

Titer Testing And Vaccination: A New Look at Traditional Practices

A Roundtable Discussion

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Titer Testing and Vaccination: Key Points

1. Many practitioners are following decades-old guidelines and vaccinating pets annually, but duration of immunity—especially for the most essential vaccines—often lasts much longer than one year (pages 1-4).
2. Risks associated with overvaccination include fibrosarcomas in cats and immunologic disease in all patients, but practitioners face many challenges in changing their recommendations (pages 4-7):
 - They must be confident that their patients are protected from disease.
 - They must convince clients that the changes will not jeopardize pets' health.
 - They must persuade clients to keep coming in for annual examinations.
3. In-office testing of antibody titers, if accompanied by clear guidelines for interpretation, will potentially assist veterinarians in making sound medical decisions that are in their patients' best interest (pages 7-12).

Titer Testing and Vaccination: A New Look at Traditional Practices

While difficult to prove, risks associated with overvaccination are an increasing concern among veterinarians. These experts say antibody titer testing may prove to be a valuable tool in determining your patients' vaccination needs.

An outdated approach?

DR. RONALD SCHULTZ: I would like our group to discuss issues related to vaccines, vaccination programs, and how we can best use antibody titers to monitor vaccinal immunity in cats and dogs. Let's begin with this question: How often should pets be vaccinated after the initial puppy and kitten vaccines are given?

DR. RICHARD FORD: That's a difficult question, and the answer depends on the specific vaccine under consideration. In the May 2001 issue of *Veterinary Clinics of North America*, there was considerable discussion, vaccine by vaccine, on recommended booster intervals for adult dogs and cats. Perhaps it would be helpful to look back in time and attempt to understand how we arrived at the annual booster recommendation in the first place.

SCHULTZ: Back in the 1950s when the first vaccines for canine distemper were being developed, Dr. James A. Baker and his colleagues at Cornell University conducted a distemper vaccine trial in dogs. When they tested the animals a year after vaccination, they found that about one-third of them had antibody titers that were not considered protective. In order to ensure immunity for dogs receiving one of the first experimental canine vaccines, Dr. Baker recommended annual revaccination for all the vaccinated dogs. In

1961, Dr. S.E. Piercy of the United Kingdom wrote the following in *Veterinary Record* about the canine distemper vaccine:

It is felt, therefore, that the usefulness of booster injections in dogs already immune is still open to question and cannot be truly evaluated until considerably more research has been done. The value of revaccinating dogs whose antibodies have declined to a low level, however, is not in doubt. Although a serum analysis (antibody titer) is the most scientific way of judging the need for revaccination, in practice, the owner would assumably be obliged to pay a fee for the examination and a further fee should revaccination be advised. The alternative and less expensive way for the owner is simply to have the animal revaccinated if there is a reason to doubt its immune status and it is likely to be exposed to infection. The practitioner is favorably placed to advise what should be done in light of such local circumstances as the incidence of canine distemper in his district, the history of the animal concerned, the risk involved in going to shows and kennels, and other similar hazards.

So it was individuals like Dr. Baker and Dr. Piercy who believed revaccination should occur annually for all dogs to ensure that those with low or no titers in the vaccinated population were protected.

FORD: And the fact is, we have not progressed beyond that 1960s approach. Only in the last few years have we questioned whether it's necessary to vaccinate dogs and cats annually. I think we would all agree that vaccinating adult cats for feline parvovirus (panleukopenia or feline distemper virus) annually is not necessary. The current recommendations out-

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Highlights

Annual vaccination guidelines are the result of studies performed in the 1950s and further publicized in the 1960s. Researchers at the time wanted to ensure immunity in the entire pet population.

Determining vaccines' duration of immunity has become an important issue as the veterinary profession, especially in regard to cats, examines whether annual vaccinations are necessary and healthy for pets.

Even under the best circumstances, some vaccines never provide complete protection from infection and disease.

While many practitioners recognize that it may be necessary to reevaluate vaccination standards, they need solid information to guide any changes they make.

lined in the 2000 Report of the American Association of Feline Practitioners (AAFP) and Academy of Feline Medicine Advisory Panel on Feline Vaccines are that adult cats be vaccinated every three years for parvovirus, herpesvirus, and calicivirus only. While no single group makes recommendations for dogs, people representing multiple groups will present guidelines for canine vaccines. These issues are of great concern to practitioners and pet owners alike. Throughout this discussion, it will be important to address the science behind duration of immunity as we know it today.

SCHULTZ: Fred, what do you think about this issue as it applies to cats?

DR. FRED SCOTT: I agree with Rich that the need for the initial series of feline parvovirus vaccinations in kittens is essential. Once cats are vaccinated and develop a good response, protection will last for many years. Annual revaccination is definitely not necessary for parvovirus. But the situation is different for herpesvirus and calicivirus. These vaccines do not provide 100% protection in cats even two weeks after vaccination. Practitioners need to realize that some vaccines, especially the respiratory vaccines, do not produce 100% protection even under the best of circumstances. The protection decreases over time, but it's still significant for many years.

SCHULTZ: Jory, how do you view this particular question in a practice situation?

DR. JORY OLSEN: I agree with your viewpoints that annual revaccinations, at least for certain vaccines, are not necessary. But it's more difficult in a referral practice to make recommendations about how often to give vaccines—first, because the information is still being gathered, and second, because we're trying not to contradict referring veterinarians. We have to rely on solid information regarding vaccine efficacy and duration of immunity, which, at this point, is not readily available. A titer can be misleading because it can be a false negative: The anti-

body titer may be low, but the animal is still immune to that disease. And even if the titer suggests the animal is immune, it may take time for certain clients and veterinarians to be comfortable with vaccinating their animals less frequently because of the long history of the one-year vaccination interval. We certainly encounter clients and, in some cases, veterinarians who are unaware of recent information on vaccine effectiveness. New information on duration of immunity needs to reach veterinarians and clients so they understand that less-frequent vaccination does not put the animals at risk. We still have some questions about the efficacy and duration of immunity of certain vaccines and how long the protection lasts. But we are confident that at least canine and feline core vaccines are effective far longer than one year as we thought in the past.



“Some vaccines do not produce 100% protection even under the best of circumstances, but the protection is still significant for many years.”

Fred Scott, DVM, PhD, DACVM

Core vaccines

SCHULTZ: Your mentioning core vaccines brings up our second question. Are there any vaccines that every dog and cat should receive? The AAFP has delineated its recommendations clearly for feline core vaccines, and, as mentioned earlier, canine guidelines should be available soon.

SCOTT: That's true. Certainly feline parvovirus, herpesvirus, and calicivirus are the big three. In most areas, rabies would also be included. But I think the AAFP has backed away from using the term *core*. What is your take on that, Rich?

FORD: That's correct; the AAFP Advisory Panel has elected not to use that term. The American Animal Hospital Association—in cooperation with representatives from other associations and groups—has formed a task force to develop

guidelines for canine vaccinations. And one of its objectives is to define *core* and *noncore*, terms we have been using to describe the vaccines that every dog and cat should receive vs. those that are optional. Arguably, this distinction does give the veterinarian an opportunity to make sound medical decisions about whether or not to administer a particular vaccine. The distinction between core and noncore vaccines is important in light of the fact that we have experienced a significant proliferation of companion animal vaccines in the last 20 years. You would have to agree that it is totally illogical to recommend inoculating every adult dog and cat every year with every licensed vaccine, yet it happens. In the absence of any kind of national vaccination standard for companion animals, I think that the concept of core and noncore vaccines is still meaningful.

SCOTT: The AAEP's last report used the terminology *highly recommended* rather than *core*. But I think the principle of core and noncore vaccines is probably easier to understand.

SCHULTZ: The AAEP may have made that change for two reasons. We've mentioned three of the four core vaccines for cats—parvovirus, herpesvirus, and calicivirus. Some disease experts were concerned about using rabies virus and others wondered about the herpes-calici complex. The concern about rabies vaccines was their association with vaccine-associated fibrosarcomas and whether they are necessary in certain cat populations (*e.g.* those that never leave the house). The concern about herpesvirus involves efficacy; and for calicivirus vaccines, concern surrounds the development of the carrier state being more common in vaccinated cats and whether the strain (serotype) of virus in the current vaccines is appropriate. There will always be some people who question a committee's definition of *core*. Yet I think the disease experts should work together to identify the vaccines that they believe most, if not all, animals should receive. Maybe that is the reason some are using the terminology *highly recommended* rather than calling them *core*—because there are concerns that not all cats should receive core vaccines. Jory, you're in a position to make

recommendations about this issue. What do you think about core vs. noncore vaccines?

OLSEN: I think the word *core*, or some version of it, is very important. It's easier for clients to understand—the experts have studied this issue and believe that these vaccines are important for all animals, no matter where they live or what their risks are. The vaccines that are necessary are clear: For cats, it's parvovirus, herpesvirus, and calicivirus. Dogs need distemper, adenovirus, and parvovirus vaccinations. Rabies vaccine is necessary for both dogs and cats.

SCHULTZ: I agree. It is essential that at least one dose of the core vaccines be given to puppies and kittens that are 12 weeks of age or older regardless of the number of vaccine doses given before that age. Rabies should be given one time between the ages of 12 and 16 weeks and then again at 1 year of age or a year after the first dose was given. Revaccination at one year is also recommended with the other canine and feline core vaccines.

Efficacy and duration of immunity

SCHULTZ: Fred, what do you think about the efficacy of the feline core vaccines?

SCOTT: If we ranked these four core vaccines, the parvovirus vaccines—both killed and modified-live types—would be the most efficacious. They produce close to 100% protection in cats, probably better than any other veterinary vaccine. Rabies vaccine would be the second-most efficacious. Calicivirus and herpesvirus vaccines would be least efficacious. But even these vaccines are 70% to 90% effective against virulent challenge a few weeks after vaccination. Their efficacy decreases slightly over many years. Our studies showed a 50% efficacy for herpesvirus vaccine after seven years, although the number of cats in the study was small. Certainly the antibodies decline over time, but for herpesvirus they are never very high although significant protection remains even after many years.

SCHULTZ: What do you think about the efficacy of distemper, adenovirus-2, parvovirus, and rabies vaccines in dogs?

Highlights

Core vaccines are those every dog and cat should receive. Core vaccines for dogs are:

- distemper
- adenovirus
- parvovirus
- rabies.

Core vaccines for cats are:

- feline parvovirus
- herpesvirus
- calicivirus
- rabies.

Although some groups, notably the AAEP, have questioned the terminology of *core* vs. *noncore* (which refers to vaccines every animal should receive vs. those that are optional), the concept is still useful.

With the proliferation of vaccines on the market, both veterinarians and pet owners need a standard that tells them which vaccines are essential regardless of where a patient lives and what its risks are.

Highlights

While some vaccines have a higher degree of efficacy for a longer period than others, all core vaccines for dogs and cats are efficacious and provide significant protection.

Most practitioners expect that a licensed vaccine is safe and effective if used correctly, but the government defines efficacy in a more limited manner—the term simply validates controlled studies and does not guarantee 100% immunity in all animals under all circumstances.

Studies have confirmed that duration of immunity for core vaccines is at least three years, but it is likely much longer.

If practitioners are going to start vaccinating patients less frequently, they need a way to evaluate immunity on an individual basis and to be confident in their recommendations. What used to be a simple process—annual vaccination—has become much more complicated.

FORD: All of the vaccines you've mentioned are excellent. While we're discussing efficacy, I think it's important to address what efficacy means to practitioners. In reality, the term *efficacy* means one thing to the USDA but something else to practitioners. Practitioners expect that if a product is licensed, it's efficacious. To most practitioners, efficacy means the vaccine works, it's safe, and it will effectively immunize animals if they follow the manufacturer's recommendations for administration. It's my impression that the term *efficacy* is, in fact, a somewhat unique term used by the manufacturer when applying to the USDA for vaccine licensure. It's a term used to validate results of controlled studies, typically in a limited number of animals, when it has been possible to demonstrate a vaccine's ability to provide protection against a defined, standardized challenge. In no way does the term *efficacy* imply the vaccine will protect all animals at all stages of life following vaccination.

SCHULTZ: I agree. Practitioners expect that if a vaccine is licensed, it should provide immunity; however, that isn't necessarily true, especially among the noncore group of canine and feline vaccines. But the canine and feline core vaccines are among the most efficacious products on the market, and canine core vaccines compare favorably to one another in terms of overall protection. I recently tested canine core vaccines (distemper, parvovirus, and adenovirus) repeatedly and found very few differences among the major manufacturers' current products. In our studies, we challenged animals and also evaluated antibody titers to determine duration of immunity for certain canine vaccines. In the challenge studies, we found a minimum of seven years' duration of immunity for distemper, parvovirus, and adenovirus vaccines. And based on antibody titers, immunity lasts even longer. All three-year rabies vaccines require protection from challenge at three years and we find antibody remains at protective levels even longer. We need to remember that these studies determined the minimum duration of immunity; the animals weren't challenged again so we don't know the full extent of immunity. Based on our studies in dogs and

Fred's studies in cats, the minimum duration of immunity for the canine and feline core vaccines is at least three years and more likely two or three times that long.

OLSEN: I agree that we have a group of vaccines that are very effective and with which we're comfortable. But we have to look at efficacy and duration of immunity as a whole new problem. The majority of veterinarians resist changing their vaccination protocols because they're uncomfortable dealing with this issue. If they have a product licensed for one year, they believe it's guaranteed to protect their patients for one year. They vaccinate their patients the next year and guarantee that same protection for another year. Now we're asking them to give the vaccine less frequently because we know it provides protection for longer than a year. Yet no one has really demonstrated the vaccine's efficacy for any set interval, and certainly not for individual animals. We see patients with certain diseases, primarily immunologic deficiencies, that are vaccinated annually but develop no titers. This response may indicate that the vaccine failed at some level. Because we didn't run titers in the past, we couldn't identify this problem; we didn't look at animals immunologically to see if they were responding to vaccines. Now we have to evaluate efficacy and duration of immunity for all these vaccines and try to determine how often they should be given. There are many considerations now for what used to be a simple process.

What's wrong with vaccinating annually?

SCHULTZ: I hear this question often, and I'm sure you do, too: Even if these vaccines provide a long duration of immunity, what's wrong with vaccinating annually? What harm will it cause? I also hear that annual revaccination is the best way to get clients to bring in their pets for examinations every year.

FORD: Let's look at that question from a somewhat different perspective. The biggest threat posed by not vaccinating every year is that the client then sees no reason to bring the patient

to the practice on an annual basis. We have taught our clients to come in every year for vaccines. To tell them their pets don't really need annual vaccinations represents a big change—one that has to be backed by solid scientific fact. We will have to justify why it's necessary to change the recommendations we've made for many years. I believe that repeated injections of immunogenic proteins can potentially be harmful. I work on the internal medicine service in a busy referral teaching hospital. My colleagues and I are all concerned about the inordinate number of cases we see of autoimmune disease like immune-mediated hemolytic anemia, thrombocytopenia, and polyarthritis—more than ever before.



“My colleagues and I are all concerned about the inordinate number of cases we see of autoimmune disease—more than ever before.”

Richard B. Ford, DVM, DACVIM

SCOTT: With any medical procedure, one has to evaluate the risks and benefits. In feline practice, the risks vs. benefits issue for revaccination became extremely important when we started to see fibrosarcomas develop after vaccination. Practitioners began to ask if yearly vaccination was in their patients' best interest, and a number of them concluded that perhaps it was not. That conclusion drove us to reevaluate our approach to vaccination in general.

OLSEN: I think we underestimate how many problems overvaccination may be causing. But, as Rich stated, it is very difficult to prove. At our practice, we think overvaccination probably causes immunologic problems or at least contributes to immunologic problems. I think there are a vast number of other diseases—immunologic or degenerative diseases such as atopy, chronic allergies, asthma, and other airway diseases—that are exaggerated by, caused by, or stimulated by overvaccination. But it is impossible to prove. Those considerations will

be the driving force in changing our thinking about vaccination intervals.

FORD: Jory, may I play “devil's advocate” with you on that point? Many veterinarians tell me that if they vaccinate every three years, the risk-to-benefit ratio is very high because they will see animals less often. As a result, they'll detect disease later or not at all. By the time they see the patient, it will be beyond help. Vaccinating annually offers them the opportunity to examine and detect disease in an animal that only has a life span of approximately 12 years.

OLSEN: But that approach is changing. Long ago animals came in for vaccination and barely got a physical exam. Then clients were being charged for vaccinations and received a complimentary physical exam; thus the importance of the exam was still downplayed. Now practitioners are figuring out what is important and trying to retrain their clients. They are starting to charge for physical exams as the primary reason for the visit, with vaccination as a sideline. They can then say to their clients, “It isn't necessary for your pet to be vaccinated this year, but I do need to perform a careful physical exam, and we'll discuss the findings together.” If we educate clients, we will continue to see their pets regularly and we won't be causing the problems associated with overvaccination. But the change is slow. Only occasionally do I see reminder cards that say, “It's time for Fifi to come in for a physical exam and be reevaluated for the need for vaccines.”

SCHULTZ: I tell practitioners that vaccines are drugs, albeit biological drugs. I remind them that they would not consider it good medicine to give an unnecessary pharmaceutical drug on a recurring basis. I think it is even worse to give a vaccine, or biological drug, that isn't necessary. The possible adverse consequences of a vaccine generally far outweigh the adverse consequences of a pharmaceutical drug. A pharmaceutical drug is usually much more restricted in its action. However, each time we stimulate

Highlights

The risks associated with overvaccination include:

- fibrosarcomas
- immune-mediated hemolytic anemia
- thrombocytopenia
- polyarthritis
- atopy
- chronic allergies
- asthma and other respiratory diseases.

However, the link between most of these problems and overvaccination is very difficult to prove.

An important concern is that if practitioners don't vaccinate annually, they may not see their patients as often—clients might not bring their pets in for annual examinations. By the time an animal develops disease and is brought to the clinic, it may be beyond help.

Practitioners are starting to educate their clients about the necessity of annual examinations, and they must continue this approach if they are going to vaccinate less frequently.

Administering drugs unnecessarily is not good medical practice, and a vaccine is a drug—with a wider spectrum of activity than a pharmaceutical agent.

Highlights

Interpreting titers correctly depends on the disease in question. Some titers must reach a certain level to indicate immunity, but with others, the presence of any antibodies at all shows protection.

It's important to know whether a kitten or puppy has been effectively immunized when it is most vulnerable to disease. Antibody titers can measure that response.

A positive test result is fairly straightforward, but a negative test result is more problematic for interpretation. It doesn't necessarily mean an animal is unprotected.

an immune response, we have to look at the effect on all body systems—not only on antibody responses or cell-mediated immunity, but also on interactions with the endocrine system and the nervous system. We all agree that vaccination should be considered an important medical practice—not just something done on an annual basis because many years ago it was the most convenient way to improve immunity in dogs given canine distemper vaccines.

Interpreting antibody titers

SCHULTZ: Now let's consider antibody titers. How can they be used to help determine the duration of immunity or efficacy for different vaccines? The answer varies by vaccine. For example, the feline herpesvirus antibody titer is typically very low, and protective immunity is not determined by the antibody titer. However, the presence of antibody, regardless of amount, would show a response to vaccine and immunologic memory. Jory suggested earlier that even animals without antibody (a negative or zero titer) can still experience protection—that is true for feline herpesvirus, but not for canine distemper or canine parvovirus. If you have no distemper titer after vaccination, that animal may be protected, but you don't know for sure—low or no titer for distemper suggests that the vaccine didn't immunize. And no titer for parvovirus is problematic for both cats and dogs. An animal may be able to resist parvovirus disease depending on its age, but the risk of disease is greater if the animal is young and didn't produce antibodies after vaccination. Titer information would be very helpful to determine if the vaccination program in the puppy or kitten was effective. That is, did that vaccine stimulate an antibody response? If you vaccinate with the conventional core vaccines, the modified-live and killed vaccines (which could include whole-killed or subunit-killed vaccines), and there is no antibody response, the animal probably has not been immunized and you should vaccinate again. The problem may be the vaccine or it may be the animal. It is important to know if the animal has responded immunologically to

vaccination, and antibody is the most effective measure of that response.

SCOTT: I agree that antibody titer interpretation varies depending on the disease in question and the causative agent involved. For some diseases, such as feline parvovirus infection, the situation is fairly straightforward. A parvovirus neutralizing antibody titer of 1:10 or greater is consistent with solid protection against infection and clinical disease caused by the virus. But as Ron mentioned, antibody titer interpretation for feline herpesvirus and calicivirus is quite different. After vaccination against feline herpesvirus, antibody titers may or may not be positive. If the titer is positive, it indicates a significant degree of protection against severe clinical disease, but the cat can still be reinfected and shed virus. If the herpesvirus antibody titer is negative, you do not know the immune status of that cat. For feline calicivirus, antibody titers are generally positive after vaccination and indicate significant protection against clinical disease, but not protection against reinfection and shed of virus. To complicate the issue with feline calicivirus, some nonvaccinated cats have low, nonspecific antibody titers that do not provide any protection.



“Titer information would be very helpful to determine if a vaccination program was effective. That is, did that vaccine stimulate an antibody response?”

Ronald Schultz, DVM, PhD, DACVM

SCHULTZ: We see sterile immunity with a variety of canine diseases, namely distemper, adenovirus, and parvovirus. Sterile immunity is the ultimate immunologic or vaccinal protection. Sterile immunity is protection against reinfection or the establishment of reinfection—thus there can be no disease. With nonsterile immunity, infection occurs, though it is localized with no or very mild clinical signs. We know from many studies that the canine antibody titers defined as protective do protect against

infection and provide sterile immunity (*e.g.* >1:80 parvovirus-2, >1:20 distemper virus, >1:50 adenovirus-1). However, that doesn't mean that an animal with a lower titer won't be protected from disease. That animal may become infected, but the infection may be limited and not lead to clinical disease. If disease does occur, it will be very mild. Thus, if a dog with a 1:4 distemper virus titer is challenged with virulent distemper virus, it will be infected but not diseased because it will have a significant increase in antibody titer and cellular immunity immediately after challenge.

FORD: The difference between sterile and non-sterile immunity confuses many practitioners. I think they equate the presence of antibody with sterile immunity. They don't understand why a cat given a respiratory virus vaccine can still experience mild upper respiratory signs after exposure to virulent virus.

SCHULTZ: For certain vaccines, such as herpesvirus and calicivirus, the best we can expect from the vaccine is limited infection with mild or moderate clinical signs of disease.

OLSEN: I have a different slant on that. I think many veterinarians are confused about what to make of antibody levels and immunity. This is no surprise because the information varies with the vaccine and the goal of vaccination for each animal. They wonder if a patient has protection when it has antibodies or no protection when it has no antibodies.

SCHULTZ: I agree that there's a lot of confusion among veterinarians, and I think teachers, like myself, have created some of that confusion. We tend to make immunology black and white, but there is almost nothing black or white about it. Everything is gray. We teach veterinary students that animals experience either humoral immunity, in which antibody plays a major role, or cell-mediated immunity, in which T cells, macrophages, and similar cells play a major role. Then students who later become practitioners believe that an animal's immune response involves one or the other. In reality, it is virtually impossible for a normal

animal's immune system to develop one response to the total exclusion of the other. Yet when we teach immunology, we don't get that fact across to the student.

A vaccinated animal develops both cell-mediated and humoral immunity in response to all vaccines. With regard to how these two parts of the immune system protect the animal, we teach that cell-mediated immunity targets intracellular pathogens and humoral immunity targets extracellular pathogens. So practitioners deduce that immunologic protection from a viral infection, an intracellular pathogen, is mediated by cell-mediated immunity, and antibodies are effective only against extracellular bacteria. Well, that's true in immunologically naïve animals (animals that have never been vaccinated). Their recovery from viral infection and disease is mediated primarily by cellular immunity because they are only starting to mount an effective immune response when the virus becomes intracellular. In contrast, vaccinated animals with pre-existing antibodies are often protected by humoral immunity. Viruses, especially those spread by aerosol or orally, are initially extracellular. So the moment they come in contact with antibodies in a vaccinated animal, they are neutralized and infection either doesn't occur, which is sterile immunity, or infection is so limited that it doesn't cause clinical disease.

Unfortunately, not enough folks teaching immunology explain the process so students understand the complexities of vaccine-induced immunity, and there are significant differences between the mechanism of protective immunity to the same pathogen in a naïve vs. a vaccinated animal. I, in academia, accept some of the blame for the confusion, but I also place some blame on my colleagues in industry, especially those who market vaccines. They have done a much better job of educating practitioners to their way of selling vaccines than immunologists have done in teaching the facts about vaccine-induced immunity.

Uses for in-office titer testing

FORD: On another point, may I ask the panel to discuss why veterinarians would use in-office tests to determine vaccine titers? I can think of

Highlights

Sterile immunity protects an animal from infection. Vaccines providing sterile immunity are those for:

- distemper
- adenovirus
- parvovirus.

Nonsterile immunity may not protect the animal from infection but will keep the infection from progressing to severe clinical disease. Vaccines providing nonsterile immunity are those for:

- herpesvirus
- calicivirus.

Vaccinated animals experience both cell-mediated and humoral immunity when exposed to pathogens such as viruses. Miscommunication about the complex nature of vaccine-induced immunity may be why many practitioners are confused about these issues.

Highlights

There are four reasons for in-office titer testing:

1. To determine whether an animal is protected (suggested by a positive test result)
2. To identify a susceptible animal (suggested by a negative test result)
3. To determine whether an individual animal has responded to a vaccine
4. To determine whether an individual vaccine is effectively immunizing animals.

In-office titer testing may help practitioners and owners become comfortable with longer vaccination intervals. This may be especially beneficial in patients most at risk for problems associated with overvaccination, such as immunologic diseases and cancer.

A negative titer test result is not the same thing as a zero titer. A negative result means the titer does not reach the threshold of providing sterile immunity.

four reasons why one would consider determining antibody titers instead of vaccinating. The first reason is to determine protection. The test result is positive; therefore, the animal is protected. The second reason is to identify susceptible animals—in other words, a negative test result. Number three is to determine the ability of an individual patient to respond to a vaccine, such as a rottweiler or Doberman. And the fourth reason is to define the ability of the vaccine to immunize. How do the other participants in this discussion feel about that?

OLSEN: We have used vaccine titers for about six years in our practice. We started using them primarily for patients with diseases that would be worsened by overvaccination, such as patients with immunologic disease and cancer in remission. We try to establish the vaccines' duration of immunity and to determine whether a patient requires vaccination at that time. I agree with Rich's four reasons, but I think the test would be used most often to determine if an animal is protected.

SCHULTZ: Fred, what do you think about practitioners using vaccine titers? How useful are they?

SCOTT: Evaluation of antibody titers prior to revaccination may be beneficial in some situations. For patients in which the risks associated with vaccination are very high, titer testing gives the veterinarian and the owner comfort in knowing that the animal has antibodies and is probably protected, so it's acceptable not to vaccinate. Evaluation of antibody titers also reassures veterinarians as they move from annual vaccinations to vaccinating every three years. If they run titers and determine that they are maintaining protection, they'll be more confident about making this change.

SCHULTZ: I talk to many practitioners who have been using titers for several years, and one reason they started using them was this comfort factor. After changing their vaccination programs, they and the client need reassurance that the patient did have immunity. Being able to measure antibody response is important to both the practitioner and the

client. And that ability will be reassuring to many owners—I think they often drive the decision to vaccinate annually. I know a number of veterinarians who are adamant about not wanting to vaccinate annually with core vaccines, yet their clients aren't comfortable with that recommendation.

FORD: All of us have agreed that the first two reasons are appropriate indications for an in-office titer test. The first reason is to define protection, which is suggested by a positive test result. And the second reason is to identify susceptibility, which is suggested by a negative test result. I think it's as important to define a negative test as it is to define a positive test result. Ron, earlier in the discussion you used the term *no titer*. The term I would use for that is *zero titer*. To say that an animal has a negative test is not the same as saying an animal has a zero titer. Would you agree?

SCHULTZ: Yes, but it would depend on the test being used. Ideally, an in-office test would be positive if an animal's titer was equal to or greater than the titer considered to provide sterile immunity and negative if it was below that level. But clearly we are talking about a different situation if a laboratory performed the titer test; the result would be a specific titer because the serum is tested at many dilutions. In the case of canine parvovirus, the titer that provides sterile immunity is approximately 1:100. That titer is determined by hemagglutination inhibition (HI) or virus neutralization (VN).

Unfortunately, the HI test is not practical to run as an in-office test. Only a few diagnostic laboratories run it—and this is a big problem for practitioners who want a laboratory to perform a valid titer test for specific vaccine antigens. There is a difference between titers run in a laboratory where they can determine the specific dilutions and an in-office test that determines titer thresholds (*i.e.* when the titer is equal to or greater than the titer for sterile immunity, it will be positive, and when it is less than that titer, it will be negative). Dogs with a positive test need not be vaccinated. Dogs with a negative test may be immune from disease, but the antibody level is not high enough to

provide sterile immunity. If you were to revaccinate the dog with a negative test, the titers should increase, whereas the dogs that are positive will have protection from disease and should even be protected from infection.

Let's consider an example: You've just given three puppy vaccinations at 6, 9, and 12 weeks, and you run the in-office test one to two weeks after the last dose of vaccine to see if the puppy is positive or negative. I would be concerned if it is negative, since that would suggest the puppy has not responded to the vaccine. In that case, I believe another vaccine should be given. When another dose is given, the test should become positive unless the titer is still below the threshold level. It is possible for the test to remain negative when the animal is either a genetically deficient nonresponder or a low responder. It would be important to examine the animal and to do further testing when continued revaccination fails to stimulate a positive antibody response. There is a high likelihood that this animal, if infected with parvovirus, would develop the disease and die.



“We use titers to try to establish the vaccines’ duration of immunity and to determine whether a patient requires vaccination at that time.”

Jory Olsen, DVM, DACVIM

Relating test results to vaccination needs

FORD: Ron, my point in asking the test-interpretation question is that if a practitioner uses an in-office titer test to evaluate a patient for immunity, the decision tree for a positive and a negative test result must be clear. What can practitioners say for sure about a particular threshold titer and the need for vaccination?

SCHULTZ: That's an important point; practitioners need to know what to do with the test results. In general, if the result is positive, the animal is above the titer threshold and would not be expected to benefit from revaccination.

If negative, the animal is below the threshold and may benefit from vaccination. But to make the appropriate decision, practitioners need to consider the results along with the animal's medical history and risk factors.

For example, if a dog has a serious disease and a parvovirus vaccination could jeopardize its health, you might follow up that negative test with a more complete titer analysis. The dog could have a 1:20 parvovirus titer, which does not provide sterile immunity, but if infected it could develop a protective immune response and not show signs of disease. The decision is clearer with a healthy dog. If the test is positive, you don't need to revaccinate; if it's negative, you should certainly consider revaccination. Again, this test is a guide in making the correct medical decision. You should still evaluate the pet's health and risk factors. Thus, if you had an in-office test with results available while the client was in the office, would it be useful? How so?

OLSEN: The test would be useful when deciding which vaccine, if any, a pet needs at the time of revaccination. It would be more convenient to get the results while the client is at the clinic than to call the next day or week and say, “Your pet does need to be vaccinated; please come back tomorrow.”

FORD: I have a question. Let's say I examine an adult dog two years after its last vaccination. At that time I choose to test this animal for canine parvovirus and canine distemper virus, and the dog has a positive test result for both. My decision tree begins at that point. Am I confident that this dog does not need to be vaccinated for another year? Do I replace annual boosters with this test? Could the dog have a negative test result within the next year or within the next week? How do I decide whether to revaccinate or wait another year and test again? Could the animal become susceptible tomorrow?

OLSEN: That can be a difficult decision, depending on the vaccine and the time frame.

Highlights

An ideal in-office test would produce a positive result if an animal had sterile immunity and a negative result if it did not. However, with a negative result, revaccination won't necessarily increase the titer to the sterile level.

Any decision about whether to revaccinate an animal needs to be considered along with the medical history and risk factors. The test is a guide, not the decision itself.

If an in-office titer test result is negative, a complete titer analysis by a commercial laboratory might provide more specific information about that patient's level of disease protection. If the result is positive, that animal has immunity and doesn't require revaccination.

An in-office titer test would be convenient for practitioners and clients by allowing them to get information about a patient's immune status during the office visit.

Highlights

Protection as indicated by a positive titer result is not likely to suddenly drop off unless an animal develops a medical problem such as cancer and receives immunosuppressive drugs. Research shows that once an animal's titer stabilizes, it is likely to remain constant for many years.

Most patients show immunity for three years after vaccination. After that point, antibody titer testing can help guide vaccination decisions.

Viral vaccines prompt an immune response that lasts much longer than that prompted by classic antigen. Lack of distinction between the two kinds of responses may be why practitioners think titers can suddenly disappear.

But if you are talking about one, two, or three years after vaccinating with core vaccines, the decision is easier because we are confident that those vaccines are effective well beyond that range. At four, five, or six years, though, it's more difficult. We don't know if the vaccine-induced immunity is going to last $5\frac{1}{2}$ or $6\frac{1}{3}$ years. We perform titer testing three years after vaccination. We are very confident of this time frame because so many patients vaccinated at three-year intervals have demonstrated protection. At three years, we start testing yearly; we have been doing this for six years.

SCHULTZ: We often talk about a titer as a snapshot in time. As it turns out, it's more like a motion picture that plays on and on. An animal's titer is highest right after vaccination. The titer then decreases but stabilizes within six months to a year and often remains at that level for many years. Both our research studies with experimental dogs and our experience at the University of Wisconsin Veterinary Medical Teaching Hospital (VMTH) support the finding that titers are very stable whether or not animals are revaccinated. We have been vaccinating animals once every three years for over five years. We've checked distemper, parvovirus, and adenovirus titers of virtually every dog that has come into our clinic and then returned. The titers are very consistent regardless of the interval since vaccination. There were no differences whether the dogs had been vaccinated two, three, or four years prior to collecting the sample for testing.

We have also examined titers of dogs in a commercial colony that were not revaccinated after the initial puppy vaccinations and found that the titers to these three viruses remain about the same year after year. That doesn't mean that the titer can't change. For example, if an animal develops cancer and is treated with immunosuppressive drugs, its titers may change significantly. But in most animals, the titers to the core vaccines remain constant for a long period. Also, frequent revaccination does not change the titer. I have also checked the distemper and parvovirus titers of research dogs for over seven years. It's amazing how similar the titers were among dogs that weren't vac-

nated during that time, compared to dogs that were vaccinated every three years and dogs that were vaccinated annually. I have not found annual revaccination to make a significant difference with regard to titers or protection. Fred, has your experience with cats been similar?

SCOTT: Yes; cats respond initially to parvovirus vaccination, and then the titers plateau. We did not detect any significant drop in postvaccination parvovirus antibody titers over a seven-year period. Parvovirus immunity is solid and long-term. Herpesvirus and calicivirus antibody titers gradually decrease over several years after vaccination, but it's not a precipitous drop. Furthermore, the titer to herpesvirus is never very high. Rich asked earlier whether a titer would be lower three months after testing. If the animal responds and the titer is tested a year or more after vaccination, it will be relatively consistent for many years. Unlike antibody titers against bacteria that tend to be relatively short in duration, antibody titers against viruses do not dramatically change unless something happens medically with the animal, such as chemotherapy, which interferes with the immune system.

SCHULTZ: This discussion points out the difference between vaccinology and immunology. We've probably misled students and practitioners in discussing what happens with a classic antigen like bovine serum albumin in a mouse; in this situation, you give a dose of antigen and get a primary response that then drops off. And you give another dose and the antibody level goes higher, then falls off again. That is far different from what happens with modified-live vaccines or even killed adjuvanted vaccines: There is very little correlation with the antibody response to classic antigen. The modified-live vaccine induces a marked response after the first dose and the response often persists at a high level for years without revaccination. This is one of the reasons that practitioners believe titers can disappear overnight. The other question I get when I talk about titers is whether research dogs respond differently to vaccination than pet dogs. With research dogs, their environment is controlled, the animals

are well-fed, and they often don't have endoparasites. Most of the research dogs are beagles, and the beagle may not be representative of other breeds. So what happens in the real world to pets that aren't cared for as well as research animals? That's one reason we are doing the studies on the VMTH animals. These animals are very diverse with regard to breed and general care. Yet when we compare the VMTH data with research colony data, there's little difference—both groups seem to provide the same general results with regard to persistence of immunity. However, there is evidence for some breed or family differences, and individual animal variations are expected.

OLSEN: We haven't discussed the challenges of titer interpretation in cats. Dr. Mike Lappin of Colorado State has measured clinic cats' titers. He showed that when they were due for parvovirus, herpesvirus, or calicivirus vaccines, 68% to 92% of the cats had titers. He was able to determine that those cats did not require vaccination, but he couldn't make a decision on the negative cats based on titer alone. Some academics and practitioners would say that since the titer test reveals nothing about what negative cats need, it's worthless. But my feeling is that it may have saved 68% to 92% of the cats from being vaccinated unnecessarily. So it's clearly beneficial. But we haven't discussed how to interpret a negative titer in a cat.

SCOTT: You're right. A positive herpesvirus or calicivirus titer indicates a significant degree of immunity, and the cat doesn't need to be revaccinated. As mentioned earlier, the one caveat to a positive calicivirus titer being protective is that a few nonvaccinated cats have a nonspecific low calicivirus antibody titer but aren't protected. The problem is that you don't know a cat's immune status with a negative test. It doesn't mean the animal is not protected, but you have no way of knowing, so you have to revaccinate those cats with negative herpesvirus or calicivirus antibody titers.

SCHULTZ: Jory, you've made a good point; we should look at what we're doing for the health of the animal that has a positive antibody test.

We are deciding not to revaccinate. If this decision affects even 50% of animals (and I know it affects considerably more with canine distemper and parvovirus), then those 50% will not receive an unnecessary drug and are spared the risk of developing an adverse reaction. The other 50%, of course, may be revaccinated and don't need to be, but that's better than 100%.

Titer testing and noncore vaccines

SCHULTZ: Practitioners often ask if there will be titer tests for diseases other than canine distemper and parvovirus. Distemper and parvovirus vaccines are only two of the many vaccines available for dogs. Practitioners want to know what they should do about determining a leptospirosis titer or Lyme disease titer.

OLSEN: There are different groups of noncore vaccines: those recommended for animals at risk and others that are noncore, nonrecommended vaccines. For example, we recommend leptospirosis vaccination at relatively short intervals for patients exposed to bodies of water or living in high incidence areas. Then we have vaccines such as coronavirus, which most clinicians would agree is a noncore, nonrecommended vaccine. So you have to categorize these vaccines and consider their duration of immunity and the risk factors of each pet.

FORD: There are 18 different types of canine vaccines on the market today. I'm not talking about different products, but different vaccines. There are 12 for the cat. And there are more in development. Determining the most appropriate protocol for the individual patient is quite complex. In clinical practice, we don't have ready access to titer testing for most of these vaccines. If your question involves how we measure the immunity provided by noncore vaccines, I assume the only way to do that is with actual laboratory challenge studies. It becomes extremely difficult to obtain serum antibody titers for what we have referred to here as noncore vaccines. Fred, what about cats? You can't rely on serum antibody titers to predict the level of immunity to feline leukemia virus (FeLV) vaccines.

Highlights

Studies show little difference in vaccine-induced immunity between dogs in research studies and dogs in the general population. Both groups retain the same persistence of immunity, although there are differences among breeds and individual animals.

A cat with a negative herpesvirus or calicivirus titer result may or may not have immunity—there's no way to know for sure. In this situation, it's probably necessary to revaccinate the cat.

Although negative test results are less clear about animals' immune status than positive results, titer testing is still beneficial if it protects a significant percentage of pets from being overvaccinated and placed at risk for adverse reactions.

Highlights

The decision whether to give noncore vaccines, such as those for Lyme disease and leptospirosis, must be evaluated in light of the patient's risk factors.

Most noncore vaccines have a relatively short duration of immunity and must be given annually to maximize protection. In this situation, titer testing would not be beneficial.

The development of in-office titer testing might aid in the development of standardization and quality assurance. Right now, results vary widely among laboratories and practitioners aren't able to rely on them with any consistency.

There is less risk associated with taking a blood sample for a titer test than giving an unnecessary vaccination.

SCOTT: No, FeLV antibody titer tests are not available commercially. And feline infectious peritonitis (FIP) antibody titers are a tremendous can of worms. There is great variation from lab to lab in the reliability of FIP antibody titer tests. These tests generally only measure feline coronavirus antibodies, and there are many questions about any correlation between a positive antibody titer and protection.

SCHULTZ: The noncore vaccines are for high-risk animals. These particular vaccines are generally bacterial products: the *Leptospira*, *Bordetella*, and *Borrelia burgdorferi* vaccines. If we recommend them because the animal is at risk, we would give them at least annually because most of these products don't have a long duration of immunity. Doing an antibody titer for those vaccines would be a moot point. Now, for that category of noncore vaccines that Jory nicely categorized as nonrecommended, I have heard them referred to as "vaccines that should never be given during the lifetime of the dog," such as coronavirus vaccine. Why would you want a titer test for an infection that rarely leads to clinical disease? If it does cause disease, it's usually in an animal that's less than 8 weeks old, so you don't need to do titer tests on those animals.

The only canine vaccines that we haven't discussed in relation to titers are two core agents: rabies virus and adenovirus. I tell practitioners that we don't need to determine these titers because canine adenovirus-1, the virus that causes infectious canine hepatitis, is an exotic disease and we're not seeing it in North America. And canine adenovirus-2 is ubiquitous in the environment and doesn't cause significant clinical disease, though it can contribute to canine respiratory disease complex. We're not in a position to decide about rabies because the law has already established revaccination intervals. If you're using a three-year rabies vaccine, the minimum duration of immunity has already been established by the USDA—that is the longest interval allowed by law for revaccination, so why would you want to do a titer? Thus, for dogs, titer tests should be available and used for the two most important infectious diseases, distemper and par-

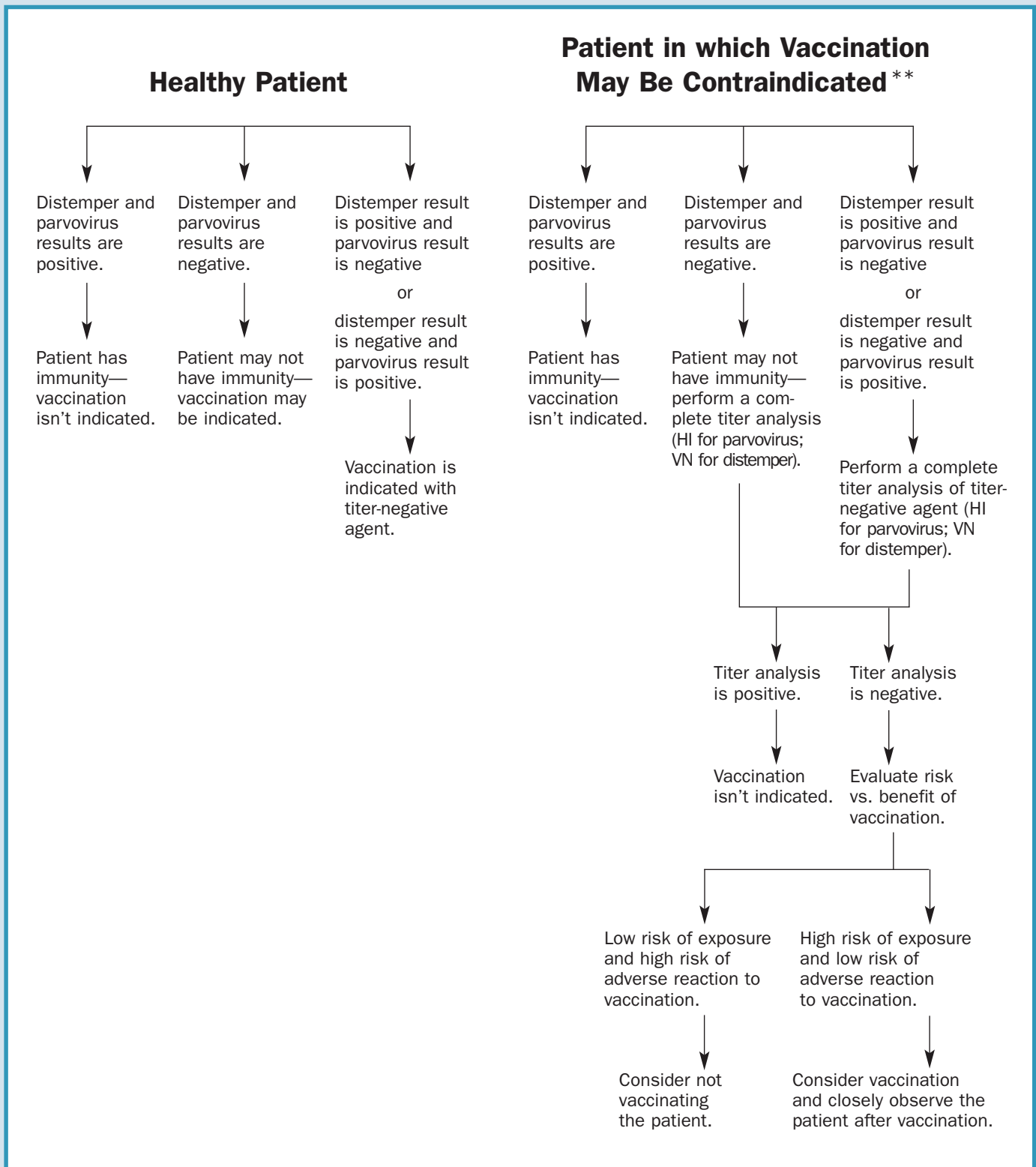
vovirus infection. We could make a similar case for feline parvovirus and calicivirus as the two most valuable for titer determinations. But for the noncore feline vaccines, such as *Chlamydia*, *Bordetella*, and FeLV, testing would not be useful.

Conclusion

SCHULTZ: The development and availability of an in-office antibody test might also provide an opportunity for standardization and quality assurance. Once the product is available, commercial laboratories can begin testing and comparing samples that have been tested with the in-office product. Currently there is no standardization among labs. Practitioners are limited on where they can have a titer done. There are few laboratories offering tests that correlate with the titers I have established in my own laboratory as providing sterile immunity. I've gone through a fairly elaborate procedure of standardizing and determining what I consider titers for sterile immunity. Unfortunately, not many laboratories have done a similar comparison. Also, I know of no commercial laboratories that perform VN tests for distemper or parvovirus. In fact, there are only a few commercial labs that do an HI test for parvovirus or a VN test for distemper. It really restricts practitioners' ability to use the laboratory titer tests to make medical decisions.

I'm excited about the possibility of an in-office test providing immediate results to aid decisions about revaccination. I'm often asked if I recommend annual titers. My answer is no because of the time and expense associated with titer testing and the variability among laboratories. I don't think a titer needs to replace annual vaccination—neither are necessary every year because of the core vaccines' duration of immunity. However, I would rather see a blood sample taken yearly from an animal for a titer check than for that animal to receive an unnecessary vaccination. I know that a vaccine may cause harm. Medically, however, I don't know of any harm that might come from taking a blood sample and doing a titer check. Also, I know there are many practitioners and owners who need assurance that an animal does have immunity. An antibody test could give them that assurance.

Interpreting Canine Distemper and Parvovirus Titer Results*



* When deciding whether or not to vaccinate, consider the patient's medical history and risk factors in addition to the test results.

** Examples include dogs with a history of adverse reactions to vaccination, immune-mediated diseases, allergies exacerbated by immune stimulation, cancer in remission, and asthma and other respiratory diseases.

VACCINATION

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