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Evaluation of Risks and Benefits Associated with Vaccination against Coronavirus Infections in Cats

FRED W. SCOTT

Cornell Feline Health Center and the Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York 14853

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I. Historical Perspectives of FIP

Historically, feline infectious peritonitis (FIP) was first described in the early 1960s by Dr. Jean Holzworth (1963). At least four earlier references to clinical cases in cats that may have been FIP included (1) a conspicuous abdominal distention due to ascites, with a retrospective diagnosis of FIP, from the State Veterinary School in Utrecht, seen in 1912–1913 and reported in 1914 (de Groot and Horzinek, 1995; Jakob, 1914); (2) an infectious pleuritis in 1942 (Bonaduce, 1942); (3) a severe exudative peritonitis of unknown etiology reported in England in 1960 (Joshua, 1960); and (4) a case of chronic organizing peritonitis in 1961 (Smith and Jones, 1961). The first detailed description of a clinical case of “FIP” was reported by Feldmann and Jortner (1964). The name
feline infectious peritonitis was coined by Wolfe and Griesemer in 1966, and it was early recognized to have an immunopathologic component (Pedersen and Boyle, 1980; Jacobse-Geels et al., 1980). Antibody-dependent enhancement (ADE) was shown to play a part in the pathogenesis of the disease (Pedersen, 1983; Weiss and Scott, 1981; Olsen et al., 1993). The first vaccine for FIP, an intranasal modified live virus (MLV) vaccine, was licensed in 1991 (Gerber et al., 1990; Gerber, 1995).

II. Current Status of FIP

The current status of FIP varies between types of cat populations. It is the most feared disease today in breeding catteries, but is less common and of less concern in the general pet population (Wolf, 1995; Kass and Dent, 1995; Addie and Jarrett, 1995). There is no effective treatment for FIP, and once classical disease occurs, mortality is nearly 100%. The only available commercial vaccine is less than 100% effective. Available laboratory tests detect feline coronavirus antibodies and therefore are not specific for FIP. Until recently, there was no test to detect FIP antigen, virus, or to identify virus carrier cats. The reliability of new antigen detection tests is still being evaluated. A cattery with enzootic FIP is difficult to manage. The great variability in incubation period of FIP (weeks, months, or even years) presents a serious challenge to prevention and control. A comprehensive review of FIP virus was published in 1993 by Olsen. This review covers the molecular biology of the virus, immunopathogenesis of infection, clinical aspects of the disease, and a discussion of vaccination for FIP. Two reviews of FIPV were published in 1995 (de Groot and Horzinek, 1995; Pedersen, 1995b). A series of manuscripts was published in Feline Practice as the Proceedings of the 1994 International Workshop on FIPV and FECV (Vol. 23 [3], 1995).

III. Causative Agent of FIP

The causative agent of FIP, feline infectious peritonitis virus (FIPV), is a pleomorphic, enveloped virus classified as a coronavirus. This single-stranded, positive-sense RNA genome virus contains three major structural proteins: (1) the “N” or nuclear protein (core protein), (2) the “M” or matrix glycoprotein (formerly called E1), and (3) the “S” or spike glycoprotein (formerly called E2) (de Groot and Horzinek, 1995; Olsen, 1993; Spaan et al., 1988).
There are at least two cell receptors for FIPV infection of cells (de Groot and Horzinek, 1995; Holmes and Compton, 1995; Olsen et al., 1992, 1993; Olsen, 1993). One is a virus receptor on the cell membrane that is specific for epitopes on the S protein. The second is the Fc receptor on macrophages for the Fc portion of IgG antibodies.

The replication of FIPV occurs at the endoplasmic membranes of infected cells (Holmes, 1985; Olsen, 1993). The virus buds into vacuoles within the cell cytoplasm, and hence the virus remains cell-associated initially. Virus is released from infected cells after the cell is destroyed (cytolysis). Replication of virus is rapid, with the replicative cycle completed in less than 24 hours.

FIPV survives in the environment much longer than was originally thought. Infectious FIPV can be recovered from contaminated dry surfaces for 3–7 weeks at room temperature, with the amount of infectious virus present gradually decreasing with time (Scott, 1991). It is not a highly labile virus as is usually reported.

FIPV is one of four viruses that make up an antigenic cluster of viruses with similar genomes. The second virus, feline enteric coronavirus (FECV), generally produces a mild enteritis, but not FIP. However, there is some indication that FECV can produce FIP-like disease. Positive antibody titers against FIPV result from FECV infection. It is preferable to refer to both FIPV and FECV as feline coronavirus (FCoV). The third virus in the group is canine coronavirus (CCV), which can infect cats, but usually with a subclinical infection. CCV antibody-positive cats can experience ADE of FIPV infection (McArdle et al., 1992). One U.K. isolate of CCV can produce clinical FIP in cats. Positive antibody titers against FIPV are produced with experimental CCV infection of cats. The last virus in the group is transmissible gastroenteritis virus (TGEV) of swine. TGEV can infect cats, usually with subclinical infection, but with positive antibody titers against FIPV (Woods and Pedersen, 1979).

All feline coronaviruses belong to a single serotype, but there are two subtypes of virus, FCoV-1 and FCoV-2, which can be differentiated by monoclonal antibody (mAbs) (Corapi et al., 1992; Fiscus and Teramoto, 1986, 1987; Hohdatsu et al., 1991; Olsen, 1993).

IV. Pathogenesis of Feline Coronavirus Infections

The pathogenesis of FCoV infection is complex and unique. The incubation period can be weeks, months, or even years, but is generally 2–3 weeks up to 3 months. Local infection or primary infection occurs in
the pharyngeal and lung epithelium, and possibly the intestinal epithelium (de Groot and Horzinek, 1995; Olsen, 1993). There is minimal clinical disease during the primary infection, often just a transient fever for one to a few days. Antibodies against FIPV first appear in serum by day 7 to day 10 after infection, and then infection of macrophages occurs. Fc receptors on macrophages enable uptake of virus–antibody complexes, and infected macrophages transport the virus throughout the body. Secondary infection then occurs in many tissues, with macrophages attaching to and migrating through the walls of veins. A perivascular reaction occurs, leading to development of a pyogranuloma, the basic lesion of FIP within tissues.

Two forms of FIP are recognized (Montali and Strandberg, 1972). Early reports described FIP primarily as wet or exudative FIP. Currently, dry or granulomatous FIP is more common than the wet form of disease. The wet and dry forms of FIP are merely variations of the same disease process. In wet FIP there is an exudative reaction at the vessel walls, with exudative fluid accumulating in the peritoneal and/or the thoracic cavities.

V. Immunology of Feline Coronavirus Infections

Immunology of FCoV infections is complicated and not fully understood. Undoubtedly, all three major components of the host's immune response come into play in a fully immune cat. However, many cats develop aspects of an immune response without developing protection. In some cases, this host response makes the cat more susceptible to exposure to FIPV rather than providing protection. Humoral immunity results in serum virus neutralizing (VN) antibodies which first appear 7–10 days after infection. There is a gradual increase in VN titers until 5–6 weeks after infection, with a hypergammaglobulinemia occurring in most cats that develop clinical FIP. The VN antibodies against epitopes on the S or spike protein usually are enhancing antibodies if the right concentration of virus and antibodies exists (Olsen et al., 1992, 1993). The subclass of IgG produced may be important in determining if true immunity occurs (Corapi et al., 1992).

Cell-mediated immunity (CMI) is believed to play an essential role in an effective immune response against FCoV (Pedersen, 1987, 1995b). Details of the CMI response have not been determined. Local immunity appears to play a significant role in preventing infection of a previously infected or vaccinated cat via anti-FCoV IgA on mucosal surfaces (Gerber, 1995; Gerber et al., 1990).
VI. Antibody-Dependent Enhancement

Immune enhancement (antibody-dependent enhancement, ADE) has been clearly shown to occur in experimental laboratory infections of cats previously infected by natural or experimental infection, and of cats previously vaccinated with Primucell FIP vaccine, experimental MLV vaccines, experimental inactivated vaccines, and experimental recombinant vaccines containing the S gene (McArdle et al., 1992, 1995; Ngichabe, 1992; Scott et al., 1992, 1995a,b; Weiss and Scott, 1981). Antibodies to the S protein produced by the host result in enhanced infection of macrophages via Fc receptors, and the infected macrophages then transport the virus throughout the body. In the enhanced infection there is a decrease in incubation time—as short as 1–2 days—after exposure to virulent FIPV. The relative amount of virus and antibodies is important in order for ADE to occur. Higher concentrations of antibody neutralize the virus, but as the concentration of antibody decreases a concentration occurs where enhanced infection results. Other related coronaviruses can cause enhanced FCoV infection in the cat, including CCV.

Infectivity of macrophages appears to be a key factor in the ability of FCoV to become a systemic infection (Pedersen, 1976; Stoddart and Scott, 1986). The infected macrophages travel in the bloodstream to various parts of the body where they attach to the walls of veins. The local infection with inflammation results in characteristic perivascular lesions identified as pyogranulomas.

VII. FIP Vaccine

A single commercial vaccine, Primucell FIP from Pfizer, is available to aid in protecting cats against FIP and FCoV infections (Christianson et al., 1989; Gerber, 1995; Gerber et al., 1990). It is a MLV, temperature-sensitive (ts) mutant produced by attenuation of the original virulent FIPV-DF2 isolate by serial passage in cell cultures at low temperature. The FIPV-DF2 isolate is a type 2 virus. Primucell FIP is licensed for intranasal administration, with two doses given 3–4 weeks apart in cats at least 16 weeks of age. Annual revaccination is recommended by the manufacturer. This vaccine stimulates local IgA and VN antibody titers in serum (Gerber, 1995; Gerber et al., 1990).

Evaluation of the risks and benefits associated with the use of this vaccine is a complicated issue. First, the severe, usually fatal nature of FIP mandates the need for a safe and effective vaccine, especially since
there is no effective treatment for this disease. If a highly effective vaccine against FIP was available, it would be used routinely in feline practice.

VIII. Risks of FIP Vaccination

The risks of vaccination with Primucell FIP appear to be minimal in most situations. The vaccine has been used for the past 7 years with no increase in the incidence of FIP reported. Field safety tests and controlled field studies have documented no increase in FIP or related disease in cats vaccinated with this vaccine (Fehr et al., 1995; Hoskins et al., 1995a; Reeves, 1995; Scott et al., 1992). In experimental studies in several laboratories, however, ADE of infection has been documented in cats vaccinated with this vaccine and a variety of other experimental FIP vaccines (McArdle et al., 1995; Ngichabe, 1992; Scott et al., 1995a; Vennema et al., 1990). Under these situations, the enhanced state results in a shorter incubation period after exposure to virulent virus, a shorter course of disease with more severe clinical signs, and a greater mortality compared to unvaccinated control cats. The major factor that determines whether enhanced disease occurs is the relative concentration of virulent virus and anti-FCoV antibodies (Corapi et al., 1992; Olsen, 1993; Olsen et al., 1992, 1993; Scott et al., 1995b).

Some investigators have stated that ADE of infection does not occur under natural or field conditions, that it only occurs under laboratory conditions (Addie et al., 1995; Fehr et al., 1995; Reeves, 1995). Although ADE does not appear to be a major problem under field conditions, apparently due to the relatively small amount of virus shed from infected and carrier cats, it is virtually impossible to determine if an individual case of FIP is a result of ADE infection or nonenhanced infection. The incubation period is the only differentiating difference, with ADE infection resulting in severe clinical FIP within 12 days after exposure to virus (Scott et al., 1995b; Weiss and Scott, 1981). Non-enhanced infection does not result in severe disease until after 12 days from exposure. Since the time of exposure to virus is almost always impossible to determine in field infections, it is likewise virtually impossible to determine with certainty whether or not a particular infection is enhanced or not. In one study of the safety and efficacy of the vaccine in two high-risk cat populations in Switzerland (Fehr et al., 1995), the authors state that the vaccine did not result in enhanced disease. Yet evaluation of the reported results indicates that three cats
developed FIP within the first month after vaccination, while none of the placebo vaccinated cats developed FIP within this time. Were these cases of enhanced disease? It is impossible to ascertain, but it is also impossible to rule out enhanced disease based on these data.

IX. Benefits of FIP Vaccination

The benefits of vaccination, unfortunately, are rather low. In FIP endemic catteries, two controlled studies have failed to show any decrease in the incidence of FIP in vaccinated cats compared to placebo vaccinated controls. In the original field study by the manufacturer of the vaccine (Fanton, 1991), 12 endemic catteries were evaluated in a controlled study, with 349 cats vaccinated twice with Primucell FIP, and 352 cats vaccinated with a placebo vaccine. During the observation period of 6 months, three cases of FIP occurred in the vaccinated group (0.86%) compared to four cases in the control group (1.1%). This difference was not statistically significant.

In a double-blind placebo controlled field study in Switzerland involving 138 purebred cats from 15 catteries (Fehr et al., 1995), the investigators were unable to show a difference between Primucell FIP vaccinated cats and placebo vaccinated controls within these FIP endemic catteries when the vaccine was used as recommended by the manufacturer (two doses of vaccine given 3–4 weeks apart starting at 16 weeks of age). There were seven FIP deaths in the vaccinated group and five FIP deaths in the placebo group during the 15- to 21-month study period.

In endemic catteries, many kittens are infected from their carrier queens at 6–7 weeks of age, long before the vaccine can be used as licensed at 16 weeks of age (Stoddart et al., 1984; Addie and Jarrett, 1995). Once a cat is infected with FCoV the vaccine will have no beneficial effect. Controlled studies on the efficacy of the vaccine in kittens younger than 16 weeks of age have not been published. Some cattery owners apparently are using the vaccine off label in kittens as young as 3 weeks of age.

In high-risk pet cat populations there is limited or no efficacy of the vaccine. In the Switzerland study mentioned earlier (Fehr et al., 1995), 609 domestic and purebred household pet cats were studied in the double-blind placebo controlled field study. During the 12 months after vaccination, FIP was confirmed in 13/31 deaths in the vaccinated group compared to 17/34 deaths in the control group. The authors state that “Death losses in placebo and vaccinate groups were equal up
to day 150 following immunization, while significantly more placebo-immunized animals died of FIP after that period." In this author's review of the data in this study (Fehr et al., 1995), there were two more deaths in the vaccinated group \((n = 12)\) compared to the control group \((n = 10)\) through 150 days, and an equal number of deaths from FIP \((n = 13\) for both groups) through 250 days after vaccination. After this 250-day period there were four deaths in the control group but no deaths in the vaccinated group. A disturbing finding is that two of the deaths in the vaccinated group occurred within the first few days after vaccination, while none of the deaths in the control group occurred within this time period. Were these cats merely incubating the disease at the time of vaccination and would have died anyway, or were these early deaths after vaccination a result of enhanced disease from the vaccine in cats that were already antibody positive? It is impossible in this review to ascertain the exact situation in these two cats. In any case, Primucell FIP did not reduce the incidence of FIP within this high-risk pet population of cats for 8 months after vaccination, or until the cats were at least 1 year of age.

The topical or intranasal vaccination with Primucell FIP stimulates VN antibodies within the sera of vaccinated cats (Fehr et al., 1995; Hoskins et al., 1995a; Scott et al., 1992, 1995a). These VN antibodies, directed against epitopes on the S protein of the virus, are also enhancing antibodies when tested \textit{in vitro} against infection of peritoneal macrophages (Olsen et al., 1992; Scott et al., 1995a; Stoddart and Scott, 1988). In our studies, 48/49 cats vaccinated with Primucell FIP had enhancing antibodies within their sera after vaccination, while none of the 23 unvaccinated controls had enhancing antibodies. Enhanced infection occurred with both FIPV-1146 and FIPV-DF2.

Efficacy of Primucell FIP depends on the dose of FIPV to which vaccinated cats are exposed (McArdle et al., 1995; Scott et al., 1995a,b). Under experimental conditions where vaccinated cats are exposed to a low dose of virulent challenge virus \((<10\) cat infectious doses), the vaccine provides protection for some cats. If vaccinated cats are exposed to \(>10\) cat infectious doses of FIPV \((10^4\) TCID\(_{50}\)), the vaccine provides no protection. With this higher challenge dose, many of the vaccinated cats are more susceptible to infection than the unvaccinated controls, resulting in an enhanced and more acute disease.

Some efficacy of the vaccine can be demonstrated when FCoV antibody-negative cats are vaccinated according to the manufacturer's recommendation prior to natural exposure to FCoV-infected cats. Reeves (1995) reported a significant reduction in clinical FIP in FCoV antibody-negative cats that were vaccinated twice when at least 16 weeks
of age, then introduced into a large cat shelter where FIP was endemic. Of 254 vaccinates, the mortality from FIP over a 16-month period after vaccination was 0.8% compared to a FIP mortality of 3.25% in 246 placebo-vaccinated cats. The calculated efficacy of vaccination, based on preventable fractions, was 75%.

Hoskins et al., (1995a,b) evaluated the efficacy of Primucell FIP in kittens vaccinated at 16 and 19 weeks of age in two studies. In one study, the number of kittens with histopathologic indications of FIP after a low-dose FIPV-DF2 challenge was reduced from 60 to 30% in vaccinated cats compared to unvaccinated controls, a 50% efficacy based on preventable fractions. In the other study, vaccinated kittens exposed to FECV-1163 had less intestinal clinical disease, less virus in the intestine, and less histopathologic damage to the small intestine compared to unvaccinated controls.

The amount of virus to which cats are exposed under normal field conditions is unknown. However, based on studies reported to date under both natural and experimental conditions, one can only conclude that the amount of virus exposure must be low. If the exposure dose of virus was high, enhanced disease would frequently be encountered. Because enhanced disease does not occur under natural conditions, or at least it is an uncommon occurrence if at all, the exposure dose of virus must be at a low level. This is consistent with what is known about the amount of virus shed from experimentally infected cats.

There is no published information on the duration of immunity produced by Primucell FIP. As with most veterinary biologics, the manufacturer of the vaccine arbitrarily recommends annual revaccination.

In summary, Primucell FIP vaccine has efficacy in preventing some clinical FIP when FCoV antibody-negative kittens at least 16 weeks of age are vaccinated twice intranasally 3 weeks apart. The vaccine has not been shown to reduce the incidence of clinical FIP when used in endemic catteries when the vaccine is routinely given to kittens at least 16 weeks of age. The use of the vaccine appears to be limited to high-risk populations, such as breeding catteries and multicat facilities, where FCoV antibody-negative cats are vaccinated.

The American Association of Feline Practitioner’s Feline Vaccination Guidelines (Elston et al., 1998) makes the following recommendations concerning FIP vaccination. “The panel considers this to be a non-core vaccine because of the low prevalence of disease in confined populations of cats. As a result, vaccination is recommended only for cats at risk of exposure to the causative organism. However, the panel was split as to what constituted risk of exposure to FIP-inducing coronaviruses. A minority of the panel members recommended vaccination of kittens
and cats with lifestyles that resulted in substantial risk of exposure to coronaviruses. Most panel members recommended that vaccination be limited to cats in specific risk situations, such as households in which FIP had been diagnosed. Those cats for which vaccination is deemed appropriate should receive a foundation series of vaccinations as kittens, according to recognized protocols. An annual booster vaccination is recommended by vaccine manufacturers; however, to our knowledge, duration of immunity studies have not been performed.”

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