8th Feline Pract. Seminar
CHC July 26-29 1996

THEORY AND PRACTICE OF IMMUNIZATION

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One of the most significant advances in veterinary medicine in the last 50 years has been the development of vaccines for the prevention of many infectious diseases that once killed large numbers of dogs and cats. Prevention is possible because it has become technologically feasible to develop safe and efficacious vaccines that are easily administered and offer long-term protection.

The purpose of a vaccination program is to prevent the development of overt clinical disease, either by preventing or limiting infection. If planned properly, vaccine programs can improve animal care by providing a convenient time for a routine health examination. This aspect of the vaccination program has been abandoned by some clinicians but should be considered a critical feature of a sound animal health program. The mechanisms by which dogs and cats are protected from infection and disease after vaccination have been and still are the subject of numerous studies by veterinary researchers and clinicians.

It is currently accepted that there are two parts of the specific host defense system:

(1) the **humoral (antibody) system**, consisting of B lymphocytes and the four immunoglobulin classes (IgG, IgM, IgA, and IgE), plus helper cells and, to assist this system, K cells, phagocytic cells, and effector molecules such as complement and properdin and

(2) the **cell-mediated immune (CMI)** system, consisting of T lymphocytes, macrophages, and a number of products of these cells called cytokines.

Current information would suggest that vaccine protection is provided by both humoral immunity and by cell-mediated immunity. With the extended use of vaccines we have found that for certain diseases it may not be possible to develop an effective vaccine and at times it may be that the vaccine will enhance or cause disease. Thus, although vaccines for the most part have been very important in preventing disease, they also can cause disease. If vaccination is known to prevent reinfection, humoral immunity is likely to be at work. This occurs with effective vaccination and protection against canine distemper, infectious canine hepatitis, canine parvovirus and feline panleukopenia virus. However, when vaccination protects against the development of clinical disease but not against reinfection (which is often the case with feline viral rhinotracheitis, a herpesvirus), cell-mediated immunity and local antibodies play important and perhaps primary roles in preventing disease.

Factors Influencing The Host Defense System

Numerous factors can influence the host defense system and thus effect the immune response to the vaccine. Factors to be considered in designing an effective vaccination program for dogs

and cats include the specific immunosuppressive or blocking effect of colostral antibody, the nature of the vaccine, the route of vaccination, the age of the animal, its general nutritional condition, concurrent infections, drug treatments and host genetic factors. These factors will be discussed briefly with respect to the possible influences that each may have on the success of an immunization program.

Maternal Antibody

One of the most common problems associated with vaccination is maternal antibody interference with active immunization. Maternal immunity, a form of passive immunity, has a vital role for neonates. It helps to protect neonates during the critical transition from the protected uterine environment of the fetus to the hostile external environment of the newborn. This transition occurs not only at a time when a neonates immune system is not fully developed but also when a neonate's immune system is naive to virtually all pathogens. Without the acquisition of maternal immunity, a neonate's chances of survival are greatly reduced. However, maternal immunity is not without its negative effects. Maternal antibody interference with immunization is the most common cause of vaccine failure, particularly in weanling and postweanling animals. It is generally believed that when this interference occurs maternal antibody binds to the vaccine antigens in such a way that the vaccine is cleared from the body before it is able to stimulate an immune response. Because maternal antibody is acquired exogenously and is not actively being replaced, it is gradually depleted as the animal matures.

Maternal antibody is degraded at a *constant* rate. Its retention time in the animal is largely dependent on the class and quantity of antibody acquired at birth. The level of maternal immunity obtained at or around the time of birth is dependent on a number of factors: the immune state of the dam, the amount of colostrum produced, the immunoglobulin (antibody) content of the colostrum, the amount of colostrum ingested and absorbed, and the age of the neonate at the time of ingestion. These factors can cause substantial variation in the amount of maternal antibody that is transferred to newborn animals, even among littermates. The most abundant class of immunoglobulin in colostrum is IgG, which has a 1/2 life of about 14 days, thus 1/2 of the maternal antibody acquired at birth would disappear every two weeks.

Because of these factors, it is difficult to accurately predict the level of maternal antibody for a specific puppy or kitten at the time of immunization. It is possible to obtain a serum sample from a given animal and determine the level of maternal antibody to each pathogen. From this information, the most appropriate immunization time for each agent can be determined. However, the cost and time requirements of such determinations could be prohibitive. The most successful and cost-effective approach to immunizing animals with unknown amounts of maternal antibody is based on multiple vaccinations, with the last immunization with multiple vaccines occurring at approximately 12 to 14 weeks of age for a puppy and approximately 12 weeks of age for a kitten.

Various immunization programs have recommended initial vaccination ages of 6, 8, or 9 weeks with repeat immunizations at 2-, 3-, or 4- week intervals. The program that is correct for your practice largely depends on your philosophy and the incidence of disease within your community. One must weigh the possible risk of infection versus the cost to the client and possible risks to the patient. We believe that a reasonable compromise for puppies would be two

to three immunizations given at regular intervals in animals between the ages of 6 and 14 weeks and for kittens two to three immunizations given at regular intervals between the ages of 6 and 12 weeks. Veterinarians frequently blame a vaccine failure on a "bad vaccine." However, it is more likely that the vast majority of vaccine failures, in animals less than 1 year of age, occur as the result of giving the last vaccination when the maternal antibody levels are sufficient to prevent active immunization with one or more components of the vaccine.

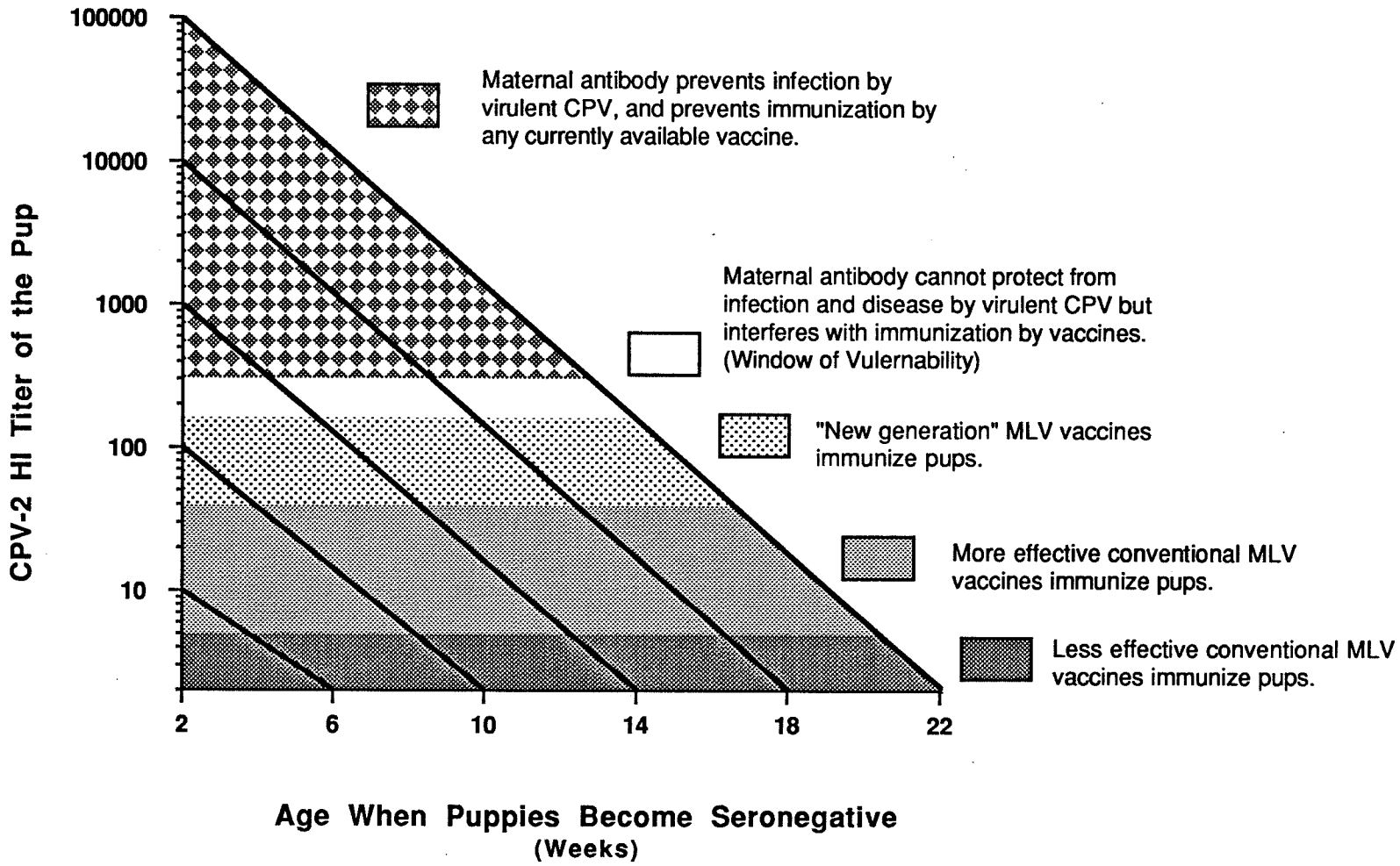
A significant problem, especially for CPV, is that virulent virus is able to infect and cause severe disease in animals with levels of maternal antibody that prevent active immunization. Until the recent development of a "new generation of CPV vaccines there was generally a 6 to 15-week "***window of vulnerability***" in heavily CPV contaminated environments depending on the vaccine in use. This was of particular concern in some breeding kennels, humane shelters, and pet stores where the level of environmental contamination with CPV is so high that virtually every puppy contracts CPV infection and some develop disease before they can be successfully immunized. In kennels with this problem, the best solution, although often difficult to implement, is to totally remove the puppies from the kennel prior to 4 to 6 weeks of age and not allow them to return until they have completed their full immunization program, at approximately 3-4 months. It is important that these isolated puppies not have direct or indirect contact with persons or equipment from the contaminated kennel until their immunization program is complete, because CPV is very stable and can persist on fomites for weeks or months. The recent development of a "new generation" of canine parvovirus vaccines has significantly reduced the "window of vulnerability" to less than 2 weeks (see Fig. 1) and most of the CPV vaccines onw on the market are highly effective.

Maternal antibody interference with canine distemper virus (CDV) immunization can be overcome by a unique approach: the development of heterotypic immunity. ***Heterotypic immunity*** is the production of an immune response to one microorganism by immunizing with a different but antigenically related microorganism. Measles virus (MV) is antigenically related to CDV. When MV is inoculated into a puppy with moderate levels of CDV maternal antibody an immune response is produced that protects the puppy from CDV disease. An important and poorly understood aspect of MV vaccine is that MV should only be given intramuscularly. ***If CDV is a problem in your practice use the combination MV/CDV product!***

Nature of the Vaccine

Certain questions must be considered if the most effective vaccination program is to be achieved. Is the vaccine virus a modified live or a non-infectious (inactivated virus) vaccine? If live virus vaccine is used, the vaccine should be handled according to directions supplied by the manufacturer so that it does not become inactive and nonantigenic. ***Live virus vaccines do not contain enough antigen to immunize the animal unless the virus can infect and replicate in the host***. Inactivated vaccines, on the other hand, have an adjuvant and sufficient antigenic mass but in general (but not always) must be administered several times in order to get an adequate and protective immune response. The question of modified live versus inactivated virus vaccines is often raised. Currently, there are no absolute answers; however, modified live virus vaccines in general are more efficacious and provide a longer period of immunity than inactivated

Figure 1


100000
10000
1000
100
10
CPV-2 HI Titer of the Pup
Maternal antibody prevents infection by virulent CPV, and prevents immunization by any currently available vaccine.
Maternal antibody cannot protect from infection and disease by virulent CPV but interferes with immunization by vaccines. (Window of Vulernability)
"New generation" MLV vaccines immunize pups.
More effective conventional MLV vaccines immunize pups.
Less effective conventional MLV vaccines immunize pups.
2
6
10
14
18
22
Age When Puppies Become Seronegative
(Weeks)

vaccines, but there are notable exceptions. It should be kept in mind that both modified live and inactivated products have a place in the immunization schedule. Adjuvants are added to inactivated vaccine to help stimulate protective immunity. Some of the most effective adjuvants cannot be used in commercial vaccines because of the severe reactions they cause. Many of the adverse reactions we see with inactivated vaccines are caused by adjuvants. As we develop and begin to use new adjuvants we are likely to see new and different reactions caused by these products. Since an adjuvant is designed to stimulate an immune response certain of the reactions are immune mediated, such as hypersensitivity reactions including those leading to mild or severe disease. Some adjuvants may even lead to an increased incidence of autoimmune disease in genetically susceptible animals and to certain forms of cancer (fibrosarcoma).

To achieve maximum success regardless of type of vaccine the entire dose of vaccine should be given as recommended; vaccines should not be divided and given to more than one animal.

Route of Vaccination

The directions specified by the manufacturer should be followed; for example, if an intramuscular route is recommended, do not give the vaccine subcutaneously. This is critical for canine rabies and measles vaccines. Significant differences in host response to certain vaccines exist and are dependent on the route of administration of vaccine. For rabies vaccine it has been reported that the intramuscular route is much more effective than the subcutaneous route. However, there are canine rabies vaccines approved for subcutaneous administration. We have also found that the intramuscular route is the only effective route for measles virus. These findings would suggest that the combined canine distemper and measles virus vaccine should be administered intramuscularly and not subcutaneously. For canine distemper and panleukopenia both the subcutaneous and intramuscular routes are effective.

The question of parenteral versus local immunization is one requiring a thorough understanding of the pathogenesis of the disease. Intranasal immunization has the advantage of inducing local antibody as well as local cell-mediated immunity in the respiratory tract. However, if the specific agent replicates in the systemic tissue and not at the local level of the epithelial cells lining the respiratory tract, there is no obvious advantage to local versus parenteral immunization. An example is canine distemper virus, frequently considered to be a respiratory infection but known to replicate initially in lymphoid tissue. In this case there is no real advantage to an intranasal product. Panleukopenia is similar, in that the disease is frequently considered an enteric infection, but the virus replicates first in the lymphoid tissue and later infects cells of the gastrointestinal tract. Oral immunization is not only less efficacious than parenteral immunization, we have found oral administration to be without effect unless there is simultaneous intranasal immunization. One should attempt to protect the site of infection; therefore, local immunization may be more efficacious when the primary site of replication is the respiratory (e.g. parainfluenza, FVR, calicivirus) or gastrointestinal tract (e.g. canine corona virus).

The practice of administering panleukopenia vaccine in food to wild cats maintained in zoos cannot be recommended, since the oral route is ineffective both for the development of antibody and for protection against challenge infection with feline panleukopenia virus.

Age of the Animal

Age is important not only because of persistence of colostral antibody in the young animal but also because the relative hypothermia that exists during the first week or two of life can cause a state of immunologic unresponsiveness especially for cellular immunity. Optimum body temperatures between 38 and 39°C are very critical for T cell as well as macrophage function in dogs and in cats. Body temperatures less than 37°C are not uncommon in puppies and kittens during the first week to 10 days of life, and this lower body temperature is capable of suppressing the cellular immune system. Because of the interdependence of the B cell system for helper T cells, the antibody response could also be affected by the lowered body temperature. Vaccination during this early period (less than two weeks of age) with live attenuated vaccines is not recommended because the animal won't respond and the vaccine can cause disease. Orphaned pups or kittens should ***receive immune serum in their formula (artificial colostrum) or parenterally to aid in*** resistance against infection and they should not be vaccinated.

There also is evidence to suggest that certain older dogs (seven years of age or more depending on breed) may have a decreased ability to produce antibody as well as a decreased CMI response due to immune senescence. Annual or every three-year revaccination during these later years may be more important to maintain an active state of immunity than in younger dogs. It is assumed that a similar situation exists for cats, but no reported information is available.

Nutritional State of the Animal

A severe nutritionally debilitated animal may not respond adequately to a vaccine. The general state of nutrition should meet minimal recommended standards to ensure that nutritional factors do not interfere with immune responsiveness. If a debilitated dog or cat is vaccinated, vaccination should be repeated when the animal's general condition has improved in order to ensure adequate immunity.

Concurrent Infections

It is important to ensure that animals presented for vaccination are not already incubating the disease. However, this is often difficult to accomplish since known exposure to clinically diseased animals frequently motivates owners to present their animals for vaccination and may lead to so-called "vaccination breakdowns." A detailed history about the possibility of exposure to infected animals should be obtained and a thorough physical examination should be performed for every patient presented for vaccination in order to minimize this risk.

Other diseases may also be associated with immunosuppression and may potentially interfere with successful vaccination. For example, the general state of T cell suppression present in cases of generalized demodectic mange may interfere with the response to vaccination or, at worst, may contraindicate use of live attenuated vaccines. Likewise, dogs infected with distemper virus develop a generalized T cell suppression four days after infection, and vaccination with other antigens during this period may result in an inadequate immune response.

Feline leukemia virus and Feline Immunodeficiency Virus are known to cause immunosuppression in some cats. The immunosuppression may interfere with protective immunity and may increase the apparent virulence of certain attenuated vaccines. Immunosuppression from either of these viruses may be a contraindication for use of modified live vaccines in the immunosuppressed animals.

Drug Treatments

Vaccines should not be given concurrently with immunosuppressive drugs such as cyclophosphamide, azathioprine, methotrexate, and corticosteroids. Corticosteroid treatment in dogs at anti-inflammatory therapeutic levels does not appear to influence antibody responses to vaccine viruses. However, primary vaccination (initial vaccination) cannot be highly recommended in dogs receiving steroid therapy. Animals that must be vaccinated while on immunosuppressive drugs should always be revaccinated several weeks after the treatment has been discontinued.

High doses of steroid are known to reactivate canine herpesvirus and feline viral rhinotracheitis virus (feline herpes) and potentially could cause infection in susceptible contacts.

Immune Serum

The potential of gamma globulin (immunoglobulins) should be re-evaluated and considered for what it is. It must be understood that for gamma globulin or immune serum to be effective it must contain high levels of antibody to the specific organism (e.g., canine distemper or feline panleukopenia) one wants to protect the animal against. Immune serum or gamma globulin will be of little or no value after the clinical signs of disease are present. However, it will be effective if given immediately after contact exposure with a diseased animal. The situations in which immune serum can be recommended are (1) when an animal enters a humane shelter, pet store, or veterinary clinic; (2) newborn, orphaned pups (give immune serum orally or parenterally); and (3) newborn pups from a bitch without canine herpesvirus antibody but experiencing herpesvirus infection.

Artificial colostrum should be given during the first three days after birth to an orphaned pup or kitten. It is made by adding one-half volume adult serum or plasma to one-half milk replacer.

Modified Live Vaccines, and Noninfectious Vaccines, (Killed Vaccines, Inactivated and Subunit Vaccines).

Several types of vaccines are currently used in veterinary medicine: modified live (attenuated) and noninfectious, (killed or inactivated and subunit vaccines) (Table 1). In ***modified live* vaccines**, the microorganisms are altered in such a way that they are no longer virulent to the majority of the host species yet retain the antigenic properties that induce a protective immune response. Modified live vaccines may be given locally or parenterally. Local administration

of certain modified live vaccines to the mucous membranes of the eyes, nose, and mouth produces not only a strong systemic immunity but also a local immune response. Local immunity is important when the point of entry of the microorganism and the target organ of the disease are the same (e.g., feline calicivirus). An effective local immune response requires a live replicating vaccine and usually cannot be produced by noninfectious vaccines (killed or subunit). Some live vaccines are not fully attenuated and may require inoculation by an unusual route to produce immunity without causing disease (e.g., feline viral rhinotracheitis vaccine for IM or subcutaneous should not be given IN or intraocularly). Care must be taken when immunizing with this type of vaccine, because aerosolization or environmental contamination may expose susceptible animals that should not be vaccinated (e.g. drug treated, very young animals), resulting in the development of a mild form of the disease. ***Modified live vaccines must replicate after inoculation*** to produce enough antigen to induce an immune response. Thus, any inactivation of a modified live vaccine before or immediately after inoculation will result in vaccine failure. Because modified live vaccines replicate in the host, they more closely resemble natural infections and generally produce a stronger and more durable protective immune response than the noninfectious vaccines (killed and subunit). Modified live vaccines may also induce interferon in the first few days after immunization, providing additional early protection against some virulent viral infections. However, this "better" immune response may have a cost: a decrease in vaccine safety. Certain modified live vaccines can induce immunosuppression, may be shed into the environment, and may revert to virulence or cause vaccine-induced disease. Thus, even though modified live vaccines generally provide a better immune response that more closely resembles the natural infection, they are not always the best vaccine on all occasions or for all animals (e.g. FeLV or FIV suppressed animals). Fortunately the problems with MLV have been a rare occurrence and modified live canine and feline vaccines have an excellent safety record. I would consider any canine or feline vaccine causing adverse reaction in less than 0.1% (1 in 1,000) to be safe.

Killed vaccines (inactivated) are believed to be safer than modified live vaccines because they cannot replicate and are unable to cause infectious diseases. However, to induce a protective immune response, killed vaccines require a large antigenic dose, often require multiple immunizations, and almost always require the use of adjuvants. These factors substantially increase the cost of inactivated vaccines and the probability of local and systemic vaccine reactions. Also, killed vaccines generally produce weaker immune responses with a shorter duration of immunity than the immune response produced by modified live vaccines. Sometimes the immune responses they produce leads to immunopathological disease at time of natural infection rather than protection from infection. However, some killed vaccines are highly effective and give immunity which is similar to modified live vaccines (e.g. feline panleukopenia, rabies). Killed vaccines should not be considered safter than modified live if they fail to provide protective immunity or induce immune mediated disease (e.g. autoimmune disease).

Subunit vaccines are not infectious. Thus, subunit vaccines and killed vaccines have some of the same advantages and disadvantages. However, instead of containing the complete microorganism as found in the modified live and killed vaccines, the subunit vaccine theoretically contains only the components of the microorganism that are necessary to produce a protective immune response (e.g. new recombinant lyme vaccine containing OSP A). The risk of developing an allergic reaction to nonessential vaccine elements is thus reduced. At present,

subunit vaccines are not frequently used in veterinary medicine because of their higher cost and lack of proven efficacy. However, with the advent of recombinant DNA technology and the recent improvements in adjuvants, subunit vaccines are becoming more common (Lyme vaccine, feline leukemia vaccine). Other types of vaccines are being researched such as synthetic vaccines, viral vectored, anti-idiotype and DNA vaccines. Synthetic and anti-idiotype vaccines have many problems and have limited usefulness at present, thus they are not likely to be marketed in the near future and if they are they are not likely to be efficacious. Viral and/or bacterial vectored vaccines are currently being used to immunize wildlife (e.g. raccoons) for rabies virus and are likely to be used for other common diseases of cats and dogs in the near future. DNA vaccines which are now being tested in a variety of species may also be used in the future to immunize cats and dogs, however, there are certain disadvantages which must be considered. For advantage and disadvantage of commercial types of vaccines and important facts to remember when using each of these see Tables 2, 3.

Table 1

Types of Viral Vaccines

Live-virus vaccines	
Virulent	Delivered by an unnatural route or at a safe age
Attenuated	Naturally occurring or derived by serial passage in eggs or cell culture or chemically mutated
	Genetic manipulation possible: temperature-sensitive, cold-adapted, or deletion mutants; or gene reassortants
Virus/or Bacteria-vectored vaccines	A virus, e.g., vaccinia virus or bacteria, is used as a vector for the gene specifying the protective antigen
Non-Infectious Vaccines	
Killed/Inactivated Vaccines	Partially purified suspensions of virus, inactivated by chemical or physical treatment
Protein vaccines	
Subunit	Partially purified protective protein extracted from virions
"Cloned"	Protein derived by recombinant DNA technology, in bacteria, yeast, or mammalian cell line
Synthetic peptide	Critical epitopes of protective protein synthesized chemically

Table 2

Advantages and Disadvantages of Attenuated Live-Virus and Non-Infectious Vaccines

Parameter	Vaccine Type	
	Attenuated live-virus, Viral Vectored	**Non-Infectious (Inactivated, Killed, Subunit)**
Route of Administration	Natural[a] or Injection	Injection (Parenteral)
Antigen per dose	Low	High or Moderate
Cost (all are inexpensive)	Low to moderate	Moderate
Number of doses needed	Single[b]	Multiple[c] (2 to 3 weeks apart)
Need for adjuvant	No	Yes
Duration of immunity	Many Years to Life	Months or Years
Revaccination	Rarely required (once or several times through life)	Frequently required, six months, yearly or every three years.
Antibody response	IgG; IgA[d], IgM	IgG, IgM (IgE)
Cell-mediated response	Good	Uncertain (no CTL response)
Heat liability[e]	Yes[f]	No
Interference	Occasional[g]	No
Side effects	Occasional mild signs	Occasional to frequent local or general reactions
Danger in pregnant animals	Most MLV are capable of causing problems	No (but caution is required since hypersensitivity or stress may cause problem)
Reversion to virulence	Possible	No
Potential for Contamination	Moderate	Low

[a]Oral or respiratory, in certain cases.
[b]For some live vaccines a second dose may be required
[c]Some inactivated vaccines require only one dose.
[d]IgA developed via oral or respiratory vaccines or if agent replicates locally when inoculated parenterally.
[e]Especially in hot climates
[f]Stabilizers added to vaccine, plus maintenance of "cold chain" delay inactivation.
[g]If administered by oral or respiratory route.

Table 3

Facts to Remember About the Use of Different Types of Vaccines

A.	*Modified Live Vaccines (MLV)*	1. Provide longer duration and more complete immunity than Non-Infectious Vaccines. 2. Cellular and secretory immunity produced. 3. Do not require multiple vaccinations for immunologic memory. 4. Often do not require revaccinating or require fewer revaccinations during life of an animal. 5. Rarely cause hypersensitivities, but may be virulent for certain individual animals or revert to virulence.
B.	*Killed-Inactivated-Non-Infectious Vaccines*	1. Provide short lived systemic immunity. 2. Cellular and secretory immunity generally poor. 3. Require multiple vaccinations for immunity. 4. Often require re-vaccination to ensure immunologic memory. 5. Often cause hypersensitivity reactions. 6. Cannot cause disease even in immunologically compromised animal, but often don't provide complete protective immunity, therefore, animal is susceptible to disease.

Proper Use, Storage, and Administration

All vaccines should be stored according to the manufacturer's recommendations. Lyophilized products should be used immediately after reconstitution and not stored for prolonged periods in the reconstituted form. Modified live vaccines are particularly sensitive to improper storage. This type of vaccine relies on vaccine virus replication to generate enough antigen to induce an immune response. Improper storage conditions may result in the inactivation of modified live vaccines and cause vaccine failures. Although modified live vaccines are more sensitive to improper storage, exposing killed and subunit vaccines to excessive heat or light may also result in reduced immunogenicity. To ensure proper immunization, careful attention should be given to the vaccine storage conditions.

It is important that a new needle and syringe be used to administer each vaccine. Reused syringes and needles may contain contaminants that inactivate the vaccine or interfere with immunization. Vaccines should only be administered at the manufacturer's recommended concentration and reconstituted using the diluent provided with the vaccine. Vaccine products from the same or different manufacturers should never be mixed together in one syringe unless specified in the package insert. Vaccine components from different products may interfere with or inactivate each other, resulting in improper immunization.

Adherence to the recommended route of administration is essential. A rabies vaccine labeled "for intramuscular inoculation only" should not be given subcutaneously. For successful immunization to occur, many modified live rabies vaccines require a well-innervated tissue (i.e., muscle). Nerves serve as a target for rabies virus replication. Viral replication is necessary for the production of enough antigen to induce a protective immune response. Thus, inoculation into the subcutaneous connective tissue (low in nerve endings) often leads to vaccine failure unless the vaccine is specifically approved for subcutaneous inoculation.

There are frequent questions about using partial doses of vaccine in small (toy) breeds to reduce the pain and reactions that often occur with a full dose. It is not possible to use a partial dose of either a modified live or a non-infectious vaccine and ensure that you have delivered an immunizing dose for all components of the vaccine. Therefore, if you find it necessary to use less than the full dose for a puppy or kitten be sure to have blood taken two or more weeks after the last vaccination and have an antibody titer performed. For puppies have canine distemper (CDV) and canine parvovirus (CPV) titers done, the CDV titer should be $\geq$ 1:10 (SN) and CPV should be $\geq$ 1:100 (HI). For kittens have panelukopenia virus (FePLV) titer done with a titer of $\geq$ 1:100 an indication of active immunity. If titers are below these values revaccinate with a full dose because the partial dose did not immunize.

It is important for veterinarians to follow vaccine recommendations not only to ensure successful immunization but also to limit their liability should an adverse reaction or vaccine failure occur.

Vaccination and Immunosuppression

We reported that certain polyvalent vaccines cause immunosuppression, as measured by a significant decrease in the *in vitro* immune function assay (lymphocyte blastogenesis test, Phillips, T.R., Jensen, J.L., Rubino, M.J., Yang, W.C. and Schultz, R.D.: Effects of Vaccines on the Canine Immune System. Am. J. Can. Res. 53:154-160, 1989). When the individual components of the immunosuppressive polyvalent vaccines were inoculated alone into dogs, the immunosuppression did not occur, leading us to believe that the suppression was caused by an interaction between two or more components of the vaccine. We were able to reproduce the

suppression of the polyvalent vaccine by combined inoculations of the CDV component and the canine adenovirus type 1 (CAV-1) or canine adenovirus type 2 (CAV-2) components from various immunosuppressive polyvalent vaccines. Although the degree of suppression induced by some of the polyvalent vaccines was significant (>80% suppression), it was transitory, persisting for 7 to 10 days. Generally, for immunosuppression to be clinically apparent, it must persist a longer time. Thus, vaccination by itself is unlikely to cause detectable adverse effects in an animal. However, under unusual circumstances, even this relatively short duration of lymphocyte suppression may become clinically important, especially if an animal is already in a partially immunosuppressed condition (e.g., nutritional deficiency). Also, it is possible that vaccine-induced immunosuppression may potentiate the severity of a concurrent disease or allow an inapparent infection to become evident (e.g. localized demodex may become generalized).

It is important that results of our study not be misinterpreted. Our results do not suggest that polyvalent vaccines should not be used. All vaccines must be demonstrated safe and efficacious to be licensed. Polyvalent vaccines are efficacious and convenient for both veterinarians and clients. However, vaccination should not be viewed as an innocuous procedure and should be performed in accordance with a manufacturer's recommendations: that is, only *healthy, clinically normal* animals should be vaccinated. If the animal is not healthy and clinically normal at time of vaccination you may need to revaccinate the animal at a later time or you may also cause severe disease and death. It should also be understood that adverse reactions can and will occur in a few animals (less than 1 in 1,000) regardless of the type of vaccine used.

Polyvalent VS. Monovalent Vaccines

Concern has been expressed about the frequent use of polyvalent vaccines in veterinary medicine. This concern primarily deals with the presumed problems of vaccine interference and antigen overload. Antigen overload occurs when the amount of antigen exceeds the ability of the immune system to respond, and vaccine interference occurs when the inoculation of one vaccine prevents the immune response to another vaccine. There is no scientific evidence that either problem occurs with the currently available canine or feline vaccines. However, as discussed earlier, some polyvalent vaccines have been shown to cause transitory immunosuppression and should be avoided when there is a high potential for concurrent immunosuppression. With monovalent vaccines, concerns about antigen overload, vaccine interference, and vaccine-induced immunosuppression are alleviated but at the expense of convenience and cost. Also as we get more and more new vaccines it will be important to give the vaccines separately or in limited combination not to overwhelm the immune system especially of a young puppy or kitten. For example a young puppy need not receive anything other than canine distemper and canine parvovirus at 6 and 9 weeks, then at 12 weeks could receive other compoents such as the canine adenovirus, canine parainfluenza virus, *Bordetella bronchiseptica* (see vaccination recommendations in tables 7 and 8).

Immunization of Hospitalized Patients

All animals entering the hospital for elective procedures, boarding, or grooming should have a current vaccination history. If not, they should be immunized at least 10 days before admission. However, an acutely ill patient that requires immediate hospitalization but does not have a vaccination history, in most cases, should *not* be vaccinated for the following reasons: (1) vaccination is not likely to be effective until at least 3 to 7 days after immunization, (2) the immunosuppression of certain polyvalent vaccines may contribute to the current admitting illness, and (3) if the admitting illness has an immunosuppressive component, vaccination may

not result in effective immunization or, worse, may result in postvaccinal disease (i.e., postvaccinal distemper encephalitis). Furthermore, if the animal has previously been immunized, it is likely that protective immunity remains. An exception to the foregoing counsel would be an outbreak of a new epizootic disease. In an epizootic outbreak, an acutely ill animal and all animals in contact with the sick animal should be immunized against the agent causing the disease, because the chances of exposure are greatly increased.

Annual Vaccinations: Why Do We Vaccinate So Often?

A practice that was started many years ago and that lacks scientific validity or verification is annual revaccinations. Almost without exception there is no immunologic requirement for annual revaccination. Immunity to viruses persists for years or for the life of the animal. Successful vaccination to most bacterial pathogens produces an immunologic memory that remains for years, allowing an animal to develop a protective anamnestic (secondary) response when exposed to virulent organisms. Only the immune response to toxins requires boosters (e.g., tetanus toxin booster, in humans, is recommended once every 7 to 10 years), and no toxin vaccines are currently used for dogs or cats. Furthermore, revaccination with most viral vaccines fails to stimulate an anamnestic (secondary) response as a result of interference by existing antibody (similar to maternal antibody interference). The practice of annual vaccination in our opinion should be considered of questionable efficacy unless it is used as a mechanism to provide an annual physical examination or is required by law (i.e., certain states require annual revaccination for rabies). It is important to ask yourself the question "why do human beings require only a few vaccinations early in life and then not again until much later (e.g. influenza) if at all, whereas dogs and cats are being immunized yearly with virtually every vaccine that is sold.

Vaccine Reactions

It is common for an animal receiving its first immunization to have a mild vaccine reaction. At the site of inoculation, a local reaction consisting of a painful inoculation, pruritus, swelling, redness, or abscess formation can occur. These local reactions are more common with inactivated vaccines, because this type of vaccine often contains adjuvants (local irritants) and also a greater amount of miscellaneous antigens than the modified live vaccines. Mild systemic reactions occur, particularly with modified live vaccines, because these vaccines have virus that replicates after immunization. Vaccine virus replication may be viewed as a mild infection that can result in temperature elevation, decreased activity, or increased irritability.

It is important that pregnant animals not be inoculated with any vaccine unless the vaccine has been approved for this use, because fetal resorptions, abortions, or birth defects may result. Inactivated vaccines have been reported to cause problems when given to pregnant dogs, possibly from the stress associated with vaccination or adverse reactions sometimes resulting from these products. ***Animals younger than 3 weeks should not receive a modified live vaccine, unless the vaccine has been shown to be safe at this early age and none have been shown safe. As a matter of routine practice pups and kittens less than six weeks of age should not be vaccinated!***

An occasional dog (1 in 1,000) developed an immune complex disease after being administered CAV-1 vaccine. This condition is called "blue eye," because the affected eye develops a bluish cast in the cornea. The blue is the result of corneal edema, occurring from the deposition of antigen-antibody complexes. This is an immune-mediated (type III hypersensitivity) reaction. The dog usually regains full vision in the affected eye. Because of this adverse reaction, and

the fact that infectious canine hepatitis caused by CAV-1 is rarely, if ever, seen in the United States most vaccines now contain CAV-2. CAV-2 vaccine does not cause blue eye and effectively protects against both virulent CAV-1 and CAV-2.

On rare occasions, ***anaphylaxis*** (type I hypersensitivity) may occur after immunizations. Anaphylaxis usually develops within an hour after immunization, but may be delayed by up to 18 to 24 hours presenting as weakness, dyspnea, vomiting, mucous membrane pallor, collapse, or death. A canine vaccine component that is most commonly associated with this reaction is the leptospirosis bacterin, although any component including certain of the vaccine adjuvants can cause anaphylaxis. Recently feline vaccines have caused more type I hypersensitivity reactions than seen previously and it is beieved that in certain cases the adjuvants have been a problem and also we have found Chlamydia may be the cause. Animals that develop anaphylaxis should not be reimmunized with the same vaccine until the causative component has been identified. Problem animals should be observed at the veterinary clinic for at least 1 hr after immunization with all vaccines. Titers can be determined rater than revaccinating animals with a history of post-vaccinal hypersensitivity reactions.

In some breeds certain families of animals seem to be at higher risk to vaccine induced immune-mediated diseases. This is not surprising since there is an important genetic component to the development of immune-mediated diseases. It is hard to predict if an adverse reaction is going to occur after vaccination, but a family history of vaccine reactions should be an indication for caution when vaccinating.

A relatively recent problem in cats has been the occurrence of vaccine induced fibrosarcomas. The incidence is not known but reportedly as frequent as 1 in 1,000 vaccinated cats. I suspect the fibrosarcomas are due to transforming elements in the vaccines such as the adjuvants as well as the viruses present in the vaccine and also in the cat. The vaccines most commonly associated with feline fibrosarcomas are rabies and feline leukemia vaccines.

Incomplete vaccine attenuation or vaccination of an immunosuppressed host can result in modified live vaccines causing the disease they are designed to prevent. Examples of this problem are feline respiratory vaccines causing a mild upper respiratory tract disease after immunization and the development of postvaccinal encephalitis subsequent to canine distemper vaccination. An even more alarming example was vaccine induction of clinical rabies in cats. The reasons why vaccines become virulent are not always known, however, it is important that veterinarians be familiar with these possible outcomes of immunization and give modified live vaccines only to approved animals that are in good general health and have no clinical indication of immunosuppression. FeLV and/or FIV positive animals may be more susceptible to the MLV vaccine components thus the killed vaccines may be more appropriate in these cats.

Most of the common acute infectious diseases of dogs and cats have been controlled through the use of conventional vaccines. Although not perfect, these vaccines are exceptionally safe and effective. The future challenge will be to continue to improve the safety and efficacy of our current vaccines and to develop new vaccine approaches for diseases that have thus far been resistant to immunization. As new vaccines have been or are developed for non-conventional infectious diseases (e.g. feline leukemia, feline infectious peritonitis, lyme disease, heartworm, cat scratch fever) with a component of the disease strongly influenced by genetic, immunologic or other factors, vaccines will be less effective and more problematic.

Vaccination Failure

A summary of the various factors that can lead to vaccination failure are listed in Table 4. The most common cause of vaccination failures in pups and kittens is interference of active immunization by maternal antibody, but many other factors lead to complete or partial failure.

Future Vaccines

Many new vaccines will be developed and licensed during the next ten years for dogs and cats. New and old technologies will be used to develop these products. Many of the new products will be sold as individual component vaccines since they will be specialty products (e.g. feline toxoplasmosis, feline immunodeficiency virus, canine rotavirus, canine herpesvirus, canine brucellosis).

Minimal Disease Prevention

The following basic recommendations are based on information from a variety of sources and years of experience performing research on vaccines and should be considered my best judgment on recommendations for vaccinating dogs and cats, Tables 5 and 6 lists the vaccines currently advailable and Table 7 and 8 are my recommendations for disease prevention in dogs and cats.

Table 4

CAUSES OF VACCINATION FAILURE

Host Factors	Vaccine Factors	Human Error
1. **Maternal Antibody interference**	1. Improper storage	1. Giving partial dose of vaccine
2. Immunodeficiencies/ Immunosuppression	2. Inactivated during handling	2. Improper mixing of products
3. Pregnancy	3. Vaccines don't always protect	3. Concurrent use of microbials/ immunosuppressive drugs
4. Age: very young or old	4. Disinfectant used on needles and syringes	4. Simultaneous use of antisera
5. Pyrexia, hypothermia	5. Wrong strain of pathogen in vaccine	5. Too frequent administration (<2 week interval) or too long between multiple doses of non-infectious vaccine (> 8 weeks)
6. Incubating disease at time of Vaccination	6. Improper or inadequate adjuvant	6. Disinfection of skin?
7. Drugs: cytotoxic, glucocorticoids (immunosuppressive)	7. Not enough antigen or too many antigens	7. Improper Vaccination Schedule
8. Anesthesia/antibiotics?	8. Non-immunogenic strain due to over attenuation	8. Wrong route of administration
9. Genetics (non-responder or poor responder	9. Poor quality vaccine	9. Wrong vaccine

? = uncertain

Table 5

Vaccines Currently Available for Dogs

Vaccine	Type of Vaccine	Age to VaccinateAs Per Manufacturer
Canine Distemper Virus (CDV)	Modified Live Virus *Killed Virus	First vaccination at 6 to 8 wks of age; second vaccination need not be given until 12 to 14 wks of age, but can be given at 9 to 11 weeks then third vaccination at 12 to 14 weeks.
Measles Virus (MV)/Combined with CDV	Modified Live Virus	Vaccinate at 4 to 8 wks of age, then vaccinate with CDV vaccine at 12 to 16 weeks. There is no need to use in dogs 12 weeks of age or older, use CDV vaccine only! Use when CDV is a known problem such as humane shelters, pet shops, kennels.
Canine Parvovirus Vaccine	Modified Live Virus *Killed Virus	Vaccination schedule same as CDV vaccine. If CPV is a known problem (clinical cases have been seen) give at 6 weeks also, give at 9 to 11 wks in addition to 12 to 14 wks.
Infectious Canine Hepatitis (CAV-1) Canine Adenovirus-2 (CAV-2)	**Modified Live Virus *Killed Virus	Vaccination schedule is same as for CDV vaccine and is commonly given with CDV in a combined vaccine. Be sure to use a product with CAV-2 NOT CAV-1.
Canine Coronavirus (CCV)	*Killed Virus Modified Live Virus	Vaccination schedule is same as for CDV vaccine and is commonly given with CDV in a combined vaccine (I do not recommend)
Rabies Virus	Modified Live Virus	First vaccination at 3 to 4 months of age; revaccinate at 1 year and every 3 years thereafter; if dog is over 4 months of age at first vaccination, revaccinate in 1 year, then once every 3 years. (Some states still may require annual vaccination)
	Killed Virus	First vaccination at 3 to 4 months; second vaccination in 3 to 4 wks; revaccinate at 1 year; revaccinate every three years. (Some states may require annual rabies vaccination.)
Canine Parainfluenza Virus (CPI)	Modified Live Virus *Killed Virus	Give as combined vaccine with canine distemper or the preferred combination is CPI with Bordetella given intranasally. The time of administration can be the same time the CDV product is given.
Canine Leptospirosis	***Killed Bacteria	If first vaccine is at 6 to 8 wks, second vaccine at 9 to 12 wks; if first vaccination at 9 to 12 wks; revaccinate when administering CDV-CAV-2 vaccine at 12 to 14 wks. Revaccinate annually if leptospirosis is a problem in your area. Because duration of immunity is limited and risk is low, this vaccine is not used in certain areas of the U.S.
Canine Bordetella	Modified Live Vaccine ***Killed Bacteria	If first vaccine is at 6 to 8 wks, second vaccine at 10 to 12 wks; if first vaccination at 10 to 12 wks; revaccinate when administering second CDV-CAV-2 vaccine at 14 to 16 wks. The preferred vaccine is to combine with CPI and give intranasally. Annual revaccination is probably necessary for dogs at high risk.
Borrelia-Lyme Vaccine	*Killed Bacteria	First vaccination at 12 or more weeks of age, second dose which is required, should be given 2 to 3 wks. later. Annual revaccination is recommended and should be done in early spring. (I do not recommend this vaccine)

*I do not recommend killed vaccine for this disease, always use the modified live product
**I do not recommend any product with CAV-1, only the CAV-2 products should be used due to post-vaccinal uveitis caused by CAV-1 vaccines
***Interval between 2 doses of killed vaccines should not be less than 2 weeks nor more than 4 to 6 weeks

NOTE: In general annual vaccinations are not necessary for most modified live viral vaccines, but they are often recommended. (See recommendation in Table 7 & 8)

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VACCINES CURRENTLY ABAILABLE FOR CATS

Vaccine	Type of Vaccine	Age to Vaccinate
Feline Panleukopenia (FPLV) (Parvovirus)	Modified Live Virus Inactivated Virus	First vaccination at 6 to 10 weeks of age; second vaccination at 12 to 14 weeks of age. Both modified live and inactivated are excellent and annual revaccination is not necessary, but recommended by manufacturer.
Feline Viral Rhinotracheitis (FVR) (Herpesvirus)	Modified Live Virus Inactivated Virus	Given at same time as FPLV vaccine and in combination. Annual vaccination is recommended by manufacturer.
Feline Calicivirus (FCV)	MLV Inactivated Virus	Given at same time as FPLV vaccine and in combination. Annual vaccination is recommended.
Feline Pneumonitis (Chlamydia)	ML	First dose at 8 to 10 weeks, second dose at 12 to 14 weeks. (I do not recommend this vaccine)
Rabies Virus	Inactivated	First dose at 12 weeks of age or older. Annual or every three years revaccination recommended depending on vaccine given and State of residence.
Feline Leukemia Virus (FeLV) (Retrovirus)	Sub Unit Inactivated Recombinant	First dose at 8 to 9 weeks, second dose at 11 to 12 weeks (both must be given) (I do not recommend these vaccines for routine immunization and only recommend in exceptional circumstances.
Feline Infectious Peritonitis (FIP)	Modified Live (Temp. Restricted)	First dose at 12 weeks, second dose at 14 to 16 weeks (I do not recommend this vaccine).

Table 7
Dr. Schultz's Vaccination Recommendations for Prevention of Canine and Feline Diseases

DOGS

Age at First Vaccination	Recommendation
6 to 8 weeks of age (I do not recommend routine vaccination at earlier age)	1st vaccination Canine Distemper (CDV) and Canine Parvovirus (PCV) only 2nd vaccine 2 to 3 weeks after first vaccination, CDV and CPV only 3rd vaccination 2 to 3 weeks later CDV, CPV, CAV-2, intranasal canine parainfluenza and *Bordetella bronchiseptica* (CPI/Bb), Rabies virus (RV)[1]
9 to 14 weeks of age	Omit the first dose of CDV and CPV follow 2nd & 3rd vaccination above
Greater than 14 weeks of age	Give one dose CDV, CPV, CAV-2, intranasal CPI/Bb[2] and RV[1].
Vaccination at 1 Yr of age	Give CDV, CPV, CAV-2, intranasal CPI/Bb[2] and RV[1]
Vaccination at 3 to 4 Yr of age	Rabies, intranasal CPI/Bb[2]
Vaccination at 6 to 7 Yr of age	Rabies, intranasal CPI/Bb[2]
Vaccination at 9 to 10 Yr of age	Rabies intranasal CPI/Bb[2]
Vaccination at 12 Yr or older	Revaccinate annually with all components of the vaccines used previously (3rd vaccination above).

[1]Separate site (intramuscular rabies vaccine preferred)
[2]If dog is boarded, goes to shows, or is kennel dog

NOTE: I do not recommend using Canine Corona Virus (CCV) vaccine at any age, but I believe if you do use CCV you need only give it up to 12 to 14 weeks of age (older dogs would never need CCV!)

I do not recommend Lyme Vaccine because of concerns about efficacy and safety. If dog should develop clinical disease, which is rare, treat it with antibiotics.

I do not recommend Leptospirosis vaccine. There are few cases of Leptospirosis and those cases are rarely caused by the two serovars in the vaccine; cross reactive immunity to leptospirosis does not occur.

Based on the current information the above recommendations will provide adequate immunity from the infectious diseases of dogs that can be prevented by current vaccines. These recommendations are provided as the minimum disease prevention program that is required and the recommendations should and need to be modified and tailored to the individual animal. It is your responsibility as the veterinarian to recommend what in your judgement is the best vaccination program for the prevention of disease in your patient and that will meet the dog's needs and satisfy the client!

Table 8
Dr. Schultz's Vaccination Recommendations for Prevention of Canine and Feline Diseases

CATS

Age at First Vaccination	Recommendation
6 to 8 weeks of age (I do not recommend routine vaccination at earlier age)	1st vaccination parenteral Feline panleukopenia virus (FPLV) Feline viral rhinotracheitis (FVR) and Feline Calicivirus (FCV) 2nd vaccine 2 to 3 weeks later FPL parenteral FVR/FCV intranasal 3rd vaccination same as second vaccination plus rabies vaccine (RV).
9 to 13 weeks of age	Same as above except omit the first vaccination, give 2nd and 3rd
Greater than 13 weeks of age	Just give the third vaccination as listed above.

Vaccination should be repeated annually or every three years for rabies
FVR/FCV could be repeated every 3 to 5 years if cat is taken to shows or boarded.

1. Rabies should be given at separate and different site from other vaccines

NOTE:

I do not recommend chlamydia vaccine

I do not recommend feline leukemia vaccine. Instead I recommend that all cats be tested for viremia (FeLV positive) and positive cats be eliminated from the population if there is any chance they will come in contact with other cats. If FeLV vaccine is used for kittens I see no need for annual revaccination.

I do not recommend feline infectious peritonitis vaccine.

Based on the current information the above recommendations will provide adequate immunity from the infectious diseases of cats that can be prevented by current vaccines. These recommendations are provided as the minimum disease prevention program that is required and the recommendations should and need to be modified and tailored to the individual animal. It is your responsibility as the veterinarian to recommend what in your judgement is the best vaccination program for the prevention of disease in your patient and that will meet the cat's needs and satisfy the client!