Vaccine Issues & WSAVA Guidelines (2015-2017)

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Dr. Jean Dodds recently gave two invited lectures on vaccine issues and guidelines for veterinarians in Israel. She would like to thank BioGal Galed Laboratories and the Israel Veterinary Medical Association for the opportunity and the wonderful time! The following is a summary of the discussion.

Update on Vaccine Issues & Guidelines (2015-2017)

- World Small Animal Veterinary Association (WSAVA) vaccine guidelines began in 2006; provide evidence-based global advice for vaccination best practices in dogs and cats.
- These guidelines and 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) in the United Kingdom are gradually changing routine vaccination practice worldwide.
- Major impact on daily small animal practice.
- Help ensure that pet owners and breeders have scientifically- based advice, and robust, safer vaccines and vaccination protocols for dogs and cats.

Excellent advice overall!

Summary Comments on Vaccine Policy

AAHA 2003 – Current knowledge supports the statement 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."

These statements still apply today [AAHA 2017; WSAVA 2010/2016/2017]

More from WSAVA 2015-2017 – From Prof. Michael J. Day

- "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."

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Key Points on Vaccine Issues

- 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 are serious, chronically debilitating and even fatal.
- Must balance this benefit/risk equation = more benefit than risk.
- "Be wise and immunize, but immunize wisely!" (Dr. Ron Schultz)

Benefits of Vaccines

- More lives saved, more animal production safeguarded than any other medical advance.
- Eradicated smallpox; nearly all polio and measles in people.
- First vaccines were against small pox, anthrax, and canine distemper.
- Significantly reduced endemics of canine distemper, hepatitis and parvovirus, but *not* in wildlife reservoirs.
- Significantly reduced endemic feline panleukopenia (a parvovirus)
- Eliminated rabies in Europe; eradicated Rhinderpest in Africa; and foot & mouth disease in Europe.

Vaccines & Population (Herd) Health

- To protect the population (herd) = 70 % immunized with "core" vaccines …… but …..
- Dog population = only about 50% immunized.
- Cat population = only about 25% immunized.
- Best "vaccine" = natural exposure, but about 50% of susceptible puppies or kittens will die of the disease.
- Vaccine non-responders and low-responders = genetic trait.

Vaccine Non-Responders

- Genetic trait: do *not* breed them.
- They will remain susceptible to the disease lifelong.
- Rate = 1:1000 for CPV (parvovirus)
    - Especially Black Labradors and Akitas
- Rate = 1: 5000 for CDV (distemper virus)
    - Especially Greyhounds
- Rate = 1:100,000 for CAV (hepatitis, adenovirus)
- Rate = unknown for cats

Adverse Reactions & Cautions

Canine Distemper Virus

- Rate = 1:100,000 for Rockborn & Snyder Hill vaccine strains.
- Rockborn strain CDV found in most of today's MLV vaccines.

- Produces PVE = post-vaccinal encephalitis, blindness & death.
- Recombinant (rCDV) Recombitek (Merial) cannot cause PVE.
- Rate = 1: 500,000 for Onderstepoort strain, but less potent.
- When MLV CDV combined with adenovirus (Hepatitis) in combo, risk of immune suppression and PVE increases – especially in puppies.

Maternal Immunity & Protection

Milk Replacer

- Feeding milk replacer proteins instead of natural colostrum will coat bowel of newborns and shut down absorption of antibodies needed for protection from disease.
- Give FFP (Fresh-Frozen Plasma) immediately to orphan or weak pups to get passive immunity; then add milk replacer.

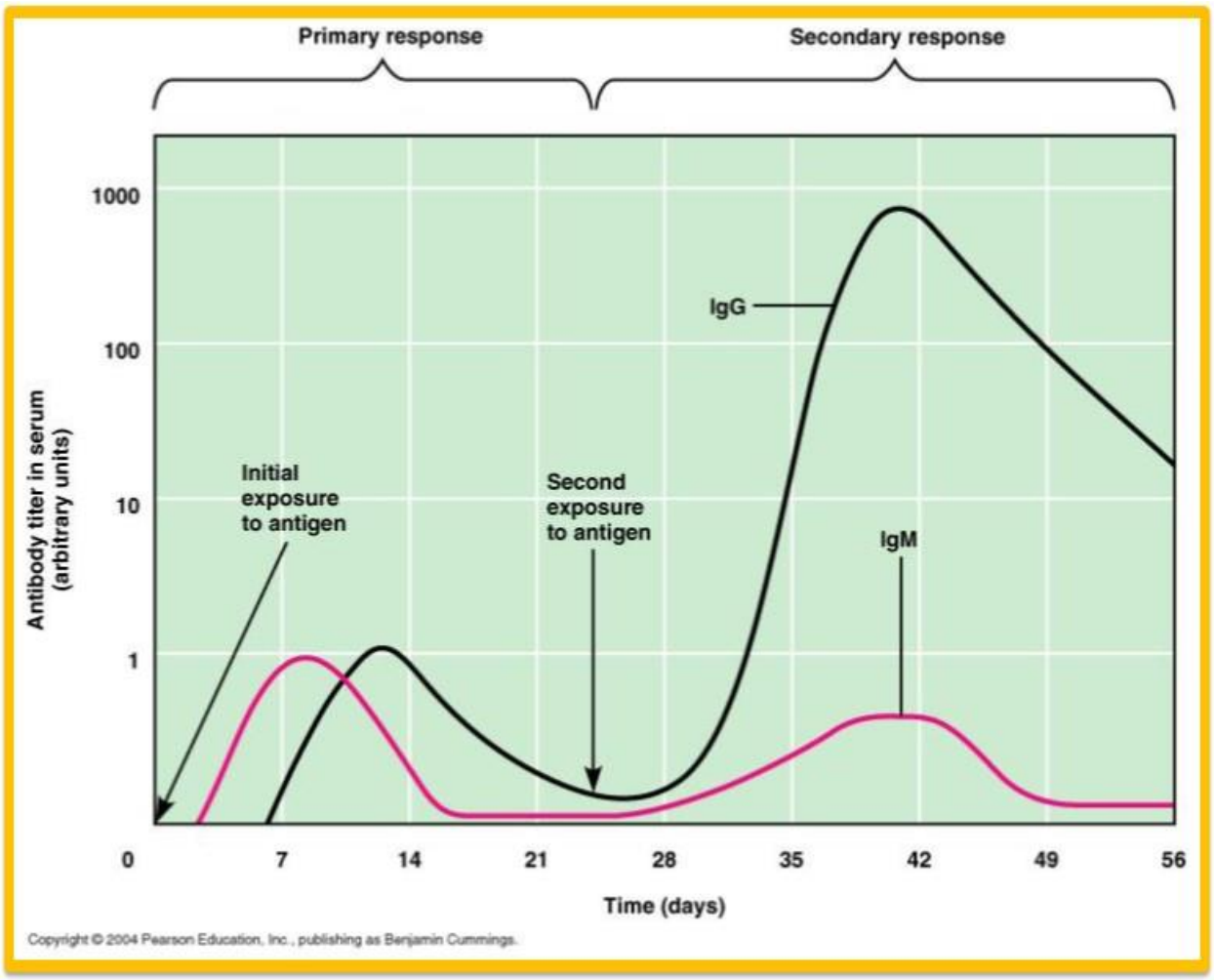
Vaccine Timing

- Last puppy vaccine at 16-18 weeks for protection
- Last kitten vaccine at 12-14 weeks for protection

New WSAVA Guidelines for Puppies & Kittens 2017

- 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).
- New recommendations for primary core vaccine 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 were generally given at 12 months of age or 12 months after completion of the primary vaccine series.
- New recommendation is to give this vaccine <u>at 6 months of age</u>; becoming the last in the primary series of 4 core vaccines.
- Can be given at time of neutering, or better, at suture removal after neutering.
- Those given 6-month core vaccines do not need one at 12 months of age.
- Alternatively, serologically test core vaccinal immunity at 6 months of age.
- 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 = committed immune memory cell immunity.

Anamnestic Immune Response



New WSAVA Guidelines for Adult Dogs & Cats 2017

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 consider that animal's risk of exposure.
- Geographical location and lifestyle factors should be taken into account.

Vaccinating pregnant pets.

- Vaccines should ***not*** be given during pregnancy.
- Vaccination with MLV and killed products during pregnancy should be avoided. The same applies to times of sex hormonal change, like estrus and pro-estrus.

- Shelters may advise vaccination, if pregnant animal was never vaccinated and there is an outbreak of disease.

Beyond the Guidelines – Vaccine Dosage

Body Mass

- Same dose intended for toy and giant breeds.
- Why?
- Modified Live Virus (MLV) vaccines (i.e. distemper, parvovirus, adenovirus-2) – immunogenic effect *not* based on body mass.
- Killed inactivated vaccines (i.e. rabies) – should be adjusted for body mass.
- Minimum/optimum doses for protection?
- Excess antigen present.

Half-Dose CDV & CPV Vaccine Study in Small Breed Adult Dogs

- Small breed adult dogs, between 3-9 years of age studied.
- Dogs were healthy; had no vaccines for at least 3 years.
- Purpose to determine if just half-dose of bivalent Canine Distemper Virus (CDV) & Canine Parvovirus (CPV) MLV vaccines elicited protective serum antibody titer responses.
- Titer levels compared pre-vaccine with 1 & 6 months later.
- Half-dose vaccine resulted in sustained protective serum antibody titers for all adult dogs studied.

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

Vaccine Dosage (cont'd)

Age

- Optimal age for full immune response
  Same for all breeds and sizes?
  12 weeks + for puppies; 10 weeks for kittens
- Earliest age for safety
  6 weeks for puppies and kittens
- Effective age varies
- MDA interferes with complete immunization – current potent vaccines produce longer lasting, passive colostral immunity.
- Dr. Schultz advocates giving one monovalent canine parvovirus vaccine at 18 weeks (as breakthrough disease has occurred).

Hormonal State During Vaccination

Avoid Vaccination

- Period just before estrus (30-45 days)
- During estrus
- Pregnancy
- Lactation

Core Vaccines*

Dog

- Distemper
- Parvovirus
- Rabies
- Adenovirus-2 for Infectious Canine Hepatitis cross-protection (in areas where prevalent)

Cat

- Feline Parvovirus
- Rabies
- Herpesvirus (in areas where prevalent)
- Calicivirus (in areas where prevalent)

Why Give 'Core' Vaccines Annually?

- Booster after 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 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, introduces 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

- No evidence that annual boosters are necessary; except in rabies endemics.
- Need to lengthen interval for "core" vaccines (every 3-7 years or more for healthy adults).
- Geriatric animals vaccinated only with caution.
- 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

CDV (distemper virus)

- Vaccinates immediately protected, if exposed simultaneously.
- MLV CDV does not shed appreciably.

CPV (parvovirus)

- Vaccinates protected after 48-72 hours; exposed pups get sick.
- MLV CPV sheds from post-vaccine days 3-14; exposure risk.
- Shed vaccine CPV not seen on Idexx SNAP, but present on CPV PCR of feces for 2 weeks.

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

- Infectious Canine Hepatitis (CAV-1) clinical cases *not* around in America for about 15 yrs (one exception).
- No vaccine for CAV-1 as adverse "blue eye" developed; CAV-2 vaccine for kennel cough which cross-reacts.
- But, giving puppies CAV-2 vaccine with CDV and CPV for distemper & parvovirus increases risk for PVE
- Can give Bordetella oral / intranasal to provide some hepatitis CAV-2 protection
- Vaccine *not* preferred despite listed in the "Core"

Kennel Cough & Flu Vaccines

Oral/Intranasal Bordetella

- Releases interferon, which impairs growth of other respiratory viruses (parainfluenza, adenovirus-2, influenza).
- Injectable Bordetella vaccine does *not* release interferon.
- Oral preferred; hypersensitivity reactions with intranasal.
- Kennel cough vaccines *not* 100% effective.

Influenza

- Mild clinical signs; many exposed dogs remain clinically normal.
- Produces fever whereas kennel cough does *not*. When combined with Streptococcus, 2-3% can die.

More on Canine Influenza

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 Flu usually presents as a fever with a cough in the early stages. For mild fever (102-103^{o} F) *no* treatment is needed. If above 104^{o} F, then secondary pneumonia can result and should be treated promptly with antibiotics and supportive care.
- We do *not* routinely give canine influenza vaccines to healthy pups or adult dogs.

- Even though canine flu viruses (H3N2 and H3N8) are highly contagious.

What About Leptospirosis?

Endemic in Israel (clinically rare) and many other parts of he world

- After initial 2-dose series, ongoing debate over need for annual Lepto boosters, as duration of immunity short-lived.
- Concerns over drift in serovars now affecting dogs, raising further questions for current use of Lepto 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; *L. ictero,* most common.
- Most common vaccine eliciting acute and per-acute adverse reactions. Disease exposure risk vs adverse vaccine reaction and benefits needs to be taken into account. Vaccine not very effective.
- Treatment with antibiotics effective; sanitation and hygiene very important, along with controlling rodents.

What About Canine Monocytic Ehrlichiosis?

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

- Tick control main preventive measure against CME.
- No commercial vaccine currently available, despite vaccine research from Yissum R & D of Hebrew University, Jerusalem.
- 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 vaccine. After infection with virulent *Ehrlichia* field strain, control dogs all had severe disease, but only 3 of 8 vaccinates had mild transient fever and rest remained healthy.
  [Rudoler N, Baneth G, Eyal O, et al. *Vaccine*, 2012 ;31(1):226-233]

What About *Spirocerca lupi* (Park Worm)?

- Common in Israel = grasses, parks, public gardens; infects countless dogs.
- Respiratory and GI tract signs, even sudden death from internal bleeding.
- Can be fatal once dog ingests infected dung beetle, or mouse, bird or lizard that ate infected beetle. Larvae released in stomach and travel through stomach lining and aorta to esophagus to lay eggs.
- Worms found within nodules in esophageal, gastric and aortic walls.
- Infected eggs are secreted in dog feces, and cycle through dung beetle repeats
- Treatment = Ivomec or Dormectin
- Prevention = Treat dogs every 3 months empirically; muzzle dogs on walks to prevent eating infected debris and feces; keep on leash; pick up & discard feces in garbage cans.

Alternatives to Current Vaccine Practices

- Measure serum antibody titers.
- Avoid unnecessary vaccines or over-vaccinating.
- Caution 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 = preferred].
- Alert caregiver to watch puppy/kitten behavior and health after boosters.
- Avoid revaccination of those with prior adverse events.

New Serum Antibody Recommendations

After the core puppy and kitten vaccine series

- Measure serum antibody titers 3-4 weeks later
- For dogs = CDV, CPV and optionally, CAV-2
- For cats = FPV
- To determine if 26-week booster is needed
- At 52 weeks, measure serum antibody titers again (preferred), or give booster

Reasons for Vaccine Titer Testing*

- To determine that 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.
  [Schultz, Ford, Olsen, Scott. *Vet Med*, 97: 1-13, 2002 (insert)]

Available Vaccine Titers for Dogs

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

Available Vaccine Titers for Cats

- Panleukopenia Virus
- Herpes Virus (Rhinotracheitis Virus)

- Calicivirus
- Rabies Virus (RFFIT: non-export)

Available Vaccine Titers for Horses

- 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)
- West Nile Virus Antibody Titer

Case Examples of Vaccinosis

- 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, even months 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:

- Young adult age
- Small-breed size
- Neutering
- Multiple vaccines given per visit
- These risks should be communicated to clients

[Moore et al, *JAVMA* 227:1102–1108, 2005]

Vaccine Conclusions for Felines*

Factors that increase risk of adverse events 30 days after vaccination

- Young adult age
- Neutering
- Multiple vaccines given per visit
- These risks should be communicated to clients, and the number of vaccines administered concurrently limited
  [Moore et al, *JAVMA* 231:94-100, 2007]

WSAVA Guidelines for Adult Dogs & Cats 2017

Adverse reactions to rabies vaccines

- More hypersensitivity cases reported than before
- Stated more common in toy breeds, especially poodles
- Likely genetic predisposition
- Dominant antigen cause = reactions to bovine serum albumin (BSA) [fetal calf serum]
- Manufacturers reducing BSA in animal vaccines
  [Dodds, W Jean. Rabies virus protection issues and therapy, Glob Vaccines Immunol 1(3):51-54,2016]

Alternative: Thimerosol (Mercury)-Free Rabies Vaccines (preferred/safer)

Rabies Challenge Study Update

- 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

The Rabies Challenge Fund research studies are now at years 7 and 8; the 5-year challenge phase results:

- USDA's rabies challenge virus given. Post-challenge results after 6 weeks met US Title 9 Code of Federal Regulations (CFR) for rabies vaccine licensing.
- Dogs survived live rabies virus challenge 5 years after receiving two rabies vaccines as puppies.
- Unvaccinated control dogs 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

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