# Dispelling the Myths of Canine Cancer and Its Treatment

Douglas Thamm, VMD, DACVIM; Colorado State University

There is still a great stigma attached to a diagnosis of cancer, and it is natural for owners of dogs with cancer to equate cancer treatment in animals with experiences they may have had with treatment of themselves, their friends or family members. Having an understanding of how cancer treatment in animals and humans differs can insure that dog owners make an informed decision when selecting treatment for their dog with cancer.

*Is cancer really a problem in dogs?* Unfortunately, yes. It is the leading "natural" cause of death in dogs. Up to 50% of dogs will be affected by some type of tumor in their lifetime.

*Why does is seem like there so much more cancer in dogs these days?* Better health care = longer life. We are getting so good at managing other husbandry-related conditions in dogs (nutrition, infectious/parasitic disease, keeping pets indoors and on leashes) that they are now living long enough to develop more old-age conditions such as heart disease, kidney disease, endocrine disease, and **cancer**. Furthermore, now that there are more cancer specialists and options for treating cancer in pets, it is being reported more frequently.

*Did something in the environment play a role in my dog's cancer? Was I feeding the wrong food?* There have been some associations proposed between certain types of cancer and environmental influences (canine lymphoma and certain herbicides or living in urban environments, canine mesothelioma and asbestos), but in the vast majority of cases no such association can be made. Thus, based on what we know currently, food additives, lawn chemicals, pesticides, cosmic rays, etc. do not seem to significantly increase a dog's risk of cancer.

*Why should I treat my dog with cancer?* Because we can! We treat many animals with chronic disease that are never cured (Diabetes, other endocrine diseases, heart disease), and cancer is another chronic disease. Furthermore, cancer is a disease that we can sometimes cure! Even in cases where cure is unlikely, there are many cancers where we can extend an excellent quality of life with treatment.

*Do we have to do XXX for this mass now? Can't we just wait and see what happens?* This applies to initial diagnostic tests **(let's wait and see if it grows),** additional surgery or other treatments to prevent local regrowth after surgery **(let's wait and see if it grows BACK)**, or therapy to delay or prevent spread **(let's wait and see if it spreads)**. Let's wait and see if it grows: In general, delay in achieving a diagnosis only serves to increase the difficulty of treatment and, potentially, the likelihood of spread. Larger tumor size is statistically associated with worse outcome for several important veterinary cancers, including canine mammary carcinoma and oral melanoma. The lump you are dealing with may very well be nothing, but if it is a tumor, the time to find that out is sooner rather than later. Let's wait and see if it grows back: Locally recurrent tumors are statistically associated with a worse prognosis in certain diseases such as canine mast cell tumor and oral melanoma, and are suspected of being worse in others. For this reason, if a tumor is incompletely removed the time to get aggressive is the very first time the tumor occurs. Let's wait and see if it spreads: In general, treatment of gross

metastatic disease is palliative at best. Asking drugs to kill a big bulky tumor is asking a lot, but asking those same drugs to have an effect against microscopic tumor cells in the lung or lymph node may be a much more reasonable goal. For example, the median survival time for dogs with osteosarcoma undergoing amputation, but not receiving chemotherapy until the time of metastasis, is approximately **6 months** whereas the survival time for dogs receiving chemotherapy for microscopic metastasis immediately after surgery is approximately **12 months**.

*Doesn't performing a fine needle aspirate/biopsy make the tumor "angry" and increase the risk of spread?* **NO.** Getting from the primary tumor into the blood stream is only one of many hurdles a tumor cell must overcome to successfully spread. There are probably many circulating tumor cells in the body all the time, but it is only those few tumor cells with the complete genetic program that allow them to survive and grow at a distant site that will be able to successfully spread. Exceptions to this rule are: (1) Some mast cell tumors may become "inflamed" following a fine needle aspirate due to histamine release, although this in no way hastens spread. This is rarely serious and can be treated or prevented with an antihistamine such as Benadryl; (2) Needle aspiration/needle core biopsy of splenic and bladder masses is inadvisable, due to the risk of local tumor dissemination in the abdomen and/or seeding of the biopsy tract. (3) It is important that needle aspirates and biopsies of cutaneous/subcutaneous masses are planned so that the biopsy tract can be incorporated into the definitive surgical excision to prevent recurrence along the tract.

*Why don't we just take the tumor off? Why do we need to do a fine needle aspirate/biopsy first?* Obtaining a diagnosis prior to surgery helps to plan the surgical approach and lets the veterinarian know whether additional tests are indicated prior to surgery. This helps avoid situations like **"Why didn't you take X-rays before surgery?"** and **"Why should I have to pay for a second surgery if you 'didn't get it all' the first time?"**. If surgical removal is used to obtain a diagnosis, it is important to understand that this is only being used as a diagnostic test, and that additional tests or treatments might be necessary, based on the results.

*Why should I pay for histopathology? Why don't you just take it off and throw it away?* If it's worth removing, it's worth submitting for microscopic evaluation. See "just wait and see" above for problems with the "we'll submit it for histopathology if it recurs" approach. Similarly, it is important to avoid submission of parts of removed tissue or a "representative section" of a removed mass. This cuts the information gleaned from the pathology report in half, as **surgical margins** cannot be interpreted.

*My Great Aunt Harriet had chemo, and she felt miserable all the time - I'd never do that to my dog!* The drugs we use to treat cancer in animals are the same drugs that humans get, but we give considerably lower doses and don't give as many at the same time to minimize the risk of adverse effects. **With most chemotherapy protocols in common use, less than 1/4 of patients experience unpleasant side effects, and 5% or less experience a severe side effect.** The rare adverse effect necessitating hospitalization can usually be fixed in 24-72 hours. The likelihood of a chemotherapy-related fatality is less than 1 in 200. Should unpleasant side effects occur, doses can be reduced, drugs can be substituted, or additional medications dispensed to minimize the likelihood of further adverse effects. These changes are effective 90% of the time.

*OK, suppose my dog is the unfortunate one that has a side effect? What kind of things are we likely to see?* This varies by agent, but in general the most common side effect is something related to the **gastrointestinal tract** – perhaps a few days of decreased appetite, mild nausea or vomiting, or loose stool. By way of comparison, it's usually not too different from what you might see if a dog got into the garbage. They might need to eat some bland food for a few days or take some anti-nausea or anti-diarrhea pills at home. Usually this doesn't persist for more than 3-5 days. Some dogs have the potential to develop a low **white blood cell count**. We check this quite frequently, and most of the time it is not low enough to be dangerous. In some cases, a patient might need some oral antibiotics at home, or a treatment might need to be delayed for a few days. If a patient develops a **serious** side effect, it is usually either REALLY BAD vomiting/diarrhea (can't keep anything down, getting weak/dehydrated) or dangerous lowering of their white blood cell count that renders them susceptible to a bacterial infection.

*I don't want my dog to go bald!* It is true that certain breeds (non-shedding breeds) can lose substantial amounts of hair from chemotherapy. It is rarely complete. Most other breeds experience little or no hair loss, although you may probably find more hair around the house and long-haired breeds have the potential for excessive matting. Hair loss from chemotherapy is non-itchy and nonpainful – it is a purely cosmetic change. Hair that is lost will typically begin to regrow approximately 1 month following the completion of therapy.

*I don't want my dog's last weeks / months / years to be in and out of the hospital, like they were with Uncle Mac when he had cancer.* Almost all veterinary chemotherapy treatments are done in an <u>outpatient</u> setting, and the majority involve quick injections rather than prolonged infusions (there are exceptions to this however). Many protocols involve a series of treatments, followed by a period of careful observation. Continuous, indefinite chemotherapy is not the norm.

*I don't want my family / guests / house / other pets to be contaminated.* Urine and feces pose a minimal risk to owners -- few drugs are excreted for longer than 48-72 hours. Common sense (i.e. wear gloves when handling urine or feces) is usually sufficient. Accidents in the house during this period should be cleaned using a dilute bleach solution and the excreta flushed down the toilet. Normal daily interactions (grooming, playing, petting, handling food and water bowls) pose no real risk. It is important to wear gloves when handling oral medications, and that chemotherapy pills should never be crushed or split, nor capsules opened.

*But what about her age? Isn't she too old for treatment?* AGE IS NOT A DISEASE! Most of the patients we treat with cancer are older dogs. Statistics regarding effectiveness, survival and tolerability of cancer therapy are usually generated in a population of older patients. Far more important than chronological age are general health (e.g. heart, liver, kidneys) and how they are feeling.

*So what are our choices? We either do chemo or put him to sleep?* Chemotherapy (and cancer therapy in general) is usually **not** an "all-or-nothing" proposition. For may tumor types, a spectrum of treatment options may be available depending on travel constraints, finances, risk of side effects, etc. For example, there are various treatments for canine lymphoma from which an owner can choose, including prednisone alone, prednisone plus doxorubicin,

cyclophosphamide/vincristine/prednisone, or a multi-agent injectable protocol such as the UW-Madison protocol. All have different costs, risks of side effects and numbers of trips required and varying degrees of effectiveness. For osteosarcoma, amputation and platinum-based chemotherapy may be the optimal treatment, but other options could include palliative radiation therapy or amputation plus doxorubicin.

*What about radiation therapy for my dog's tumor?* Radiation therapy can be very useful for certain tumors. Since it is a local treatment, it is **most often used to treat local disease**, e.g. tumors with a high likelihood of aggressive local infiltration and regrowth but a low risk of spread. Common examples include postoperative treatment of incompletely excised low-or intermediate-grade mast cell tumors, soft-tissue sarcomas, oral tumors such as fibrosarcoma, squamous cell carcinoma and dental tumors, and perianal tumors. It can be used prior to surgery in certain cases to render an inoperable tumor more amenable to surgery. It can also be used as the primary therapy for certain tumors such as nasal tumors. Finally, it can be used to improve quality of life in some highly metastatic tumors such as osteosarcoma and malignant melanoma. The majority of "definitive" or "full-course" radiation therapy protocols in common use involve a series of 10 to 25 treatments delivered either Monday through Friday or three days per week for several weeks. Although there is no reason why these treatments cannot be delivered on an outpatient basis, many animals will spend some of the time in the hospital for practical, travel-related reasons. Most "palliative" or "coarsely fractionated" radiation therapy protocols will involve 1 to 6 weekly treatments on an outpatient basis.

*But won't he be horribly sick from radiation?* Radiation therapy is a **local** form of therapy – the radiation is only delivered to the site of the disease. Thus, systemic side effects (nausea, fatigue, bone marrow suppression) generally do not occur. However, **each treatment does require very brief anesthesia** or heavy sedation to insure that the radiation is delivered to the correct spot. In theory, there could be systemic adverse effects as a result of the anesthesia, but they are very rare in the patient with normal organ function.

*What about radiation burns?* It's true that animals receiving radiation therapy can develop varying degrees of a sunburn-like reaction at the site where the radiation is delivered. These can range from mild redness and itchiness to moist, oozing or ulcerated skin. Many animals will need to wear an Elizabethan collar to prevent self-trauma and/or receive oral antibiotics and/or pain medications during this period. These effects typically do not start until the second or third week of treatment and are resolved within 2-4 weeks after the completion of radiation therapy. The animal can be left with an area of irradiated skin that is permanently hairless, the hair may grow back only partially, and may turn white within the radiation field. Chronic, long-term side effects are rare, with the exception of the eyes in animals receiving radiation therapy for nasal, oral or brain tumors.

*Will he be radioactive when he comes home?* The standard form of radiation therapy in animals is **external beam**, i.e. radiation is shone down from an external source, practically not that different from a diagnostic X-ray except using higher energy particles. Animals undergoing radiation therapy pose no health risk to their owners and they are not radioactive.

References

Withrow SJ. Why worry about cancer in pets? *In* Withrow SJ, MacEwen EG (eds): Small Animal Clinical Oncology, 3rd Ed. Philadelphia: Saunders, 2001. pp. 1-3.

Harvey A, Butler C, Lagoni L, Durrance D, Withrow SJ. A bond-centered practice approach to diagnosis, treatment and euthanasia. *In* Withrow SJ, MacEwen EG (eds): Small Animal Clinical Oncology, 3rd Ed. Philadelphia: Saunders, 2001. pp. 672-682.

Chun R, Garrett L, MacEwen EG. Cancer chemotherapy. *In* Withrow SJ, MacEwen EG (eds): Small Animal Clinical Oncology, 3rd Ed. Philadelphia: Saunders, 2001. pp. 92-118.

Moore AS. Radiation therapy for the treatment of tumours in small companion animals. *Vet J* 2002;164(3):176-87.

Thrall DE. Biologic basis of radiation therapy. *Vet Clin North Am Small Anim Pract* 1997;27(1):21-3.

**Biographical Profile**

Dr. Thamm is an Assistant Professor of Oncology at the Colorado State University Animal Cancer Center, within the College of Veterinary Medicine and Biomedical Sciences. He is also a member of the Developmental Therapeutics Section of the University of Colorado Comprehensive Cancer Center and the Cell and Molecular Biology Graduate Program at Colorado State University. Dr. Thamm received his Bachelors and V.M.D. degrees from the University of Pennsylvania. He completed a Residency in Medical Oncology at the University of Wisconsin, and was employed as a postdoctoral researcher there for 5 additional years. He is the author of over 30 peer-reviewed publications, 10 book chapters and 70 research abstracts in the field of veterinary oncology and cancer research. His clinical interests include novel targeted, cytotoxic and biotherapies for animal cancer and the translational application of these therapies to human oncology. His laboratory interests focus on tyrosine kinase growth factor receptors in canine and feline neoplasia, and on novel strategies to increase cancer cell sensitivity to chemotherapy.

*Dr. Thamm's research has been supported by the following grant:*

*591: In Vitro Effects of the Milk Thistle Extract Silibinin in Canine Tumor Cells*

# Cancer Stem Cells: A New Way To Look at an Old Disease

Jaime Modiano, VMD, PhD; University of Minnesota

Cancer and Public Health. Undoubtedly, cancer is among the conditions that will have the most significant impact on the health and well being of people and their pets during the 21st century. The entity that is cancer has been recognized since the times of the ancient Greeks, but it was only in the latter part of the 20th century that we began to understand why cancer happens. As the art and science of medicine and veterinary medicine reduced morbidity and mortality from other causes and the expected lifespan increased, cancer became more prevalent in the human and canine populations. Today, cancer is the leading cause of death in people under the age of 85, and it is the most common cause of disease-related death in dogs. It is estimated that ~30% of people and dogs will get cancer in their lifetime, and in dogs, more than half of those affected will die from their disease.

Despite these grim statistics, we cannot ignore advances that we have achieved in diagnosis and treatment of cancer. With proper standard of care, cancer patients can reasonably expect to add at least 10% of a lifetime after their diagnosis and many patients survive cancer and lead normal, productive and healthy lives. Because cures are difficult to define, the treatment goal today is to make cancer a manageable chronic disease. Improved application of existing therapies (surgery, chemotherapy, and radiation), as well as new therapies coming on line can achieve this for a large number of patients. However, sometimes the price is too high - either because the side effects are unacceptable or because the treatment is cost prohibitive. Both of these are greater obstacles in veterinary medicine, where quality of life is paramount and where health care reimbursements from insurance are not the norm. It is this segment of the population, then, that most preoccupies us and fuels our desire to continue probing the inner workings of cancer so that we can realistically design better strategies to prevent, diagnose, and treat this condition.

Cancer as a Disease of Stem Cells. With that background, we can appreciate the importance of thinking outside the box. What if we ask questions about why we fail so often, as opposed to trying to incrementally build on small gains? It is this type of thinking that has led to a revised theory about the origins of cancer that may revolutionize how we approach this disease.

For >40 years we have known that cancers arise from a single cell (clonal expansion) and that a series of mutations are necessary for the cell of origin to acquire the malignant phenotype. However, the dominant theory assumed that all cells possessed an equal capacity for self-renewal (see below for definition). It also assumed that proliferation was a stochastic ("random") process driven entirely by environmental selection of favorable mutations. However, self-renewal and differentiation potential are the key elements that define what a stem cell is. So a competing theory now exists whose main tenet is that cancer is a consequence of malignant transformation of cells that retain properties of stem cells, but harbor defined mutations that endow them with malignant properties. It is not entirely a different concept, but simply a different way of looking at the same data, and it is intellectually satisfying because it explains much about cancer that was difficult to reconcile with the old models.

What is a Cancer Stem Cell? The first and most important thing to note is that normal stem cells,

such as those harvested for regenerative therapies are **not** the same as cancer stem cells. The American Association for Cancer Research (AACR) convened a Workshop in February, 2006 to achieve a consensus definition of a cancer stem cell. Based on that workshop, the consensus definition was "*a cell within a tumor that possess the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor*." For this reason, it is important to define cancer stem cells based on their ability to recapitulate a continuously growing tumor. In essence, this means a tumor that can be serially passaged *in vivo* (in a laboratory mouse) by one (or very few) cell(s), and thus the term in its strictest definition is synonymous with "tumor-initiating cell" or "tumorigenic cell". The term "cancer stem cell" is somewhat unfortunate as it can easily be interpreted mean that such cells derive from stem cells of the corresponding tissue. In fact, cancer stem cells may indeed arise from normal stem cells by mutations that make them cancerous, but this may not be the case in all tumors. That is, it is possible that more differentiated cells can acquire the capacity for self-renewal and become immortalized through multiple mutations, so it is this differentiated cell, and not the tissue stem cell, that eventually evolves to become a full-blown cancer stem cell.

It is important to note that proliferation is not the same as self-renewal. A self-renewing cell division results in one or both daughter cells (progeny) that have essentially the same ability to replicate and generate differentiated cell lineages as the progenitor cell. Stem cells can undergo symmetrical self-renewing division, causing identical daughter cells that retain "stemness" or self-renewal capacity, or asymmetrical self-renewing division, resulting in one stem cell and one more differentiated progenitor cell that can continue along a defined lineage or lineages. It also is possible that some stem cells may divide symmetrically to form two progenitor cells, leading to stem cell depletion. Promoting this latter form of division would be a way to deplete the cancer stem cell population by differentiation, and may hence constitute an alternative strategy to inducing cell death to treat cancer.

Do Cancer Stem Cells Really Exist? The existence of cancer stem cells is now documented; they are characterized by peculiar phenotypes, by defined sets of genetic mutations, and by their ability to form tumors that can be serially passaged in laboratory animals. In the case of lymphoma or leukemia, <1 in 250,000 tumor cells has the properties that define a cancer stem cell. Similar results have been obtained for a variety of solid tumors, although much work remains to be done to define the "cancer stem cell" for many types of cancer.

Clinical Implications of Cancer Stem Cells. The cancer stem cell model can explain various paradoxical findings regarding tumors and their natural history. It accounts for the relatively small number of genes that are disproportionately associated with a multitude of cancers, for the ability of multicellular organisms (like people and dogs) to reach reproductive age and attain long lives without cancer, and perhaps most importantly, for the observed nature of tumor relapse and metastasis. Cancer stem cells divide infrequently and are thus resistant to most of the types of treatments we use for cancer (which rely on killing rapidly dividing cells). Even though they divide rarely, cancer stem cells have the potential to regenerate the full complement of progeny that originally comprised the tumor. Thus, failure to eliminate cancer stem cells with - or after cessation of - chemotherapy sets the stage for tumor re-growth and relapse, which would not occur if the surviving cells lacked the capacity for self-renewal). The acquisition of additional mutations, possibly due to the therapy itself, allows the remaining cancer stem cells to generate

new progeny with enhanced survivability in novel environments, favoring aggressive, metastatic phenotypes. This suggests that, in order to achieve sustained remissions, we will need to devise treatment regimens that target the cancer stem cell compartment.

Cancer Stem Cells and Canine Tumors. The stem cell theory of cancer has not been conclusively proven in dogs, but we have seen subpopulations of cells in hemangiosarcoma and in lymphoma that have phenotypes consistent with stem cell origin. For hemangiosarcoma, we extended these observations to define a phenotype that firmly established the bone marrow origin of this tumor, and allowed us to distinguish hemangiosarcoma cells from other bone marrow-derived cells and from normal circulating endothelial cells. This led to the development of a useful diagnostic test for hemangiosarcoma. More recently, we have shown that the tumors harbor specific subpopulations that retain the "primitive" (stem cell-like) characteristics and may harbor unique gene expression signatures. In fact, the relative frequency of these cells may explain the observed differences in the clinical behavior of these tumors. Our current work focuses on defining these cancer stem cell populations and their usefulness to predict responses to standard of care, as well as to identify new treatments to effectively target these cells. The premise that appropriate activation of the immune system might be able to eliminate both the cancer stem cells and their progeny is among the concepts that we plan to explore in an ongoing clinical trial for osteosarcoma that is supported jointly by the NCI and the AKC CHF.

**Biographical Profile**

**Dr. Jaime Modiano** hails from Mexico City, where he graduated from the baccalaureate program at Colegio Columbia. He did undergraduate work in Biomedical Sciences at Texas A&M University in College Station, TX for three years before moving on to veterinary school at the University of Pennsylvania. He completed his veterinary training and PhD in Immunology at Penn, followed by a residency in Veterinary Clinical Pathology at Colorado State University, and a post-doctoral fellowship at the National Jewish Center for Immunology and Respiratory Medicine in Denver, CO. He was appointed to the faculty in the Department of Veterinary Pathobiology at Texas A&M University as Assistant Professor between 1995 and 1999. Dr. Modiano returned to Denver from 1999 to 2007; there, he held Scientist and Senior Scientist appointments at the AMC Cancer Research Center and he was Associate Professor of Immunology and Full Member of the Cancer Center at the School of Medicine of the University of Colorado Health Sciences Center. In July of 2007, Dr. Modiano joined the College of Veterinary Medicine, School of Medicine, and Comprehensive Cancer Center at the University of Minnesota, where he continues his research program as Professor of Comparative Oncology holding the Al and June Perlman Endowed Chair.

Between 2001 and 2003, Dr. Modiano served as Director of Cancer Immunology and Immunotherapy for the Donald Monk Cancer Research Foundation; he also is a partner at Veterinary Research Associates, LLP, a company focused on development and implementation of diagnostics for veterinary medicine and a founder/scientist at ApopLogic Pharmaceuticals, LLC, a biotechnology company focused on development of cancer therapeutics. His research program has had uninterrupted support from federal and private sources for 13 years, leading to co-authorship of more than 50 peer-reviewed scientific manuscripts, and ~200 abstracts, presentations, and book chapters focused on various aspects of immunology, cancer cell biology,

the genetic basis of cancer and applications of gene therapy.

Dr. Modiano is married to Dr. Michelle Ritt, a board certified specialist in Veterinary Internal Medicine. They share their home with Logan, a champion agility Gordon setter and Quetzal, a German Shepherd Dog.

*Dr. Modiano's research has been supported by the following grants:*

*1626T: Significance of Tumor Suppressor Genes in Canine Cancer*
*2254A: Heritable and Sporadic Genetic Lesions in Canine Lymphoma and Osteosarcoma*
*615A-T: Heritable and Sporadic Genetic Lesions in Canine Lymphoma*
*947B: Heritable and Sporadic Genetic Lesions in Canine Osteosarcoma*

# What Everyone Needs to Know About Canine Vaccines and Vaccination Programs

Ron Schultz, PhD; University of Wisconsin - Madison

For many veterinary practitioners canine vaccination programs have been "practice management tools" rather than medical procedures. Thus, it is not surprising that attempts to change the vaccines and vaccination programs based on scientific information have created great controversy and unique methods of resistance to the proposed changes have been and are being developed. For some practitioners the issues are not duration of immunity for the vaccines, nor which vaccines are needed for the pet, instead it is felt that every licensed vaccine should be given to every pet on an annual or more often basis. Ironically this is fostered by the fact that multivalent products with 7 or more vaccine components can be purchased for the same price or less than a product with one or two vaccine components. A "more is better" philosophy prevails with regard to pet vaccines. On many occasions practitioners say that "I know many of the vaccines I administer probably aren't needed but it won't hurt to give them and who knows the animal may need them some time during their life because of unknown risk." I have also been told by many practitioners that "I believe the duration of immunity for some vaccines like distemper, parvovirus and hepatitis is many years, but until I find another way to get the client into my office on a regular basis I'm going to keep recommending vaccines annually." Annual vaccination has been and remains the single most important reason why most pet owners bring their pets for an annual or more often "wellness visit." The importance of these visits for the health of the pet is exceptional. Therefore, dog owners must understand the vaccines are not the reason why their dog needs an annual wellness visit. Another reason for the reluctance to change current vaccination programs is many practitioners really don't understand the principles of vaccinal immunity. A significant number of practitioners believe:

1) the annual revaccination recommendation on the vaccine label is evidence the product provides immunity for (only) one year. – Not True

2) that they are legally required to vaccinate annually and if they don't they will not be covered by AVMA liability insurance if the animal develops a vaccine preventable disease - Not True. Furthermore, certain companies will not provide assistance if practitioners don't vaccinate annually with core vaccines. Not True – In fact most of the companies have now demonstrated their core products provide at least 3 years of immunity.

3) that not revaccinating will cause the animal to become susceptible soon (days or a few weeks) after the one year. – Not True

4) if the animal is not revaccinated at or before one year the "whole vaccination program needs to be started again". – Not True

5) if they don't continue to revaccinate annually, diseases like canine distemper, canine parvovirus and infectious canine hepatitis (CAV-1) will "reappear and cause widespread disease similar to what was seen prior to the development of vaccines for these diseases." – Not True

6) that if the revaccination "doesn't help, it won't hurt." – Not True

7) that giving a vaccine annually that has a duration of immunity of 3 or more years provides much better immunity than if the product is given only once during the three years. – Not True In fact, there are regional/state rabies programs that suggest annual rabies vaccination programs provide better protection than revaccination once every three years regardless of whether a 1 year or 3 year rabies product is used. – Not True

8) that parvovirus vaccines only provide six months of immunity, thus they must give them semi-annually and the CPV-2 vaccines need to be given with coronavirus vaccine to prevent enteritis. – Not True

9) "It's much cheaper to revaccinate the pet annually than it is to treat the disease the animal will develop because it didn't get revaccinated annually." The "better safe than sorry" philosophy - It is less expensive to prevent disease. However, if the core vaccines are given as a puppy and again at a year of age, then annual vaccination is not needed. Furthermore, if a vaccine is given that is not needed and it causes an adverse reaction that is unacceptable and very expensive.

10) they need to revaccinate all new dogs/cats coming to their clinic irrespective of vaccination history even when vaccination records are available from another clinic. Presumably the "other clinic" used the wrong vaccine or didn't know how to vaccinate. – Not True

11) "Dogs need to be revaccinated annually up to 5 to 7 years of age, then and only then would vaccination every three years be okay." – Not True

12) "Surgical procedures, including anesthesia, are immunosuppressive thus dogs should be vaccinated prior to or shortly after surgery." – Not True

13) "Because boarding kennels require annual or more often (kennel cough every 3 to 6 months) vaccination, practitioners must continue vaccinating annually with all vaccines." – Not True – help change the kennel rules through education and just use the vaccines that need to be given (eg Kennel Cough.)

Note: There are kennels that require every licensed vaccine and the vaccines must have been given within 1 year or less prior to admission – help change these rules! Those kennels that are members of the American Kennel Association should be following the AAHA Guidelines, but many kennels do not belong to this association.

It will be necessary to correct many of these and additional misunderstandings by providing education to veterinary practitioners, kennel owners and pet owners before significant changes in vaccination programs can or will occur to reduce the over-vaccination of both cats and dogs. However it is equally important that we don't, in our efforts to prevent over-vaccination, fail to vaccinate often enough, fail to vaccinate all or as many pups with the core vaccines, fail to use products that are necessary, or to use products that don't provide protection in our pets.

I believe every practitioner, kennel owner and dog owner should know the following general information about canine vaccines and vaccination programs. <u>What vaccines are needed for all</u>

puppies? I do mean all pups, as we only vaccinate 50% of dogs. If we could increase this percentage to 75%, we would be able to eliminate many of the diseases prevented by core vaccines. The "core vaccines," those that every pup should receive and identified as core by most canine vaccine experts in the United States, include: 1) Canine Parvovirus type 2 (CPV-2), 2) Canine Distemper virus (CDV), 3) Canine Adenovirus type 2 (CAV-2), 4) Rabies Virus (RV). When do the core vaccines need to be given? As a minimum, puppies should be given at least one dose at 16 weeks of age or older. Preferably, they should be given three or more times starting at 6 to 9 weeks then at an interval of 2 to 4 weeks revaccinate 9 to 12 weeks then again at 14 to 16 weeks. It is critical that the last dose be given at 14 to 16 or more weeks of age. It is important not to give them earlier than 6 weeks unless there is a significant risk of a specific disease, then give only the vaccine for the disease you want to prevent (e.g. CPV-2). Never vaccinate a pup less than 4 weeks of age. The most effective canine core products currently include modified live and recombinant vaccines alone or in combination. The combination products with CPV-2, CDV and CAV-2 currently often include canine parainfluenza (CPI) virus. New "core only" products have been and are being developed that don't have CPI, however, the CPI will not cause a problem if and when used as a parenteral 5 way combination product.

After the puppy series is completed, revaccination is recommended again at one year of age or one year after the last puppy vaccination. Rabies must be given again at 1 year, then every 3 years, whereas, the other core vaccines need not be given again for at least 3 or more years. There is no benefit from annual rabies vaccination and most one year rabies products are similar or identical to the 3-year products with regard to duration of immunity and effectiveness. However, if they are 1 year rabies vaccines, they must be legally given annually! Rabies vaccine is the only canine vaccine requiring a minimum duration of immunity study. However, revaccination annually does not necessarily improve immunity. However, annual vaccination does significantly increase the risk for an adverse reaction in the dog. I would recommend, if you really want to be sure the puppy vaccination program was successful, that a CDV and CPV-2 antibody titer be performed 2 or more weeks after the last puppy vaccination. Laboratory tests as well as "in-office test" for CDV and CPV-2 tests are available. If there is no antibody, revaccinate and perform a test two or more weeks after revaccination. If you still don't have antibody, change the product and vaccinate again. Antibody tests (titers) are very useful at these times to ensure the animal is immunized. The problem with antibody tests is they are very expensive, thus in general, these tests won't be used. As an alternative to revaccinating at one year for CDV, CPV-2 and CAV-2, I would revaccinate at 6 months to ensure the animal has responded rather than waiting until 1 year. Then, revaccinate not more often than every 3 years. The minimum duration of immunity for the core vaccines except rabies is at least 7 years based on challenge and/or titers (Table 1). Thus revaccinating annually will not improve protection. Ironically "the better safe than sorry philosophy" can be equally applied to less vaccination, since the animal that develops an adverse reaction (e.g. hives, facial edema, anaphylaxis) from a vaccine that wasn't needed is an example of "being sorry, not safe!"

What about all the other vaccines currently available for the dog? They are non-core or optional vaccines that should only be given to animals that need them and only as often as needed. There are also some vaccines that are **not recommended** for any dogs. The duration of immunity is not known for certain non-core products, the efficacy is limited or not known and the risk vs. benefit factors are not always well established nor understood. The minimum duration of

immunity for *Leptospira* vaccines is probably less than one year, thus if required for a high risk dog, they may need to be given as often as semi-annually. Considering the low efficacy, the adverse event rate and the minimal risk for leptospirosis in many regions of the US, certain practitioners are not using the current products. However if an animal is in a high-risk environment for leptospirosis, the product to use should contain the 4 serovars (there is no significant cross protection among the 4 current serovars) and the animal should be vaccinated starting not earlier than 12 weeks of age, revaccinate in 2 to 4 weeks, revaccinate at 6 months of age, revaccinate at a year of age and then you may have to revaccinate as often as every 6 to 9 months for optimal protection. Using this program the animal should not develop clinical disease but it can get infected and shed organisms in its urine. Bordetella immunity may be less than one year and the efficacy for the products is not well established. Many animals receive "kennel cough" vaccines that include Bordetella and CPI and/or CAV-2 every 6 to 9 months without evidence that this frequency of vaccination is necessary or beneficial. In contrast, other dogs are never vaccinated for kennel cough and disease is not seen. CPI immunity lasts at least 3 years when given intranasally, and CAV-2 immunity lasts a minimum of 7 years parenterally for CAV-1. These two viruses in combination with *Bordetella bronchiseptica* are the agents most often associated with kennel cough, however, other factors play an important role in disease (e.g. stress, dust, humidity, molds, mycoplasma, etc.), thus kennel cough is not a vaccine preventable disease because of the complex factors associated with this disease. Furthermore, this is often a mild to moderate self limiting disease. I refer to it as the "Canine Cold." My preference when a kennel cough vaccine is used is that it should be the intranasal rather than the parenteral, but some dogs will not allow someone to administer the vaccine intranasally.

There is a new virus of dogs, an "equine-like influenza virus," that first infected greyhounds in Florida in 2004 that caused respiratory disease. At this time it is not known whether this virus, referred to as canine influenza virus (CIV), is an important cause of canine respiratory disease, nor if it will be an emerging disease of dogs. Questions about the role of influenza virus or for that matter, viruses other than CPI and CAV-2, bacteria other than *Bordetella bronchiseptica*, various mycoplasmas and other factors causing kennel cough, which I refer to as "Canine Respiratory Disease Complex," exist and must be answered.

The geographic distribution of Lyme disease would suggest vaccination would only be of benefit in certain regions of the US, thus widespread use of this product is neither necessary nor desired. Although Wisconsin is an endemic area for Lyme disease, we have used very few doses of Lyme vaccines in our VMTH and we have not seen significant numbers of cases of Lyme disease. However in certain areas of western and northwestern Wisconsin and eastern Minnesota, many cases of confirmed Lyme disease are seen in both vaccinated and unvaccinated dogs. Tick control for prevention and antibiotics for treatment must be used in high risk areas. Immunity to Lyme vaccines have been shown experimentally to last up to one year. Giardia is a new vaccine that may be of value in certain circumstances, but there have not been adequate field studies to demonstrate the need nor the benefit of this vaccine. To date no one has demonstrated a benefit for coronavirus vaccine. In the vaccination guidelines from the American Animal Hospital Association, neither Giardia nor Coronavirus vaccines are recommended unless they can be proven to be beneficial for a specific animal. There are also new vaccines for snakebites (*Crotalus sp.)* and for periodontal disease (*Porphyrius sp.)* and a therapeutic vaccine for treatment of canine melanomas.

At present most canine core vaccines are given more often than needed, but a few non-core vaccines probably not often enough to be of benefit. Also, many vaccines are given that are not needed or that cannot be shown to provide a benefit for the specific animal. Vaccines are medical products that should only be given if needed and only as often as is necessary to provide protection from diseases that are a risk to the health of the animal. If a vaccine that is not necessary causes an adverse reaction that would be considered an unacceptable medical procedure, thus use only those vaccines that are needed and use them only as often as needed.

Vaccination programs are changing and they will continue to change. The vaccination program must be tailored to the individual animal. Vaccines are medical products that should not be used as practice management tools. My general philosophy is to vaccinate more animals in the population, but vaccinate with only those vaccines that the animal needs and only as often as required to maintain protective immunity. For some products vaccination may occur once or twice in a life time, whereas for other products it may be every 6 to 9 months.

**Be wise and immunize, but immunize wisely!**

| Table 1: Minimum Duration of Immunity for Canine Vaccines | | |
|---|---|---|
| Vaccine | Minimum Duration of Immunity | Methods Used to Determine Immunity |
| CORE VACCINES | | |
| Canine Distemper Virus (CDV) | | |
| Rock born Strain | 7 yrs/15 yrs | challenge/serology |
| Onderstepoort Strain | 5 yrs/9 yrs | challenge/serology |
| Canarypox Vectored rCDV | 3 yrs/4 yrs | challenge/serology |
| Canine Adenovirus-2 (CAV-2) | 7 yrs/9 yrs | challenge-CAV-1/serology |
| Canine Parvovirus-2 (CPV-2) | 7 yrs/10 yrs | challenge/serology |
| Canine Rabies | 3 yrs/5 yrs | challenge/serology |

**Why Vaccination Programs are Changing**

Why, when you know from personal experience that life-long immunity exists for many human vaccines, do you have great difficulty believing a canine vaccine can provide life-long immunity? Perhaps I and my colleagues that teach immunology to veterinary medical students have failed to explain the basics of vaccine induced "immunologic memory." Immunologic memory is as the term implies the immune system's ability to remember the vaccine antigens that it has seen at an earlier time in life, allowing the immune system to respond in a manner that will protect you or your dogfrom specific infections and/or diseases.(1,2)

Immunologic memory is responsible for the duration of immunity that develops after recovery from natural infection/disease and after vaccination with modified live virus (MLV) or killed virus (KV) vaccines. Similarly bacterial infections and vaccines or bacterins (killed bacterial vaccines) provide immunologic memory. However, in general, immunologic memory to killed viral vaccines and to bacterial vaccines (or bacterins) is not as long lived as it is to MLV vaccines. The duration of immunity or length of immunologic memory varies among the agents causing the diseases. For example, our immunologic memory for measles virus is life-long. How do we know that it is lifelong? No one has published any controlled studies, but we know after recovering from measles infection and/or vaccination with a MLV vaccine, immunity is life-long because people rarely get measles even though they rarely receive another dose of vaccine. In contrast to the MLV vaccine, the killed measles vaccines that were used for a short period of time about 25 years ago failed to give life-long immunity. Many individuals receiving killed vaccines were either inadvertently infected or had to be revaccinated with a MLV when they were 15 to 20 years of age to provide life long immunity. How many people do you know that were vaccinated with the modified live measles virus product, in use for approximately 40 years, or that had measles as a child, then developed measles later in their life? I'm sure your answer must be very few or none!

A very similar story to measles can be told for canine distemper virus (CDV) in the dog. CDV is in the same virus family as measles virus and it shares many similarities with MV. As you may know, MV vaccines have been and were available until recently for dogs to prevent disease (not infection) caused by CDV. Those of you over the age of 50, may remember canine distemper when it was a devastating disease killing many animals with more than 50% of infected puppies often dying from the disease. If you are old enough, were observant enough and had an opportunity to follow dogs that recovered from natural infection with CDV you know that dogs recovering from CDV, like their human counterpart recovering from measles, rarely, if ever, developed acute distemper during the rest of life, even when not revaccinated. Like measles immunity in humans, immunity from canine distemper infection confers immunologic memory resulting in life- long immunity. How do I and my older, wiser and now retired colleagues and canine infectious disease experts, Dr. Max Appel, Dr. L.E. (Skip) Carmichael, and Dr. Larry Swango know that distemper immunity is life long? We know because we had the opportunity to follow dogs that recovered from infection with CDV or puppies that were vaccinated once or twice with MLV CDV and lived for 7 or more years and never developed disease even though they were exposed to CDV via natural outbreaks or experimental challenge with CDV. We also know the vaccinated or recovered dogs had life long immunity because we and others performed antibody titer tests for years on the dogs after they recovered from infection or after puppy vaccination. These dogs all had titers showing that immunologic memory was present. Most of the dogs had titers that provide sterile immunity (protection from infection) much like the measles titers found years later in many vaccinated or naturally infected people. However even if the dogs didn't have sterile immunity but still had antibody, they had immunologic memory. An antibody titer no matter how low shows the animal has immunologic memory since memory effector B cells must be present to produce that antibody. Some dogs without antibody are protected from disease because they have T cell memory, that will provide cell mediated immunity (CMI). CMI will not protect from reinfection, but it will prevent disease. When an animal is antibody negative it may have T cell immunologic memory, but I generally consider a CDV antibody negative dog not to be protected, therefore, I recommend revaccination!. Some researchers, including myself, have had the opportunity to follow the duration of immunity for dogs living in natural or experimental environments that are free of CDV and CPV-2 (6). Why is it important that observations are made on dogs and cats that are not exposed to the virus? Because in those environments it is possible to demonstrate that immunologic memory is independent of natural or overt stimulation with the wild type virus or the vaccine virus. However, in a normal environment where infection occurs, "natural vaccination" or exposure and infection with the specific agent can and does occur at least for certain agents and in certain animals, but the infected animals do not get sick. Ironically when animals have "sterile immunity" their immune system is rarely boosted by natural exposure since infection does not occur. If infection does not occur, there is no stimulation of the specific memory T or B cells, thus the antibody titer does not increase. A severe outbreak of CPV-2 occurred in a large commercial breeding kennel, where more than 90% of puppies got sick and 50% of puppies from 4 weeks to 24 weeks of age died. However, none of more than 50 dams with sick and dying puppies had a significant increase in antibody titer, none had virus in their feces and none showed clinical signs of CPV-2 disease, all excellent indicators the dams had sterile immunity (did not get infected)!

Is immunologic memory and duration of immunity to all human viruses life-long? The answer is NO! Natural infection with many human viruses and the vaccines for those viruses provide life-long immunity (e.g. measles, mumps, rubella), whereas other viruses and/or the vaccines for them provide short duration of immunity (e.g. human cold viruses, influenza virus) and for additional viruses there is no immunity from infection or experimental vaccines (e.g. HIV).

The three most important viral infections of dogs all provide life-long immunity, they are CDV, CPV-2, and CAV-1. If a puppy is immunized with the three MLV vaccines used to prevent these diseases, there is every reason to believe the vaccinated animal will have up to life-long immunity! The vaccines that prevent the diseases caused by these 3 viruses plus rabies vaccine are the "Canine Core Vaccines" or those vaccines that every puppy should receive. My own dogs, those of my children and grandchildren are vaccinated with MLV CDV, CPV-2, CPI, and CAV-2 vaccines once as puppies after the age of 12 weeks. An antibody titer is performed two or more weeks later and if found positive our dogs are never again vaccinated. I have used this vaccination program with modifications (CAV-2 replaced CAV-1 vaccines in 1970's and CPV-2 vaccines were first used in 1980) since 1974! I have never had one of our dogs develop CDV, CAV-1 or CPV-2 even though they have had exposure to many dogs, wildlife and to virulent CPV-2 virus. You may say that I have been lucky, but it is not luck that protects my dogs, it is immunologic memory.

An important factor contributing to life long immunity in addition to the memory T and B cells and the "memory effector B cells" (long lived plasma cells) of the specific (adaptive) immune system is the innate immune resistance associated with age. It is well known in all species that the young animal is more susceptible to infection and disease than a mature animal. In the case of human infections that period of increased susceptibility is often the first few years of life, and especially the first year. In the puppy and the kitten it is often the first 3 to 6 months of life, but it can be up to 1 year of age that the animal is more susceptible to disease. For example, dogs less than a year of age are much more likely to develop severe parvoviral disease than susceptible (immunologically naïve) dogs over one year of age even though at both ages the animals are very susceptible to infection with CPV-2. Similarly a susceptible cat less than one year of age and especially cats less than 3 months of age are at much greater risk of becoming persistently infected with feline leukemia virus than a susceptible cat that is greater than one year of age at the time of infection. Thus innate as well as specific immune factors contribute to age-related resistance and these factors are highly complex and not completely understood. However, age related resistance plays a critical role in life-long or long term immunity. This does not imply that older dogs and cats cannot get infected and develop disease, it is that they are much less likely to get disease when compared to the younger animal.

I and my colleague, Dr. Fred Scott, first proposed a three year revaccination program for dogs and cats more than 25 years ago, when we published an article in Veterinary Clinics of North America 8(4) 755-768, 1978. Today, a three year revaccination program has been recommended in the AAHA Canine Vaccination Guidelines and the American Association of Feline Practitioners Vaccine Guidelines for Cats. The proposed change for revaccination with "Core Vaccines" from annual to triennial revaccination has been very controversial for many reasons, however, the reasons have little or nothing to do with "immunologic memory" or duration of immunity. No one has nor can anyone in the future, show that there is any immunologic benefit

from annual revaccination with MLV CDV, CAV or CPV-2. In fact, it may even be difficult to show an immunologic benefit for revaccination at three year intervals since most animals have long term immunity for CDV, CAV-1 and CPV-2. Some among you are probably convinced that there is life long immunity to certain vaccines used in dogs and cats, but few of you after many years of performing annual revaccination are willing to take the risk, however small it may be, to adopt the puppy vaccination program. However, you should feel confident that adopting, a three year revaccination program for CDV, CAV and CPV-2, will not increase the risk for diseases caused by these 3 viruses, just as a once every three year revaccination, rather than annual revaccination, with the killed rabies vaccines does not increase the animal's risk for rabies.

You and your veterinarian will need to determine what vaccines and vaccination program is best for your pet and their patient respectively. The program selected may only include core vaccines that are given once in the lifetime of the dog or the program may include all vaccines with revaccination on an annual or more often basis, or it may be a vaccination program in between these two extremes depending on what your pet's needs are and what, in the medical judgment of your veterinarian, is best for their patients. Furthermore, it is likely your decision depend on the life style of your pet, its medical history, health status, age, pregnancy status and other important factors.

## FREQUENTLY ASKED QUESTIONS (FAQ)

**1. Is there a risk of over-vaccinating a pet (e.g. injecting it too often, or using vaccines that are not required for the specific pet)?**

Yes – Vaccines should not be given needlessly, as they may cause adverse reactions. Vaccines are medical products that should be tailored to the needs of the individual animal.

**2. May I mix different types of vaccines in the syringe?**

No - One should never mix different vaccine preparations in the syringe unless specified by the data sheet.

**3. May I co-inject different vaccines (not part of a single commercial product) into the same animal?**

Yes – but different vaccines should be injected into separate sites that are drained by different lymph nodes.

**4. May I use smaller vaccine doses in small breeds to reduce the risk of adverse reactions?**

No - The volume (e.g. 1.0 ml) as recommended by the manufacturer generally represents the minimum immunizing dose, therefore the total amount must be given.

**5. Should the large dog (Great Dane) be injected with the same volume of vaccine as the small dog (Chihuahua)?**

Yes - Unlike pharmaceuticals that are dose-dependent, vaccines are not based on volume per body mass (size), but rather on the minimum immunizing dose.

**6. May I vaccinate the anaesthetized patient?**

It is best not to do this if possible - the patient may develop a hypersensitivity reaction and vomit, leading to an increased risk of aspiration. Also, anaesthetic agents may be immunomodulatory.

**7. May I vaccinate pregnant pets?**

No - Vaccination with MLV and killed products during pregnancy should be avoided, if at all possible.

**8. May I vaccinate pets that are on immunosuppressive or cytotoxic therapy (e.g. for cancer or immune-mediated diseases, such as those with an autoimmune or hypersensitivity pathogenesis)?**

No - Vaccination especially with MLV products should be avoided as they may cause disease; vaccination with killed products may not be effective or may aggravate the immune-mediated disease.

**9. How long after stopping immunosuppressive therapy do I wait before vaccinating a pet?**

A minimum of 2 weeks.

**10. May I vaccinate every week if an animal is at high risk of disease?**

No - Vaccines should not be given more often than every other week, even when different vaccines are being given.

**11. When should the last vaccine dose be given in the puppy and kitten vaccine series?**

The last dose of vaccine should be given at around 16 weeks of age.

**12. May I inject a killed vaccine, followed at a later time with a MLV for the same disease?**

No - The killed vaccine may induce an effective antibody response that will neutralize the MLV in the vaccine, thereby preventing immunization. It would be preferable to give the MLV vaccine first and if/when needed, revaccinate with the killed vaccine preparation.

**13. May I inject a modified live intranasal *Bordetella* vaccine?**

No - The vaccine can cause a severe local reaction and may even kill the pet.

**14. May I give a killed *Bordetella* vaccine destined for parenteral use intranasally?**

No - This will not stimulate a specific response to the *Bordetella*; you should give a live vaccine via the intranasal route, as specified by the data sheet.

**15. Are precautions necessary when using MLV FHV-1/FCV parenteral vaccines in cats?**

Yes - Mucosal (e.g. conjunctival and nasal) contact with the preparation must be avoided, because the vaccine virus can cause disease.

**16. Can nosodes (holistic preparations) be used to immunize pets?**

No - Nosodes cannot be used for the prevention of any disease. They do not immunize because they do not contain antigen.

**17. Should dogs and cats with a history of adverse reaction or immune-mediated diseases (hives, facial oedema, anaphylaxis, injection site sarcoma, autoimmune disease, etc.) be vaccinated?**

If the vaccine suggested to cause the adverse reaction is a core vaccine, a serological test can be performed, and if the animal is found seropositive (antibody to CDV, CPV-2, FPV) revaccination is not necessary. If the vaccine is an optional non-core vaccine (e.g. *Leptospira* bacterin) revaccination is discouraged. For rabies, the local authorities must be consulted to determine whether the rabies vaccine is to be administered by law or whether antibody titre may be determined as an alternative.

**18. May I use different vaccine brands (manufacturers) during the vaccination program?**

Yes – It may even be desirable to use vaccines from different manufacturers during the life of an animal, because different products may contain different serotypes (e.g. of feline calicivirus).

**19. Should I use a disinfectant (e.g. alcohol) on the injection site?**

No - The disinfectant might inactivate an MLV product, and it is not known to provide a benefit.

**20. Can vaccines cause autoimmune diseases?**

Vaccines themselves do not cause autoimmune disease, but in genetically predisposed animals they may trigger autoimmune responses followed by disease – as can any infection, drug, or a variety of other factors.

**21. May I split vaccines in combination products?**

Yes - For example, *Leptospira* bacterins are often the diluent for the viral antigen combination. The "viral cake" may be resuspended in sterile water, and the *Leptospira* bacterin be given separately at another site or time, or discarded.

**22. Will a single vaccine dose provide any benefit to the dog or cat?**
**Will it benefit the canine and feline populations?**

Yes - One dose of a MLV canine core vaccine (CDV, CPV-2 CAV-2) or a feline core vaccine (FPV, FCV, FHV-1) should provide long term immunity when given to animals at or after 16 weeks of age. Every puppy and kitten 16 weeks of age or older must receive at least one dose of the MLV core vaccines.
If that were done, herd (population) immunity would be significantly improved. Even in the USA with its good vaccination record, probably <50% of all puppies and <25% of all kittens ever receive a vaccine. We must vaccinate more animals in the population with core vaccines to achieve herd immunity (e.g. 75% or higher) and prevent epidemic outbreaks.

**23. When an animal first receives a vaccine that requires two doses to immunize (e.g. killed vaccines like *Leptospira* bacterins or feline leukemia virus), and it does not return for the second dose within ≤6 weeks, is there any immunity?**

No - A single dose of a two-dose vaccine does not provide immunity. The first dose is for priming the immune system, the second for boosting. If a second dose is not given within 6 weeks of the first, the regime must start again, making sure the two doses are given within 2 to 6 weeks. After those two doses, revaccination with a single dose can be done at any time.

**24. May I give a MLV product to a wild, exotic species or to a domestic species other than to the ones which the vaccine was licensed to protect?**

No - Never. Many MLV vaccines have caused disease in animal species other than those for which they had been licensed. Even worse: the vaccine could be shed from those animals, regain virulence through multiple passages and cause disease even in the target species for which it had been developed. The consequences could be catastrophic!

A highly effective and very safe vaccine for species that are susceptible to CDV is a canary poxvirus-vectored recombinant CDV vaccine that is available as a monovalent product for ferrets or a combination product for dogs. The monovalent vaccine is being used in many wild and exotic species susceptible to CDV.

**25. May I vaccinate a puppy that is at high risk of getting CDV with a human measles vaccine?**

No - Due to an insufficient amount of virus, the human MV vaccine is not immunogenic in the puppy. Measles virus vaccines made specifically for the dog (sometimes combined with CDV) will give temporary protection at an earlier age than a CDV vaccine. At 16 weeks or older, the puppy must be vaccinated with a CDV vaccine, to achieve permanent immunity.

**26. I know that maternally derived antibodies (MDA) can prevent active immunization with MLV vaccines - but can they also block immunity to killed vaccines?**

Yes - MDA can indeed block certain killed vaccines. If the killed product requires two doses, as is often the case, and the first dose is blocked by MDA, then the second dose will not immunize. In this circumstance, the second dose will prime (if not blocked), and a third dose is required to boost and immunize.

This is not true for MLV, where - in the absence of MDA - it only takes a single dose to prime, immunize, and boost. Nevertheless two doses are often recommended, particularly in young animals, to be sure one is given when MDA cannot block. That is why in the puppy or kitten series, the last dose should be given at around 16 weeks of age or later.

**27. I have been told that certain canine MLV combination core products need only be given twice, with the last dose at an age as young as 10 weeks. Is that accurate?**

No - it is not. No combination core product currently available will immunize an acceptable percentage of puppies when the last dose is given at 10 weeks of age. The last dose should be given at around 16 weeks of age, regardless of the number of doses given earlier.

In the presence of MDA, MLV vaccines either immunize or they don't, and the animal will be either immune or not immune - there is nothing in between. MLV vaccines do not give a little immunity with any dose when blocked by MDA.

**28. For how long can a reconstituted MLV vaccine sit at room temperature without losing activity?**

At room temperature, some of the more sensitive vaccines (e.g. CDV, FHV-1) will lose their ability to immunize in 2 to 3 hours, whereas other components will remain immunogenic for several days (e.g. CPV, FPV).

**29. May I give the same type of vaccine parenterally and intranasally, for example the canine and feline vaccines used to prevent respiratory diseases ('kennel cough' and feline upper respiratory disease)?**

Yes - But be sure to give the product approved for that route. If you use the parenteral MLV vaccines containing FCV and FHV-1 locally, you could cause disease in the cat. If you use the killed FCV and FHV-1 vaccines locally, you would not get any immunity and might cause significant adverse reactions. If you gave the intranasal live 'kennel cough' vaccine parenterally, you could cause a severe necrotizing local reaction and even kill the dog, whereas giving the parenteral killed *Bordetella* vaccine intranasally will not immunize and may cause a hypersensitivity reaction.

However, both types of products can be given at the same time or at various times in the life of the animal. Vaccinating both parenterally and intranasally may actually provide better immunity than vaccinating at only one site. Thus parenteral vaccination provides protection in the lung but little or no immunity in the upper respiratory tract (especially local secretory IgA and CMI), whereas intranasal vaccination will engender good secretory IgA and local CMI and non-specific immunity (e.g. type I interferons), but will not always provide immunity in the lung.

**30. Are there dogs and cats that cannot develop an immune response to vaccines?**

Yes - This is a genetic characteristic seen particularly in some breeds, and these animals are called 'non-responders'. Genetically related (same family or same breed) animals will often share this non-responsiveness. If the animal is a non-responder to a highly pathogenic agent, like canine parvovirus or feline panleukopenia virus, the infected animal will die if infected. If it is a non-responder to a pathogen that rarely causes death, it may become very sick but will survive (e.g. after a *Bordetella bronchiseptica* infection).

**31. Are there mutants (biotypes or genotypes) of CDV or CPV-2 in the field that the current vaccines cannot provide protective immunity against?**

No. - All the current CDV and CPV-2 vaccines provide protection from all the known isolates of CDV or CPV-2, respectively, when tested experimentally as well as in the field.

**32. How long after vaccination does it take for the dog to develop immunity that will prevent severe disease when the core vaccines are used?**

This is dependent on the animal, the vaccine, and the disease.

- The fastest immunity is provided by CDV vaccines – MLV and recombinant canarypox virus vectored. The immune response starts within minutes to hours and provides protection within a day to animals without interfering levels of MDA and dogs that are not severely immunosuppressed.
- Immunity to CPV-2 and FPV develops after as few as 3 days and is usually present by 5 days when an effective MLV vaccine is used. In contrast, the killed CPV-2 and FPV-2 vaccines often take 2 to 3 weeks or longer to provide protective immunity.
- CAV-2 MLV given parenterally would provide immunity against CAV-1 in 5 to 7 days; when given intranasally, however, the same level of immunity to CAV-1 is not present until after 2 or more weeks.
- Time from vaccination to immunity is difficult to determine for FCV and FHV-1 because some animals will not develop any immunity.

**33. Will the current 'kennel cough' vaccines provide any protection from disease caused by the new canine influenza virus?**

No - The racing greyhounds that have been found infected and that developed disease had been routinely vaccinated 3 or more times a year with commercial 'kennel cough' vaccines. Canine influenza virus is antigenically unrelated to any other virus of dogs, but related to Equine Influenza Virus.

**34. If an animal has gone beyond the time that is generally considered to be the maximum DOI for the vaccine (7 to 9 years for CDV, CPV-2, CAV-2; >1 year for *Leptospira*, *Bordetella bronchiseptica*; >3 years for rabies), do I have to start the series of vaccinations again (multiple doses 2 to 4 weeks apart)?**

No - For MLV vaccines, multiple doses are only required at the puppy or kitten age, when an animal has MDA.

**35. What can I expect from the core vaccines in terms of efficacy in the properly vaccinated puppy/dog and kitten/cat?**

- Dogs properly vaccinated with MLV or recombinant CDV, CPV-2 and CAV-2 would have ≥98% protection from disease. Similarly we would expect a very high protection from infection.

- For the properly vaccinated cat that had received MLV vaccines, we would estimate that ≥98% would be protected from disease and infection with FPV.
- In contrast, we can expect FCV and FHV-1 vaccines, at best, to protect from disease, especially in a highly contaminated environment (e.g. shelter) and protection would be seen in 60 to 70% in a high risk environment and higher in the household pet cat.

**36. Are serum antibody titres useful in determining vaccine immunity?**

Yes - Especially for CDV, CPV-2 and CAV-1 in the dog, FPV in the cat and rabies virus in the cat and dog. Serum antibody titres are of limited or no value for the other vaccines. Assays for CMI are of little or no value for any of the vaccines for various technical and biological reasons. Such factors are less of an issue for serological tests where it is much easier to control many of the variables. However, discrepant results are still obtained, depending on the quality assurance program of the given laboratory.

**37. Do puppies develop immunosuppression after the initial series of core vaccines?**

Yes - If a combination product containing MLV-CDV and MLV-CAV-2 with other components is used, a period of immunosuppression lasting approximately 1 week develops, beginning 3 days after vaccination. If the combination vaccine does not contain either MLV-CDV or MLV-CAV-2, then such suppression does not occur.

**Biographical Profile**

**Dr. Ron Schultz** earned his BS degree (1966), MS (1967) and PhD in Immunology and Veterinary Pathology (1970) from the Pennsylvania State University. From 1970 to 1978 he was an Assistant then Associate Professor at NY State College of Veterinary Medicine, James A. Baker Institute, Cornell University. He established the first Veterinary Clinical Immunology Laboratory in the US while on the faculty at Cornell. He also served as Associate Director of the Human Health Service Laboratory at Cornell University. From 1978 to 1982 he was a Professor and Director of the Veterinary Clinical Immunology Laboratory that he established in the School of Veterinary Medicine, Auburn University. He accepted his current position as Professor and Chair of the Department of Pathobiological Sciences, School of Veterinary Medicine, UW-Madison in 1982. At the time he accepted this position he was the only member of the department which now has many faculty, staff and students, including faculty in the Wisconsin Veterinary Diagnostic Laboratory. He is an honorary diplomate of the American College of Veterinary Microbiologists. Dr. Schultz has won several awards, is a member of numerous professional organizations and served or serves on numerous Editorial Boards and National and International advisory panels He is on the AAHA Canine Vaccine Task Force, the AAFP Feline Vaccine Task Force that provide Guidelines for Canine and Feline Vaccines and Vaccination Programs as well as the Vaccine Guideline Group for the World Small Animal Veterinary Association. He has served on National Academy of Science panel to review USDA Grants Programs and was recently invited to be a Member of the Assessment Panel to review research programs of the USDA's Agriculture Research Service Laboratories throughout the US.. He was the first president of the American Association of Veterinary Immunologists and has been

president of the Conference of Research Workers in Animal Disease. He has published more than 200 papers on the immunology and microbiology of animal disease, clinical immunology and vaccinology and has edited several books and holds multiple patents. He has trained more than 50 graduate students and postdoctoral fellows in his laboratories at Cornell, Auburn and Wisconsin. He has received millions of dollars in extramural research funds for research primarily to study diseases of dogs, cats and cattle and also received funding for instructional training programs.