A physical examination, fecal parasite screen, and vaccine needs assessment should be performed at least yearly for all cats. The American Association of Feline Practitioners (AAFP) recently published the third version of the Feline Vaccine Advisory Panel Report (Richards et al. 2006; www.aafponline.org). These guidelines are an excellent source of information for veterinarians to use when individualizing vaccination protocols. Vaccine antigens were divided into those that were considered core (FPV, FCV, FHV-1, and rabies), noncore (FeLV, FIV, Bordetella bronchiseptica, and Chlamydophila felis), and not generally recommended (Giardia and FIP). The purpose of this session is to review new information concerning the safety and efficacy of FVRCP vaccines.

**FVRCP Vaccination**

All healthy kittens and adult cats without a known vaccination history should be routinely vaccinated with an intranasal or parenteral vaccine that contains FPV, FCV, and FHV-1 (FVRCP). Multiple modified live products and killed products are available and the products available in the United States were recently reviewed (Richards et al. 2006). In general, modified live FVRCP vaccines are recommended for kittens housed in environments at high risk for exposure to FPV. Modified live FVRCP vaccines for intranasal administration can induce protection against FHV-1 as soon as 4 days after administration (Lappin et al. 2006b), so this route of administration may be preferred for kittens housed in environments at high risk for exposure to FHV-1. Modified live products should not be administered to clinically ill, debilitated, or pregnant animals. Administration of intranasal FVRCP vaccines can induce transient, mild sneezing or coughing, and the owners should be so informed.

For kittens thought to have no more than routine risk of exposure to FPV, FCV, or FHV-1, it is currently recommended that FVRCP vaccines should be administered starting no sooner than 6 weeks of age, with boosters every 3–4 weeks until 16 weeks of age. Older kittens and adult cats with unknown vaccination history should be administered 2 killed or 2 modified live FVRCP doses 3 to 4 weeks apart.

For kittens thought to have high risk of exposure to FPV, like those housed in animal shelters or pet stores, the AAFP panel currently recommends parenteral administration of modified live FPV containing vaccines as early as 4 weeks of age, particularly during an outbreak. However, intranasal administration of modified live FVRCP vaccines instead of or in addition to parenteral administration of modified live FVRCP vaccines may be superior for protection against FCV and FHV-1 in these environments. The current AAFP Advisory Panel recommends a booster FVRCP vaccine 1 year later.

Based on several challenge studies, it appears that there is no need to administer FVRCP vaccines more frequently than every third year after the 1-year booster vaccine; it is possible the duration of immunity is much longer.

Serological test results for antibodies against FPV, FCV, and FHV-1 can be used to aid in the determination of vaccine needs (Lappin et al. 2002). Validated serological tests are available at New York State Veterinary Diagnostic Laboratory (Ithaca, NY) and Heska Corporation (Loveland, CO).

Some variants of FCV induce systemic vasculitis in cats (virulent systemic calicivirus, VS-FCV), and clinical signs can be severe in some cats previously vaccinated with FVRCP vaccines (Hurley et al. 2004). These variants arise from endogenous caliciviruses. Outbreaks documented to date generally resolve spontaneously. A killed, virulent FCV containing vaccine line is now available (Fort Dodge Animal Health, Fort Dodge, IA).

Whether it will be beneficial to administer this vaccine strain of FCV to cats is currently unknown, as the incidence of disease is unknown and the ability of the vaccine to cross protect against other VS-FCV on challenge is also unknown. However, serum from vaccinated cats has neutralized 6 of 9 virulent systemic strains in vitro. An additional potential benefit is that vaccines containing more than one FCV strain may induce superior cross protection against other FCV strains that also can induce severe clinical signs of disease. The AAFP recently posted an informational brief concerning the vaccine (www.catvets.com/professionals/guidelines/feline_friendly/).
FVRCP-Associated Illness

Overall, vaccines for cats are very safe. In my opinion, vaccines for cats undoubtedly have saved many more cats than they have hurt. Core vaccine antigens as defined by the American Association of Feline Practitioners Vaccine Guidelines Committee should be administered to all cats; non-core antigens should be selected based on needs of the individual cat (Richards et al. 2006). The most significant problem associated with feline vaccines has been injection-associated sarcoma. Previously, this problem seemed most apparent in cats administered adjuvanted rabies virus and feline leukemia virus vaccines. However, recent information suggests that injection site sarcomas can occur with any type of vaccine. For example, in the United Kingdom in 2005, 23 of 39 injection site sarcomas reported in cats occurred at the site a live vaccine (non-adjuvanted) was administered (Dyer et al. 2007).

While generally very safe, modified live FVRCP vaccines have been associated with a number of clinical abnormalities, including fever, infection of the fetus, induction of a chronic carrier state, polyarthritis, and upper respiratory tract disease. Parenteral administration of FVRCP vaccines occasionally leads to vaccination site sarcomas (Burton & Mason 1997).

We recently reported recombinant antigens of feline herpesvirus 1, calicivirus, and panleukopenia virus for use in serological assays (Lappin et al. 2002). In the same work, we showed that serology could be used to accurately determine need for FVRCP vaccination in cats if validated assays are utilized. While titrating the recombinant antigen based ELISAs by comparing to ELISAs performed using whole viruses, we discovered that vaccinated cats make antibodies against a commonly used cell culture line.

The Crandall-Rees feline kidney (CRFK) cell line has been used to propagate feline viruses for years. While isolated from a kidney, the cell line has characteristics of a fibroblast. During virus purification for vaccine production (FVRCP) or immunoassay development, it is impossible to remove all CRFK proteins or other cell constituents. Thus, CRFK proteins contaminate the viral preparations, and commercially available FVRCP vaccines grown on the cell line contain CRFK proteins. As a consequence, during the course of routine immunization, cats are exposed to CRFK proteins and may mount an immune response against those proteins. Since the CRFK cell line is derived from a feline cell line, administration of FVRCP vaccines induces antibodies that also bind to feline tissues. We have now performed several studies to assess the problem.

In the first study (Lappin et al. 2005), our objectives were to determine whether cats inoculated with FVRCP vaccines grown on the CRFK cell line develop antibodies against CRFK lysates or renal cell lysates (FRC), whether cats hypersensitized with CRFK lysate develop antibodies against CRFK cell lysates or FRC lysates, and whether FVRCP vaccination or hypersensitization with CRFK cell lysates induces clinical pathological or histopathological abnormalities over a 56-week period. We assessed 3 FVRCP vaccines for SQ administration and 1 FVRCP vaccine for intranasal/intraocular administration. CBC, serum biochemical panel, urinalysis, microalbuminuria assay, and ELISAs to detect antibodies against CRFK lysate or FRC lysate were performed on samples collected at intervals during the study. Renal biopsies were assessed for abnormalities independently by 2 pathologists. None of the cats was positive for antibodies against CRFK lysate or FRC lysate prior to inoculation. All 6 cats administered CRFK lysate alone were positive in the CRFK ELISA on multiple sample dates in the CRFK ELISA. Neither of the cats receiving intranasal/intraocular vaccination achieved the positive cutoff value in the CRFK ELISA. Five of the six cats administered a parenteral vaccine were positive in the CRFK ELISA at least once during the study. All 6 cats administered CRFK lysate were positive on multiple sample dates in the FRC ELISA. All 6 cats administered a parenteral vaccine were positive on multiple sample dates in the FRC ELISA. Neither of the cats administered the intranasal/intraocular vaccine was positive in the FRC ELISA. Signifi cant CBC, serum biochemical, urinalysis, microalbuminuria, or histopathologic abnormalities were not detected during the study. We concluded that parenteral administration of vaccines grown on the CRFK cell line and SQ inoculation of CRFK lysate alone induced CRFK antibodies and FRC antibodies in most cats in this study. However, the clinical pathological and histopathological results suggest that even hypersensitization with CRFK proteins was not associated with detectable renal dysfunction, renal inflammatory disease, or glomerular disease in the 56-week time period studied.

In the first study, renal biopsies were collected 6 weeks after the last vaccination or hypersensitization (Lappin et al., 2005). It is possible that inflammation of renal tissues occurred but was transient and resolved by the time of biopsy. We have completed a follow-up study (Lappin et al. 2006a) in which we hypothesized that interstitial nephritis would be detected in cats hypersensitized with CRFK lysates, boosted with CRFK lysates, and then biopsied 2 weeks after the booster. We documented interstitial nephritis in 3 of 6 cats hypersensitized with CRFK lysates, but
not cats vaccinated with the intranasal FVRCP vaccine. None of these 3 cats had significant inflammation detected 1 year previously. One of the 6 cats recently died of interstitial nephritis. However, it is important to emphasize that the cats in the study had been inoculated multiple times with CRFK proteins over the first year of the study. Whether this occurs after parenteral administration of CRFK-contaminated FVRCP vaccines using routine vaccination protocols remains to be proven.

In our first study to determine CRFK antibodies in vaccinated cats, we only had 2 cats per group. Thus, a larger study (Lappin et al. 2004) was performed with 5 groups of cats (1 intranasal vaccine and 4 parenteral vaccines). In that study, we showed that parenteral administration of FVRCP vaccines induces a statistically greater magnitude of antibody response to CRFK proteins than intranasal administration of a FVRCP vaccine. These findings were expected because parenteral inoculation of CRFK lysates to immunocompetent cats would be expected to induce an immune response. The viruses used in the production of the FVRCP vaccine for intranasal administration are also grown on CRFK cells. However, while the viruses in the vaccine are alive, the CRFK cell line components that contaminate the vaccine are not. Thus, we believe the reason cats inoculated with this intranasal vaccine do not develop CRFK antibodies relates to immune exclusion of the CRFK cell line components by the mucosal lining the nose and mouth. We are in the process of determining the immunodominant CRFK antigens recognized by feline antibodies (Whittemore & Lappin 2005). We have identified 3 immunodominant antigens and will study these antigens further. Antibodies against 2 of the 3 antigens have been associated with autoimmune disorders in people.

At this time, we have not directly linked FVRCP vaccination to auto-immune diseases in cats. To further assess for disease associations with administration of CRFK-containing FVRCP vaccines, we are currently performing the following studies: 1. determination of the source and distribution of CRFK proteins in feline tissues; and 2. correlation of CRFK antibodies with presence of biochemical abnormalities in a group of client-owned cats in the United States. A general recommendation at this time would be to not use parenteral FVRCP vaccine at an interval shorter than every third year. In addition, FVRCP antigens should not be split and given yearly, as that may result in increased exposure to the cell culture antigens.

References/Suggested Reading


