*Review Article*

# Vaccine Issues and the World Small Animal Veterinary Association (WSAVA) Guidelines (2015-2017)

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## ABSTRACT

The World Small Animal Veterinary Association (WSAVA) vaccine guidelines began in 2006; and provide evidence-based global advice for vaccination best practices in dogs and cats. These guidelines were updated in 2016/2017, which along with others, such as those of the American Animal Hospital Association (AAHA), American Veterinary Medical Association (AVMA), American Association of Feline Practitioners (AAFP) and British Association of Homeopathic Veterinary Surgeons (BAHVS), are gradually changing routine vaccination practices worldwide. They have had a major impact on daily small animal practice, and help ensure that pet owners and breeders are offered scientifically-based advice, and robust, safer vaccines and vaccination protocols for dogs and cats.

**Keywords:** Vaccines; Immunity; Innate Immunity; Adaptive Immunity; Immune Memory; Vaccinosis; Adverse Events; Adjuvants; Excipients

## BACKGROUND

In 2003, the American Animal Hospital Association (AAHA) indicated that current knowledge supports the statements that, "No vaccine is always safe, no vaccine is always protective and no vaccine is always indicated. Misunderstanding, misinformation and the conservative nature of our profession have largely slowed adoption of protocols advocating decreased frequency of vaccination. Immunological memory provides durations of immunity for core infectious diseases that far *exceed* the traditional recommendations for annual vaccination. This is supported by a growing body of veterinary information as well as well-developed epidemiological vigilance in human medicine that indicates immunity induced by vaccination is extremely long lasting and, in most cases, lifelong." (1-3).

These statements were groundbreaking at the time, and still apply today (2-7).

Additionally, Professor Michael J. Day indicated, "Vaccination should be just one part of a holistic preventive healthcare program for pets that is most simply delivered within the framework of an annual health check consultation. "Vaccination is an act of veterinary science that should be considered as individualized medicine, tailored for the needs of the individual pet, and delivered as one part of a preventive medicine program in an annual health check visit." (6-8).

Key Points on Vaccine Issues as summarized by the present author are (9-15):

Modern vaccine technology has afforded effective protection of companion animals against serious infectious diseases. But, this advancement brings an increased risk of adverse reactions (vaccinosis). Some reactions are serious, chronically debilitating and even fatal. Therefore, we must balance this benefit/risk equation, which affords more benefit than risk. As Professor Ronald D. Schultz stated, "Be wise and immunize, but immunize wisely!" (13, 15). Furthermore, although we have all learned in our educational journey over the years about vaccination issues, it should be remembered to base decisions upon the veterinarians' experience and specific case

management required for each patient – thinking "outside-the-box" whenever applicable.

## DISCUSSION

### Benefits of Vaccines

More lives have been saved, and more animal production agriculture has been safeguarded than any other medical advance for people and animals (9-17). Vaccines have eradicated smallpox and nearly all polio and measles in people. The first vaccines developed centuries ago were to protect against small pox, anthrax, and canine distemper. Since then, vaccine technology and development has improved to the extent that today's vaccines have significantly reduced endemics of canine distemper, hepatitis and parvovirus, and endemic feline panleukopenia (also a parvovirus) but *not* in wildlife reservoirs (9-15). Rabies has essentially been eliminated in Europe but not in other countries including North America and Israel; Rhinderpest has been eradicated from Africa; and foot & mouth disease no longer is found in Europe (10-20). Foot and mouth disease is still present in free-ranging livestock in the northwestern areas of America and the Canadian border.

### Vaccines & Population (Herd) Health (21)

To protect a population (herd), 70% of animals must be immunized with "core" vaccines. However in, the dog population only about 50% are immunized, and the cat population only about 25% are immunized. The best "vaccine" is natural exposure, but this is unsafe as about 50% of susceptible puppies or kittens will die of the disease.

### Vaccine Non-Responders (9, 10)

Vaccine non-responders and low-responders are heritable traits, so these animals should *not* be used for breeding, especially the females as they will not provide adequate maternally-derived passive immunity to their offspring. These genetic non- and low-responders will remain susceptible to the disease throughout their lives.

- Estimated Rate of Non-Responders is 1:1000 for CPV (canine parvovirus), especially common in Black Labrador Retrievers and Akitas
- Estimated Rate of Non-Responders is 1:5000 for CDV (canine distemper virus), especially seen in Greyhounds.
- Estimated Rate of Non-Responders is 1:100,000 for CAV (canine hepatitis, adenovirus).
- Estimated Rate of Non-Responders is unknown for cats.

### Adverse Reactions & Cautions (9, 10, 18, 22-30)

### Canine Distemper Virus (18, 27)

The development of multivalent vaccines is an attractive methodology for the simultaneous prevention of several infectious diseases in vulnerable populations. Both canine distemper virus (CDV) and rabies virus (RABV) cause lethal disease in wild and domestic carnivores. While RABV vaccines are inactivated, the live-attenuated CDV vaccines retain some residual virulence for highly susceptible wildlife species (18). Recombinant bivalent vaccine candidates were selected for study using a recombinant vaccine strain rabies virus particles, which concurrently displayed the protective CDV and RABV glycoprotein antigens. Ferrets immunized twice with a mixture of recombinant rabies viruses carrying the CDV fusion and attachment glycoproteins were protected from lethal CDV challenge, whereas all animals that received recombinant rabies viruses carrying only the CDV attachment protein died. Irrespective of the CDV antigens used, all animals developed protective titers against RABV, illustrating that a bivalent rabies virus-based vaccine against CDV induces protective immune responses against both pathogens (18).

Recent genotyping of CDV strains has revealed a new strain that first appeared in 2011 and was detected in dogs from multiple states in the Southeast region of the United States. It was the main strain detected among the clinical samples that were typed from 2011–2013, including wildlife submissions. Genome sequencing demonstrated that it was highly conserved within a new lineage and preliminary serologic testing showed significant differences in neutralizing antibody titers between this strain and the strain commonly used in vaccines. Thus, this emerging CDV strain may be associated with a stable reservoir in the wildlife population, and could allow for vaccine escape (26).

CDV Adverse Vaccine Reaction Rate is 1:100,000 for Rockborn & Snyder Hill vaccine strains. The Rockborn strain of CDV is still found in most of today's modified Live vaccines (MLV), and can produce post-vaccinal encephalitis

(PVE), blindness & death. The recombinant (rCDV) Recombitek (Merial) does not cause PVE.

CDV Adverse Vaccine Reaction Rate is 1: 500,000 for the Onderstepoort strain, but it is less potent. When MLV CDV is combined with adenovirus (canine hepatitis) in a combo vaccine, the risk of immune suppression and PVE increases – especially in puppies (10).

### Maternal Immunity & Protection (8, 14)

#### Milk Replacer

Feeding milk replacer proteins instead of natural colostrum will coat the bowel of newborns and shut down absorption of antibodies needed for protection from disease. It is recommended to give canine fresh-frozen plasma (FFP) immediately to orphan or weak pups after birth in order to obtain passive immunity. Thereafter a milk replacer can be added.

### Vaccine Timing (1-3, 9, 13)

Last puppy vaccine should be given at 16-18 weeks for full protection.

Last kitten vaccine should be given at 12-14 weeks for full protection.

### WSAVA Guidelines for Puppies & Kittens 2017 (3,6)

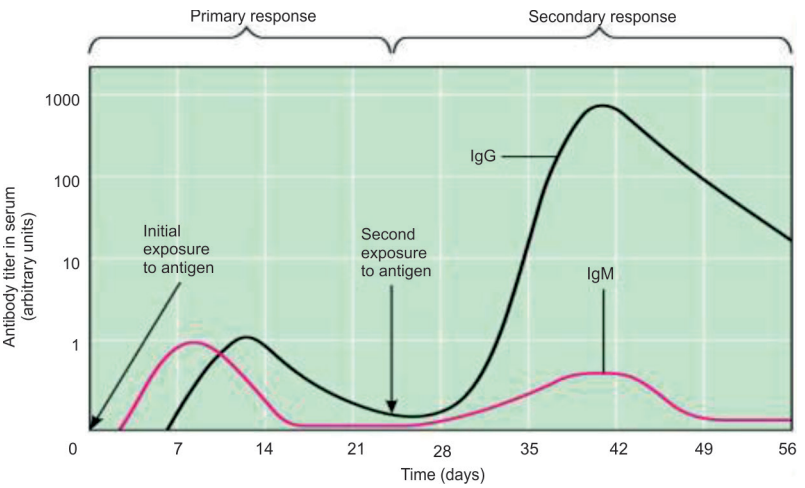
About 10% of puppies & kittens fail to respond to a primary "core" vaccines when the last one is given at 12 weeks of age, because they have persistent blocking maternally derived antibody (MDA). Thus, the new recommendations for the primary core vaccines are:

- First vaccine at 8-9 weeks of age
- Second vaccine 3-4 weeks later
- Third vaccine at 16 weeks of age or older

After that, core vaccines should generally be given at 12 months of age or 12 months after completion of the primary vaccine series. The new recommendation, however, is to give one more booster vaccine at 6 months of age; thereby becoming the last in the primary series of 4 core vaccines. It can be given at the time of neutering, or preferably, at the time of suture removal after neutering.

Those pets given 6-month core vaccines do not need another one at 12 months of age.

**The Anamnestic Immune Response**




Alternatively, serologically test core vaccinal immunity at 6 months of age can be carried out. Seropositivity reflects an endogenous immune response, and the animal is protected. Protection is assured based upon serum titer levels, no matter how high the titer for CDV, CPV, CAV-2 and FPV.

Any measurable serum titer level equates to the presence of committed immune memory cell immunity, as illustrated by the anamnestic immune response chart below (14).

### WSAVA Guidelines for Adult Dogs & Cats 2017 (6 ,8)

#### Booster Vaccines

Core vaccines should be given to all adults, but not more often than every three years. Serological and challenge studies indicate that protection is likely much longer (7-9 years).

Core and non-core revaccination needs of adults should take into account that animal's risk of exposure. Geographical location and lifestyle factors also should be considered.

### Vaccinating pregnant pets (6, 8)

Vaccines should *not* be given during pregnancy. Vaccination with MLV and killed products during pregnancy should be avoided whenever possible. The same applies during times of sex hormonal change, like estrus and pro-estrus. Shelters may advise vaccination, if a pregnant animal was never or unlikely to have been vaccinated and there is an outbreak of infectious disease.

## Beyond the Guidelines – Vaccine Dosage (9, 10, 15)

### Body Mass

Same dose according to the product label is intended for toy and giant breeds. Why is that?

We are told that MLV vaccines (i.e. canine distemper, parvovirus, adenovirus-2) – induce their immunogenic effects that are *not* based on body mass. In contrast, we are told that killed inactivated vaccines (i.e. rabies) – should be adjusted for body mass, but dose adjustments are not legally permitted. So what are the actual minimum and optimum vaccine doses needed for protection, when they all include a large excess of antigenic mass?

### Half-Dose CDV & CPV Vaccine Study in Small Breed Adult Dogs (15)

Small breed adult dogs, between 3-9 years of age were studied by this author. They were healthy; and had not received any vaccines for at least 3 years. The purpose of the study was to determine if only a half-dose of bivalent CDV and CPV MLV vaccine elicited sustained protective serum antibody titer responses.

Serum antibodty titer levels were compared pre-vaccine and at one and six months later. Results documented that the half-dose bivalent vaccine produced sustained protective serum antibody titers for all the adult dogs studied (15).

[Note: This finding contradicts the statement about reduced volume based upon pet size from the WSAVA 2016 Guidelines.]

### Age

Is the optimal age for eliciting a full immune response the same for all breeds and sizes?

Experience suggests that a humoral immune response occurs around 12 weeks of age for puppies; and at 10 weeks for kittens. The earliest age for safely vaccinating is around 6 weeks for puppies and kittens, despite the fact that breeders may vaccinate as early as 4 weeks of age and the fact that the effective age varies. As residual MDA interferes with complete immunization, we need to keep in mind that our current potent vaccines produces longer lasting, passive colostral immunity.

Dr. Ron Schultz advocates giving one monovalent canine parvovirus vaccine at 18 weeks (as breakthrough disease has occurred when the CPV vaccine was stopped before 16 weeks).

### Hormonal State During Vaccination (8-10)

Avoid vaccinations in the period just before estrus (30-45 days); during estrus; pregnancy; and lactation.

## Core Vaccines (3, 5)

### Dog

Distemper; parvovirus; rabies; and adenovirus-2 for infectious canine hepatitis cross-protection (only needed in areas where prevalent).

### Cat

Feline parvovirus (panleukopenia); rabies; herpesvirus (in areas where prevalent); and calicivirus (in areas where prevalent).

### Why Give 'Core' Vaccines Annually? (6, 8)

A booster after the puppy & kitten series (3-4 doses beginning at 6-8 weeks, repeated every 2-4 weeks until 16 weeks) can be given at 6 months and/or 12 months of age. Alternatively, test serum vaccine antibody titer instead of giving a 6- or 12- month booster. After that, 'core' vaccines are labeled and intended to be given to adults *not* more often than every three years.

Giving adult boosters more often will *not* increase amount of protection, however it may introduce unnecessary vaccinal antigens and excipients, and increases risk of adverse events (vaccinosis).

For Canine Distemper, Canine Adenovirus, Canine Parvovirus and Feline Panleukopenia virus, true immunization creates 'sterile immunity' so the animals *cannot* be re-infected.

### Periodicity of "Core" Booster Vaccinations (6, 8-10)

No evidence that annual boosters are necessary; except in rabies endemics. There may be need to lengthen the interval for "core" vaccines (every 3-7 years or more for healthy adults). Geriatric animals should be vaccinated only with caution. It is advised rather to monitor serum antibody titers instead.

[Note: Rabies vaccine required annually in pets in Israel; exposure risk from wildlife, especially jackals (*Canis aureus*) coming mostly from Jordan. In 2017, Israel had 49 cases of rabies from 42 places in the northeast; 28 jackals, 10 beef cattle, 1 dairy cow, 1 sheep, and 7 dogs.]

**Vaccination, Exposure & Protection** (14-16)

**CDV (Canine Distemper Virus)** (18, 27)

Vaccinates are immediately protected, even if exposed to CDV simultaneously. The MLV CDV vaccines do not shed vaccine virus appreciably.

**CPV (Canine Parvovirus)** (28)

Vaccinates are protected after 48-72 hours; so that CPV exposed pups can get sick. The MLV CPV vaccines shed vaccine virus from post-vaccine days 3-14; posing an exposure risk. Shed vaccine CPV is not detected by the Idexx SNAP, but present on CPV PCR of feces for 2 weeks. The positive CPV PCR results do *not* reflect CPV disease!

**What About Adenovirus-2 (CAV-2) for Hepatitis ?**

Infectious Canine Hepatitis (CAV-1) clinical cases have *not* been documented in America for about 15 yrs (with one exception). Vaccines for CAV-1 are no longer available, as an adverse antigen-antibody ocular immune precipitate ("blue eye") can develope ; CAV-2 vaccine for kennel cough is now used instead to act as a cross-reactive virus. However, giving puppies CAV-2 vaccine with CDV and CPV for distemper & parvovirus increases the risk for developing PVE. Can give Bordetella oral/intranasal to provide some hepatitis CAV-2 protection? This author prefers *not* to vaccinate puppies with CAV-2, as the disease isn't present today in America plus there's the increased risk of PVE – despite it being listed in the "Core" vaccination list.

**Kennel Cough & Flu Vaccines** (5)

**Oral/Intranasal Bordetella**

This vaccine releases the pet's own interferon, which impairs growth of the other respiratory viruses (parainfluenza, adenovirus-2, influenza). The oral form is preferred, however, as hypersensitivity reactions can occur with the intranasal and vaccine material sprays over the nose and face . By contrast, the injectable Bordetella vaccine does *not* release interferon. Finally , kennel cough vaccines are *not* 100% effective.

**Canine Influenza**

Mild clinical signs arec typically seen, and many exposed dogs remain clinically normal.

Produces fever whereas kennel cough does *not*, although when combined with Streptococcus, 2-3% of cases can die.

**Best way to *clinically* distinguish canine influenza from kennel cough:**

Kennel Cough typically does *not* produce a fever unless it subsequently leads to pneumonia in debilitated dogs.

Canine influenza usually presents as a fever with a cough in the early stages. For mild fever (102-103° F) *no* treatment is needed. If above 104° F, then secondary pneumonia can result and should be treated promptly with antibiotics and supportive care.

This author does *not* routinely give canine influenza vaccines to healthy pups or adult dogs, even though the canine flu viruses (H3N2 and H3N8) are highly contagious.

**Leptospirosis?** (29, 30)

**Endemic in Israel (but clinically rare) and many other parts of the world**

After initial 2-dose series, ongoing debate has continued over the need for annual Leptospirosis boosters, as the duration of immunity short-lived. Concerns over drift in serovars now affecting dogs, is raising further questions for current use of Leptospirosis bacterins.

Current vaccines only cover 2 or 4 clinically significant serovars out of 7: *L. icterohaemorrhagiae, L. grippotyphosa*, *L. canicola* and *L. Pomona.*

In Israel, *L. hardjo* and *L. balum* are also seen where *L. ictero* is the most common. Leptospirosis vaccines remain the most common vaccine eliciting acute and per-acute adverse reactions. Disease exposure risk versus adverse vaccine reaction and benefits needs to be taken into account. The vaccines are *not* very effective. Treatment with antibiotics is effective; and sanitation and hygiene are very important, along with controlling rodents.

**Canine Monocytic Ehrlichiosis?** (31)

**CME = major, potentially fatal, tick-borne dog disease caused by *Ehrlichia canis*. Prevalent worldwide – including Israel**

Tick control is the main preventive measure against CME. *No* commercial vaccine currently available, despite vaccine research from Yissum R & D of Hebrew University, Jerusalem (30). A vaccine made from attenuated strain of *E. canis*. Efficacy assessed in 12 dogs, divided into 3 groups: 4 vaccinated twice, 4 only once, and 4 controls. Vaccinates showed no adverse signs from the vaccine. After infection

with virulent *Ehrlichia* field strain, control dogs all had severe disease, but only 3 of 8 vaccinates had a mild transient fever and rest remained healthy.

### *Spirocerca lupi* (Park Worm)?

Common in Israel. Produces respiratory and gastrointestinal tract signs, and even sudden death from internal bleeding. Can be fatal once dog ingests an infected dung beetle, or mouse, bird or lizard that ate an infected beetle. Larvae released in stomach and travel through stomach lining and aorta to esophagus to lay eggs. Worms are found within nodules in esophageal, gastric and aortic walls.

Infected eggs are secreted in dog feces, and the cycle through dung beetle repeats. Treatment is Ivomec or Dormectin. Prevention approaches include treating dogs every three months empirically; muzzling dogs on walks to prevent eating infected debris and feces; keeping them on a leash; and picking up and discarding feces in garbage cans.

### Alternatives to Current Vaccine Practices (1-10, 14, 22-38)

**Measure serum antibody titers.**

Avoid unnecessary vaccines or over-vaccinating. Use caution before vaccinating sick or febrile animals. Tailor specific minimal vaccine protocol for dogs/cats breeds or families at risk for adverse reactions.

Start core vaccination series later (9-10 weeks, dog; 8 weeks cat) [WSAVA states that at 6-7 weeks, 4 doses are needed with last one at or after 16 weeks; if starting at 8-9 weeks, only 3 doses are needed, which is preferred].

Alert caregiver to watch puppy/kitten behavior and health after boosters.

Importantly, avoid revaccination of those with prior adverse events.

### New Serum Antibody Recommendations (2, 14-16)

**After the core puppy and kitten vaccine series**

Measure serum antibody titers 3-4 weeks later.

For dogs, measure titers for CDV, CPV and optionally, CAV-2.

For cats, measure FPV.

Measure titers to determine if a 26-week booster is needed.

At 52 weeks, measure serum antibody titers again (preferred), or give booster, if warranted.

### Reasons for Vaccine Titer Testing (14-17)

To determine that an animal is protected (by a positive test result).

To identify a susceptible animal (by a negative test result).

To determine whether an animal has responded to a vaccine.

To determine whether a specific vaccine is effectively immunizing.

### Available Vaccine Titers for Dogs (14-18)

Distemper Virus; Parvovirus; Adenovirus –2 (hepatitis); Bordetella; Leptospirosis; Lyme disease; Corona Virus [*not* recommended]; and Rabies Virus (RFFIT: non-export).

### Available Vaccine Titers for Cats (3, 26)

Panleukopenia Virus; Herpes Virus (Rhinotracheitis Virus); Calicivirus; and Rabies Virus (RFFIT: non-export).

### Available Vaccine Titers for Horses (32)

Equine Herpes (EHV –1, and – 4) (rhino); Equine Encephalitis (EEE, WEE, VEE; Equine Influenza; Equine Viral Arteritis; Potomac Horse Fever; Rabies Virus (RFFIT: non-export) and West Nile Virus Antibody Titer.

### Vaccinosis Reactions

Acute and Subacute Reactions – anaphylaxis and anaphylactoid – occur minutes to several days post-vaccination; can be severe and even fatal.

Delayed and Chronic Reactions – usually occur 5-21 days post-vaccination; peak time is 10-14 days. Can be delayed longer, and even months later with rabies vaccines.

Clinical signs vary from seizures, immune-mediated damage of blood and other tissues/organs, even death.

### Vaccine Conclusions for Canines

**Factors increasing risk of adverse events 3 days after vaccination:** (25)

Young adult age; small-breed size; neutering; multiple vaccines given per visit. These risks should be communicated to clients.

### Vaccine Conclusions for Felines (3)

**Factors that increase risk of adverse events 30 days after vaccination:** (20)

Young adult age; neutering; multiple vaccines given per visit. These risks should be communicated to clients,

and the number of vaccines administered concurrently limited.

**WSAVA Guidelines for Adult Dogs & Cats 2017** (3,6,11)

**Adverse reactions to rabies vaccines** (11)

More hypersensitivity cases reported than before; stated to be more common in toy breeds, especially poodles. Likely a genetic predisposition.

Dominant antigen in the vaccines that causes the reactions is bovine serum albumin (BSA) [fetal calf serum] Manufacturers are reducing the use of BSA in animal vaccines.

Alternative: Thimerosol (Mercury)-Free Rabies Vaccines (preferred/safer) (11, 12).

**Rabies Challenge Study Update**

[www.rabieschallengefund.org]

Rabies remains a serious and almost always fatal disease in many countries, including the recent outbreaks in Israel. In Israel, rabies is an endemic disease; annual vaccination of dogs is legally required. Cats are given rabies vaccine during outbreaks but *not* required by law.

No documented cases of rabies in North America in vaccinated, truly immunized dogs and cats for 2 decades. While most pet dogs are vaccinated for rabies, fewer cats have historically been vaccinated until recent laws have required it.

**RCF Challenge Trials 2017**

[www.rabieschallengefund.org]

**The Rabies Challenge Fund research studies are now at years 7 and 8; the 5-year challenge phase results:** USDA's rabies challenge virus was given. Post-challenge results after 6 weeks showed that some but not all study beagles survived live rabies virus challenge 5 years after receiving two rabies vaccines as puppies. Unvaccinated control beagles were humanely euthanized once they showed very early clinical signs of rabies. Serum samples collected yearly are being assayed with rabies serum virus neutralization and memory cell immunity tests.

**KamRab by Kamada (for Humans)** [www.kamada.com]

Rabies immune globulin (Human) is produced for post-exposure prophylaxis against rabies infection. Kamada's Rabies Immune globulin received US Food and Drug Administration (FDA) approval in August 2017. Used for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal.

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