a foremost concern for clinicians, and these data provide scientific assurance of extended vaccine-induced duration of immunity. As expected, the FPV antigen generated the strongest result, with 100% efficacy demonstrated. Two control groups, including both age-matched and 10- to 12-week-old kittens,

were used to demonstrate FPV challenge severity. One hundred percent of cats in both control groups exhibited leukopenia, which is indicative of systemic feline panleukopenia.<sup>15</sup> In contrast, 100% of vaccinates remained free of clinical disease and leukopenia. These contrasting observations attest to both the strength of the test challenge and the strength of the protection conferred by the vaccine. It should also be noted that these results exceed the 9 CFR requirement for immunogenicity testing that at least 80% of the FPV controls exhibit leukopenia following challenge.

In addition, the core feline respiratory antigens in the test vaccine provided significant disease attenuation. It should be noted that the AAAP guidelines state that for many diseases,

cines have indicated that FRV vaccination is known to result in low SN titers but that any detectable antibody titer ( $\geq 1:2$ ) is sufficient to provide substantial protection.<sup>1,8,11</sup> Similar to findings reported by other investigators in which FRV vaccination reduced the severity and duration of clinical disease,<sup>8,10,11,16</sup> our test results demonstrated that the severity of clinical signs among control cats was significantly greater than in vaccinates following challenge. The strength of the FRV challenge was indicated by the fact that 100% of control cats, exceeding the 80% required by 9 CFR for immunogenicity testing, exhibited clinical signs more serious than fever following challenge.

Similarly, the expectation for the FCV component was to decrease disease signs and dura-

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including FRV and FCV, the value of the corresponding vaccines is to lessen the severity of clinical disease among cats subsequently exposed to virulent virus rather than to provide complete disease protection.<sup>3,4</sup> Although the limitation of respiratory virus vaccines has been heartily discussed, especially in terms of vaccine-induced duration of immunity, vaccination against FRV and FCV has been shown to induce an immune response that lessens the severity of disease and is highly recommended for all cats.<sup>4,5</sup>

Results here showed that the FRV and FCV vaccine components provided both extended duration of immunity and statistically significant protection from severe clinical signs of disease. Previous studies involving FRV vac-

tion, in line with previously published investigations,<sup>8,10,11,16</sup> Test results reported here exceeded these expectations by demonstrating 100% protection for vaccinates against oral ulcers in the face of a challenge that produced severe clinical disease in 100% of control cats. The significance of this protection lies in the fact that oral ulcers are considered the most prominent pathologic feature of FCV infection and in fact may be the only clinical sign seen.<sup>17</sup>

An important point to note is that the AAAP Advisory Panel presented its recommendations as guidelines and not as protocols that fit every situation. The AAAP guidelines reiterate the importance of conducting individual patient risk assessment at least annually in conjunction with regular physical examinations and com-



prehensive wellness care to determine the most appropriate vaccination protocols. Vaccination needs of adult cats change depending on such factors as age, environment, and general health, and thus their needs should be assessed at least annually and modified as needed based on changes in age or health, environment, and risk of exposure to infectious agents.<sup>4</sup> These individual assessments will also determine if a patient's risk factors indicate the need for additional non-core antigens, such as *C. psittaci*, *Bordetella bronchiseptica*, and feline leukemia virus.

Clients should be informed that vaccination is a medical procedure that offers both risk and value and will be performed only after individual patient assessment has been conducted. To provide the best care possible, practitioners need to stress the importance of all aspects of comprehensive health care, including regular examinations and annual evaluation of vaccination needs. In addition, particularly in the case of feline respiratory disease, a combined vaccination and management program is required to achieve maximum disease control and prevention, especially in multiple-cat households or large boarding facilities.<sup>16-18</sup>

## CONCLUSION

Using real-time challenge-of-immunity methodologies, study results met or exceeded 9 CFR requirements to demonstrate that this new multivalent modified-live test vaccine provided a statistically significant reduction in virulent FRV-associated clinical signs ( $P = .015$ ); 100% protection against oral, lingual, and nasal ulcers associated with FCV ( $P < .001$ ); and 100% protection against clinical disease and leukopenia following virulent FPV challenge ( $P < .005$ ). These results also established that the vaccine provided a minimum of 3 years' duration of immunity following second vaccination in cats 8 weeks of age or older. These findings

provide scientific evidence via gold standard real-time challenge data that this vaccine will support veterinarians who would like to follow recent recommendations from the AAFP and other leading influencers and implement triennial FRV, FCV, and FPV revaccination protocols in adult cats. These are the only nonrabies feline challenge data that add to the pivotal work of Scott and Geissinger and, for this vaccine, provide the further challenge data requested by the profession to support AAFP-recommended use at 3-year intervals.

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