Canine Vaccines:

Dispelling the Myths

“Vaccination remains the single most effective method for protecting against infectious disease in healthy animals.”

Veterinary Products Committee Working Group Report on Vaccines

"Vaccination plays a very valuable role in the prevention and control of major infectious diseases in cats and dogs. Although adverse reactions to vaccination...occasionally occur, the overall risk/benefit analysis strongly supports their continued use"

Veterinary Products Committee Working Group Report on Vaccines

"In view of the occasional occurrence of adverse reactions, the working group recommends that the product literature indicates that:

1) **The regime for booster vaccinations is based on a minimum duration of immunity rather than a maximum**
2) **A risk/benefit assessment should be made for each individual animal by the veterinarian in consultation with the owner with respect to each vaccine and frequency of its use"**

Are we vaccinating too much?

•Are Boosters Necessary?

"If a modified live virus vaccine is given after 6 months of age, it produces immunity which is good for the life of the pet."

-Dr. Ihor Basko, "Vaccination Newsflash"

True or False

False

Dogs immunized repeatedly with commercial vaccines do not always maintain adequate neutralizing antibody titers

Neutralizing Antibody Titers of 9 Dogs (5-6 years old) Previously Vaccinated with Commercial Rabies Vaccines at 0.5, 1.5, 2.5 and 5.5 (6 year olds) Years (*T. Tims et al., Vaccine 18:2804-2807 [2000]*)	
Dog No.	*Neutralizing Antibody Titer (IU/ml)**
51-99	< 1:5 (< 0.05)
52-99	< 1:5 (< 0.05)
53-99	1:270 (3.2)
54-99	1:56 (0.7)
55-99	1:25 (0.3)
56-99	< 1:5 (< 0.05)
57-99	< 1:5 (< 0.05)
58-99	< 1:5 (< 0.05)
59-99	< 1:5 (< 0.05)
% of Dogs with Protective Titers	**33.3%**

*Minimum Protective titer = $\geq$0.1
(=0.5 for importation into rabies-free countries)

Are Boosters Necessary?

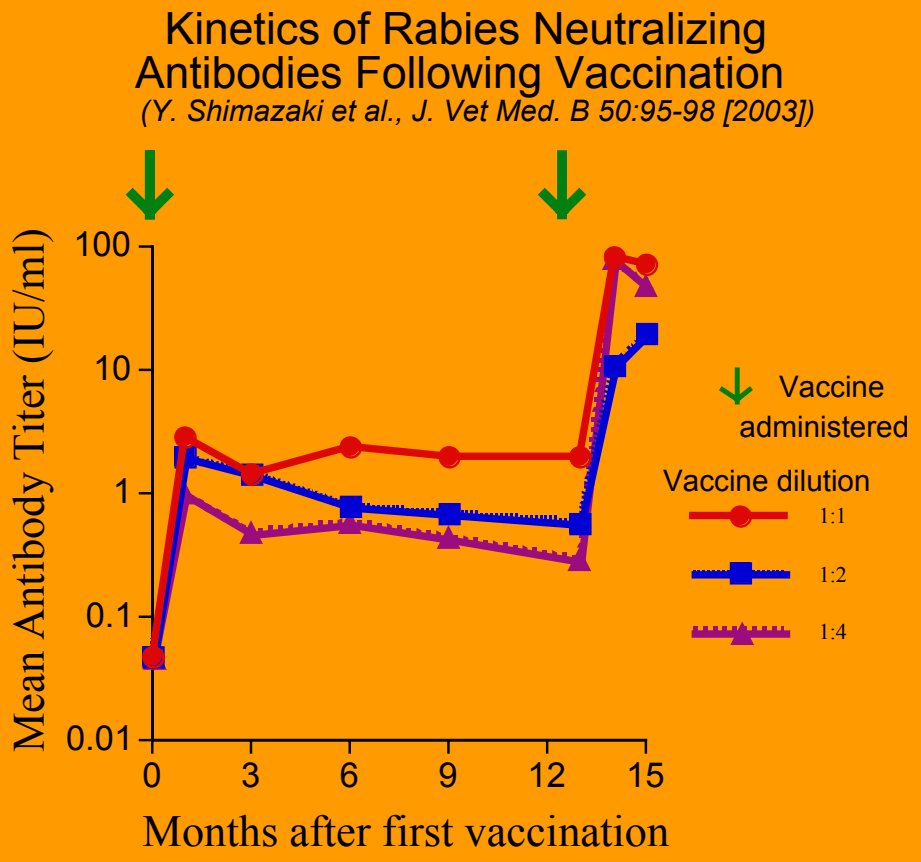
"If another MLV vaccine is given a year later, the antibodies from the first vaccine neutralize the antigens of the second vaccine and there is little or no effect."

-Dr. Ihor Basko, "Vaccination Newsflash"

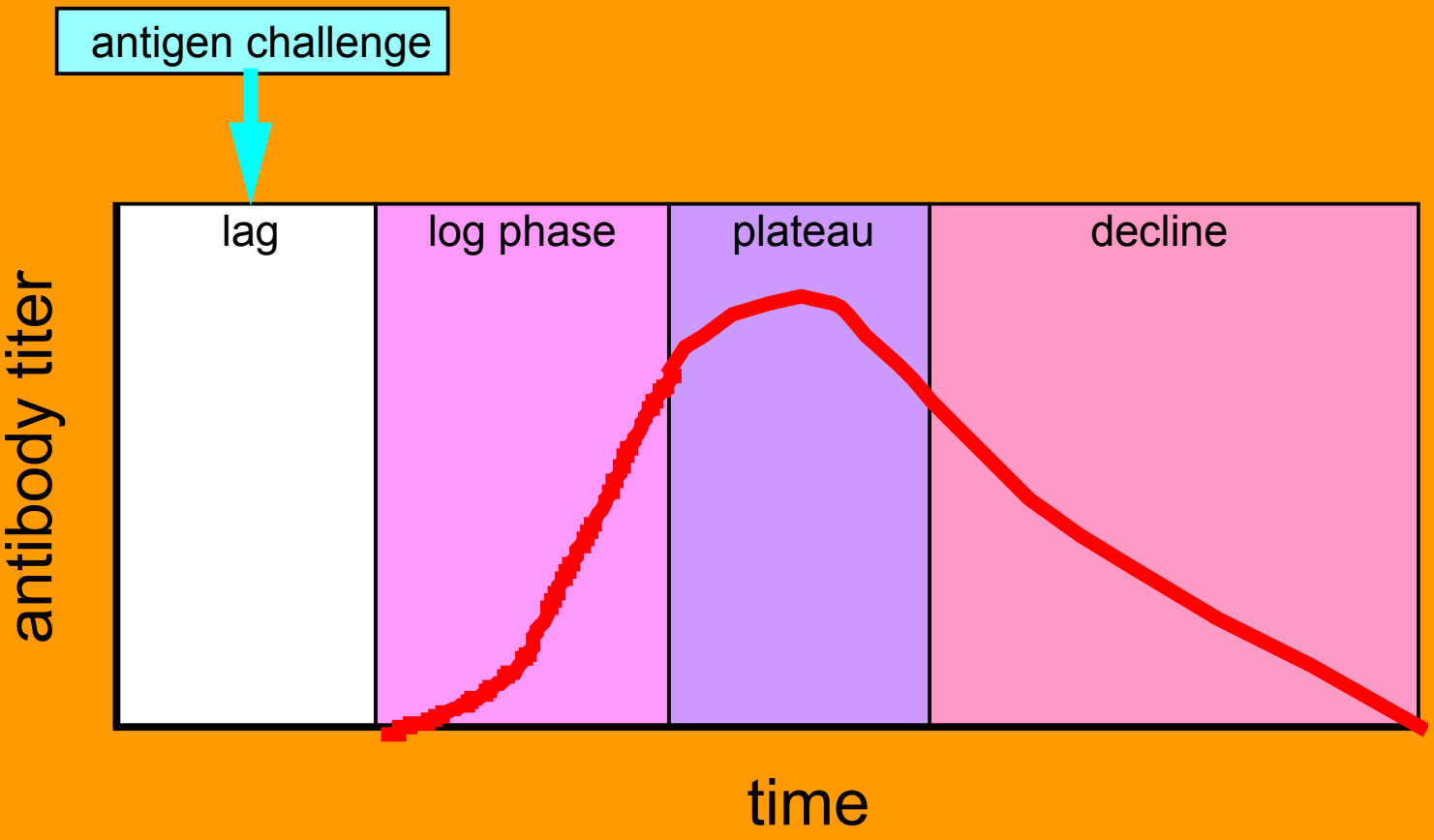
True or False

False

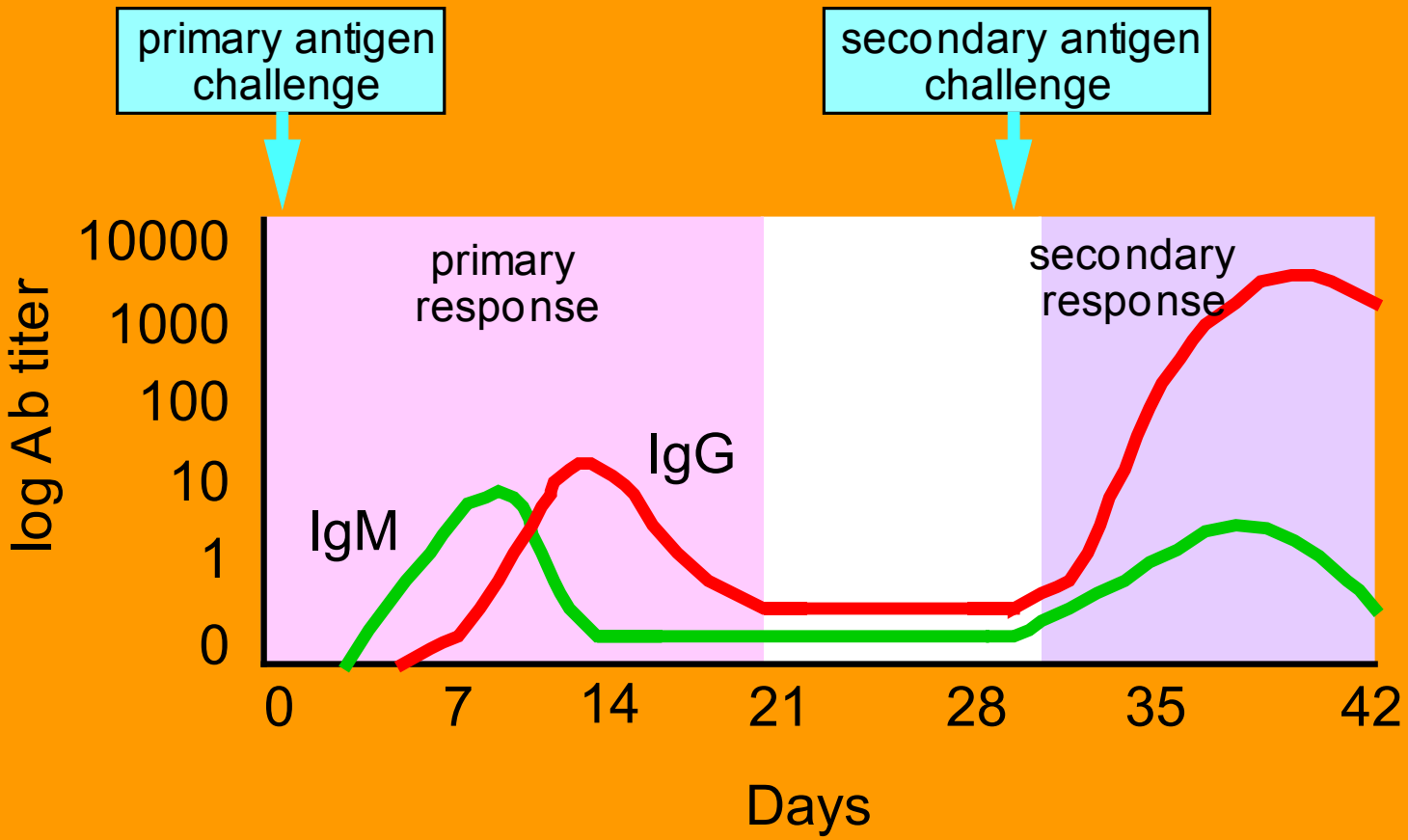
Even dogs seropositive for rabies neutralizing antibodies show an enhanced secondary antibody response to a booster vaccine



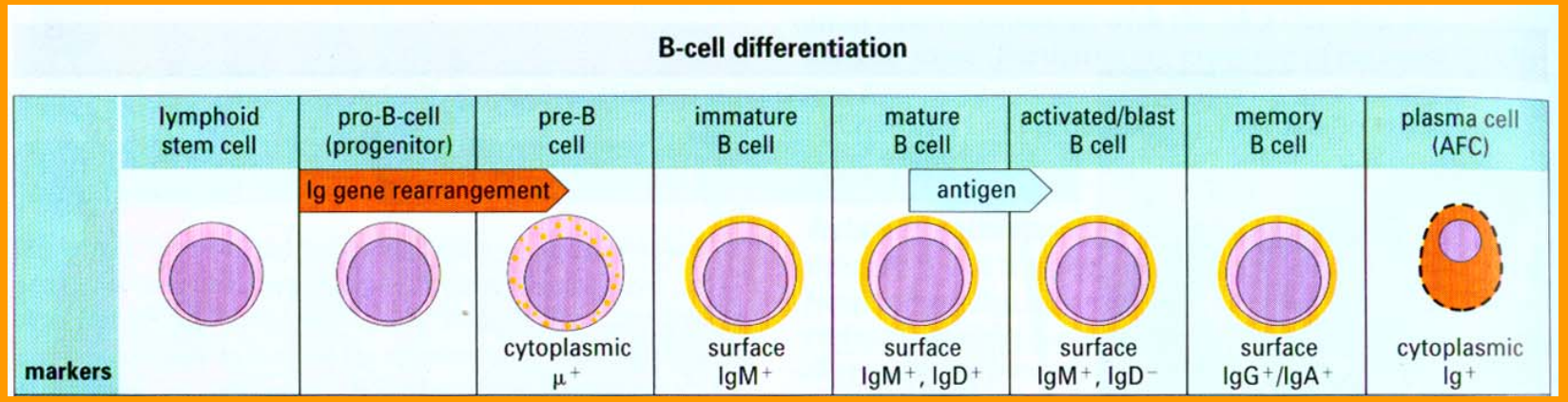
There are Four Phases of Primary Antibody Response



Primary and Secondary Antibody Responses



The Making of an Antibody



Repeat administration of a vaccine (boostering) is required for the immune system to switch from an IgM antibody response to an IgG antibody response

Are Annual Boosters Necessary?

"There is no scientific documentation to back up label claims for annual administration of MLV."

-Dr. Ihor Basko, "Vaccination Newsflash"

True or False

Results of Rabies Challenge (NYC-Ga Strain) at 1 and 3 years after a single intramuscular immunization with various vaccines

Vaccine*	Results of 1 Year Challenge		Results of 3 Year Challenge	
	% Dogs with Neutralizing Antibodies	Dogs Surviving Challenge	% Dogs with Neutralizing Antibodies	Dogs Surviving Challenge
LEP (TC)	88	9/10 (90%)	87	29/30 (97%)
LEP (TC)	73	10/10 (100%)	69	26/29 (90%)
ERA (TC)	73	10/10 (100%)	57	27/30 (90%)
LEP (CE)	70	10/10 (100%)	54	28/30 (93%)
HEP (TC)	63	10/10 (100%)	42	27/29 (93%)
CVS (adj)	13	7/10 (70%)	0	17/29 (59%)
SMB	95	10/10 (100%)	48	27/27 (100%)
SMB	67	10/10 (100%)	28	23/29 (79%)
None	0	0/10 (0%)	0	3/30 (10%)

* LEP (Low Egg Passage); HEP (High Egg Passage); ERA (Elizabeth Rokitniki Abelseth); CVS (challenge virus strain); SMB (Suckling Mouse Brain)

Comparison of Route of Vaccine (HEP) Administration in a Rabies Challenge (NYC-Ga Strain) 3 Years after Immunization

Vaccination	Dogs with Neutralizing Antibodies	Dogs Surviving Challenge
Intramuscular		
Undiluted	29/30 (97%)	30/30 (100%)
Diluted 1:10	6/10 (60%)	10/10 (100%)
Diluted 1:100	4/10 (40%)	9/10 (90%)
Subcutaneous		
Undiluted	4/29 (14%)	17/29 (59%)
Diluted 1:10	0/9 (0%)	2/9 (22%)
Diluted 1:100	0/8 (0%)	2/8 (25%)
None	0/30 (0%)	0/30 (0%)

Results of Rabies Challenge (Fox Strain) at 4 and 5 years after a single intramuscular immunization with ERA Vaccine

Vaccination Challenge	Dogs with Neutralizing Antibodies	Dogs Surviving Challenge
4-Yrs Post-vaccine		
Yes	5/10 (50%)	7/10 (70%)
No	0/9 (0%)	0/9 (0%)
5-Yrs Post-Vaccine		
Yes	7/14 (50%)	13/14 (93%)
No	0/14 (0%)	5/14 (36%)

Neutralizing Antibodies in Dogs and Protection from Rabies Challenge

Antibody Test	Antibody Titer				
	< 5	**5-9**	**10-19**	**20-39**	**= 40**
MNT	56/251 (22%)	9/100 (9%)	9/92 (10%)	1/63 (2%)	0/171 (0%)
RFFIT	84/241 (35%)	13/112 (12%)	9/119 (8%)	0/87 (0%)	0/201 (0%)

Results expressed as the number of dogs that died/number of dogs challenged and % mortality

Are we vaccinating too early?

Vaccination Schedules

- **Immunization and Puppies**

"Puppies receive antibodies through their mother's milk. This natural protection can last for 8-14 weeks...puppies should not be vaccinated at less than 8 weeks."

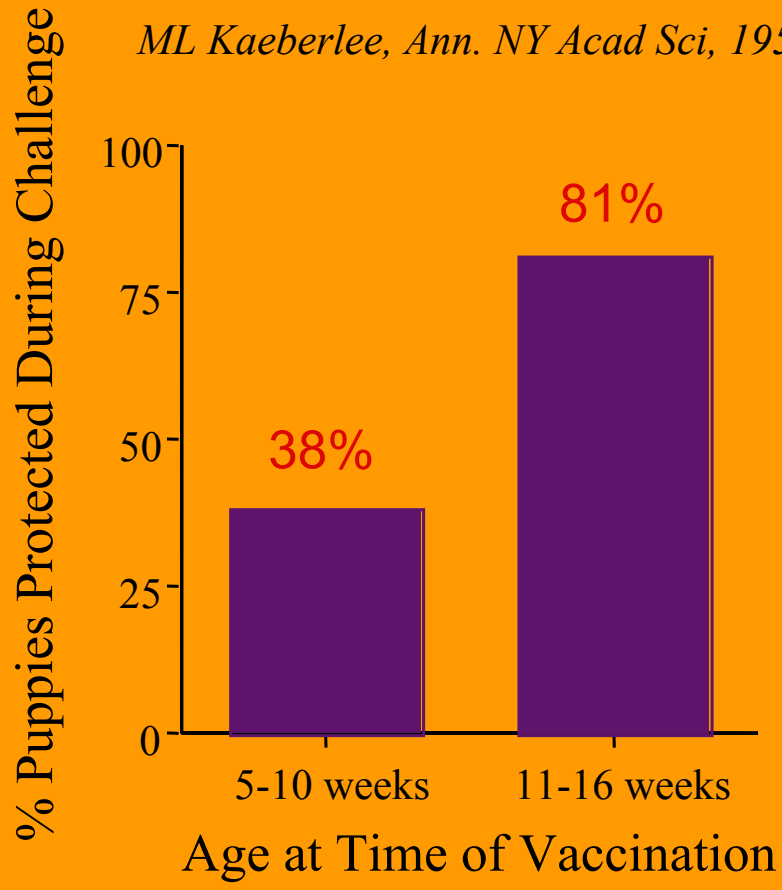
-Dr. Ihor Basko, "Vaccination Newsflash"

True or False

False

Such statements are based upon results from studies conducted with first generation vaccines, like this data reported in 1958.

ML Kaeberlee, Ann. NY Acad Sci, 1958.



Differences in Commercial Vaccines (1994) to Induce Protection Against CPV Challenge in Puppies Immunized at 5-6 weeks

	* Dogs Protected from CPV Challenge						
Vaccine	None	V1	V2	V3	V4	V5	V6
Protected Dogs/Total Dogs in Group (% Protected)	0/8 (0%)	0/8 (0%)	0/8 (0%)	0/8 (0%)	0/8 (0%)	8/8 (100%)	8/8 (100%)

Maternal antibody titers in pups at time of vaccination were between 1:20 and 1:320

Larson and Schultz, Am J Vet Res, 1997.

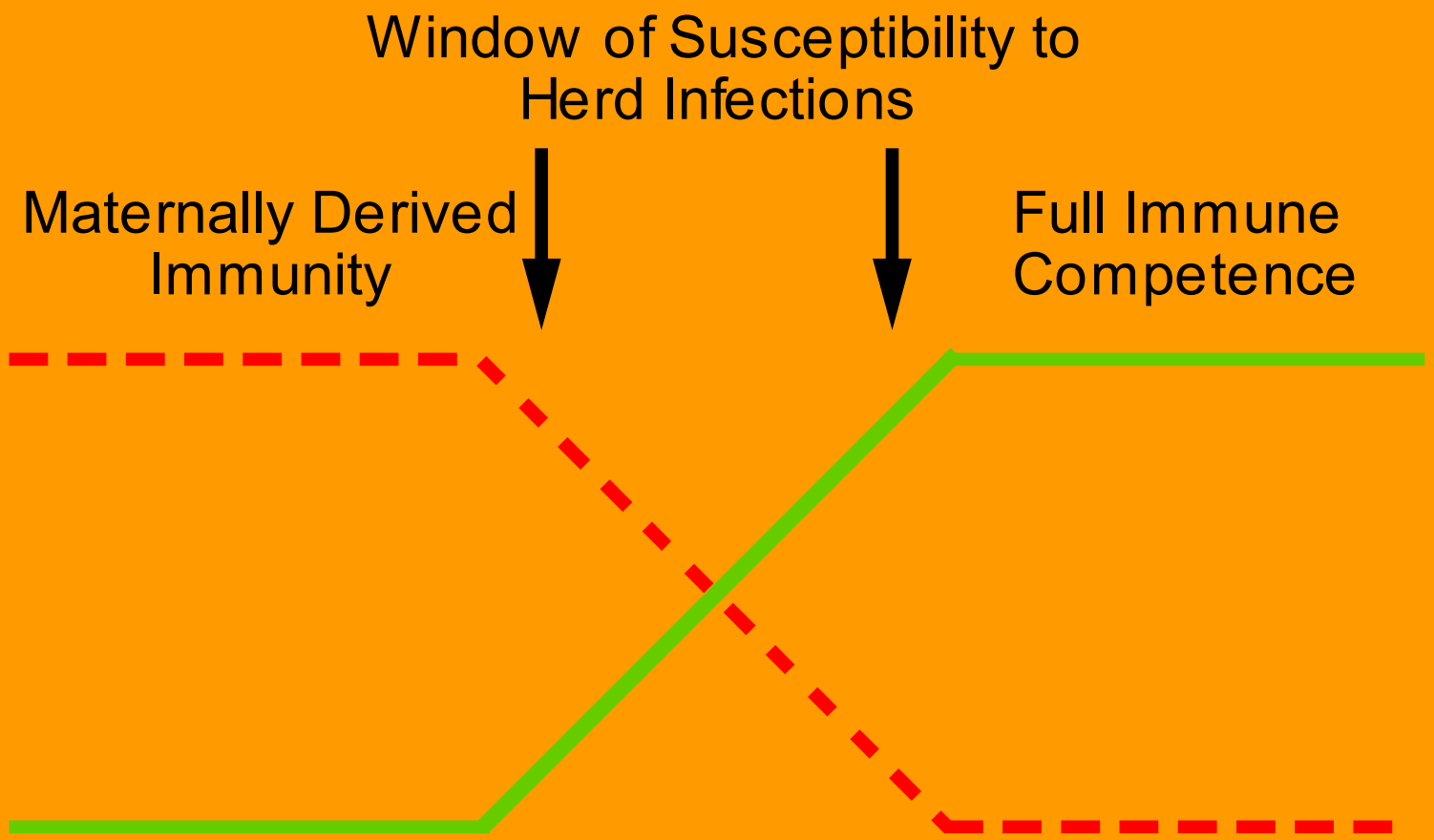
Factors other than age determine whether a vaccine will effectively overcome maternally-derived antibodies to produce effective protection

- **Level of maternal antibody**
- **Specific type of maternal antibody**
- **Immunogenicity of the vaccine**
- **Vaccine titer**

The Challenge of Providing Protective Immunity

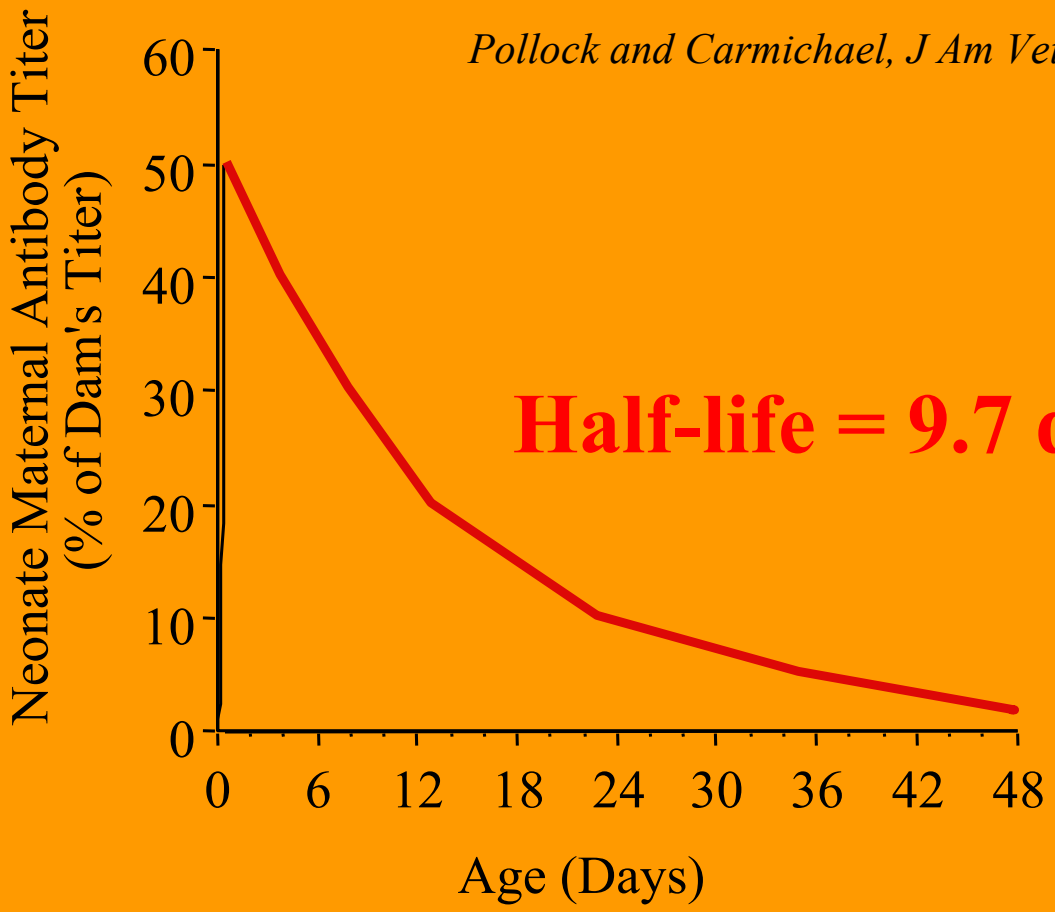
To provide sufficient antigen-challenge to evoke a protective immune response in the presence of maternal antibodies and a naïve T cell environment while not inducing immunosuppression

Level of Maternal Antibody



Kinetics of CPV Maternal Antibodies in Neonate Puppies

Pollock and Carmichael, J Am Vet Med Assoc, 1982



Half-life = 9.7 days

Immunogenicity of low-passage, high-titer MVCPV vaccine in pups with maternally derived antibodies

	Prevaccination Maternally-derived HI Titer							
	< 8	8	16	32	64	128	256	Total
# Pups	29	17	45	33	13	3	6	146
# Protected	28	16	45	31	13	2	6	141
%	97	94	100	94	100	67	100	97

Protection was determined based on the vaccine's ability to induce a 4-fold or greater increase in HI titer to > 64.

CM Hoare et al., Vaccine, 1997.

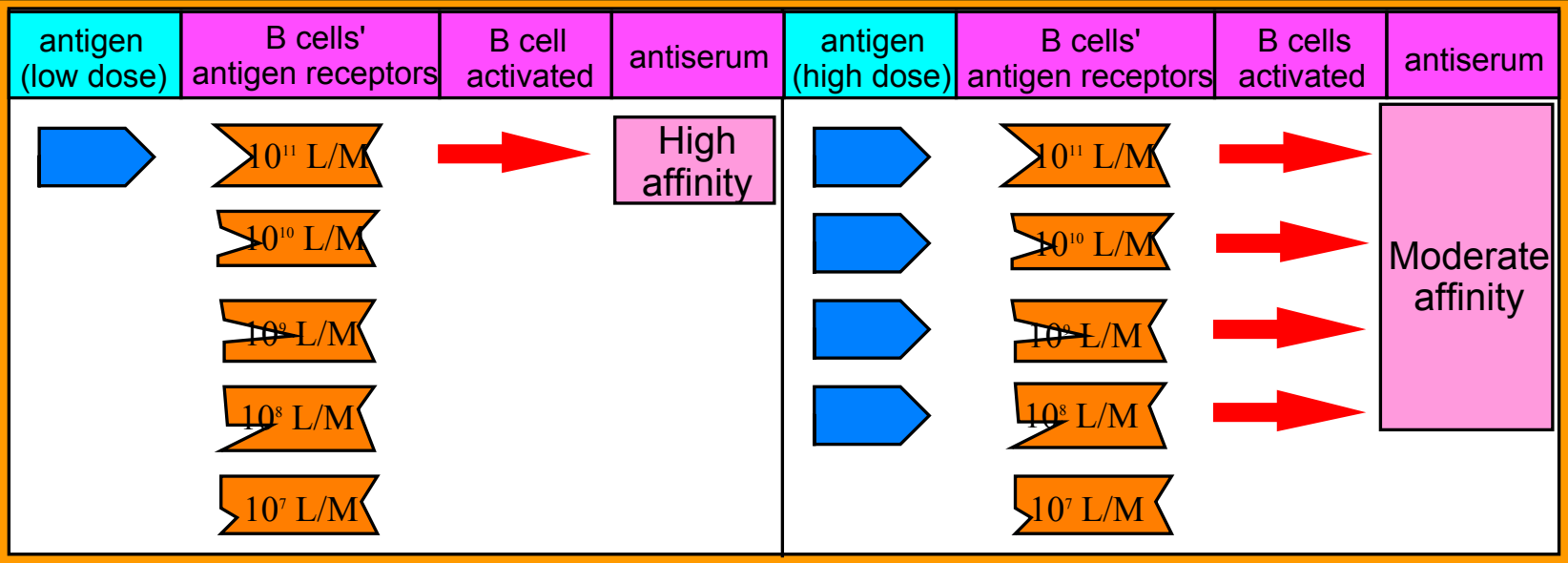
Comparison of Attenuated Vaccines

Low Passage Vaccine (Less Attenuated)	High Passage Vaccine (More Attenuated)
Pro	Pro
Induces active immune response even in presence of maternal antibodies	Safer (Reduced risk for infectivity)
Con	Con
Greater risk for subclinical infectivity and other adverse side effects	Susceptible to maternal antibody interference (Active immune response may be delayed up to as late as 16 weeks of age)

Comparison of Vaccine Titer

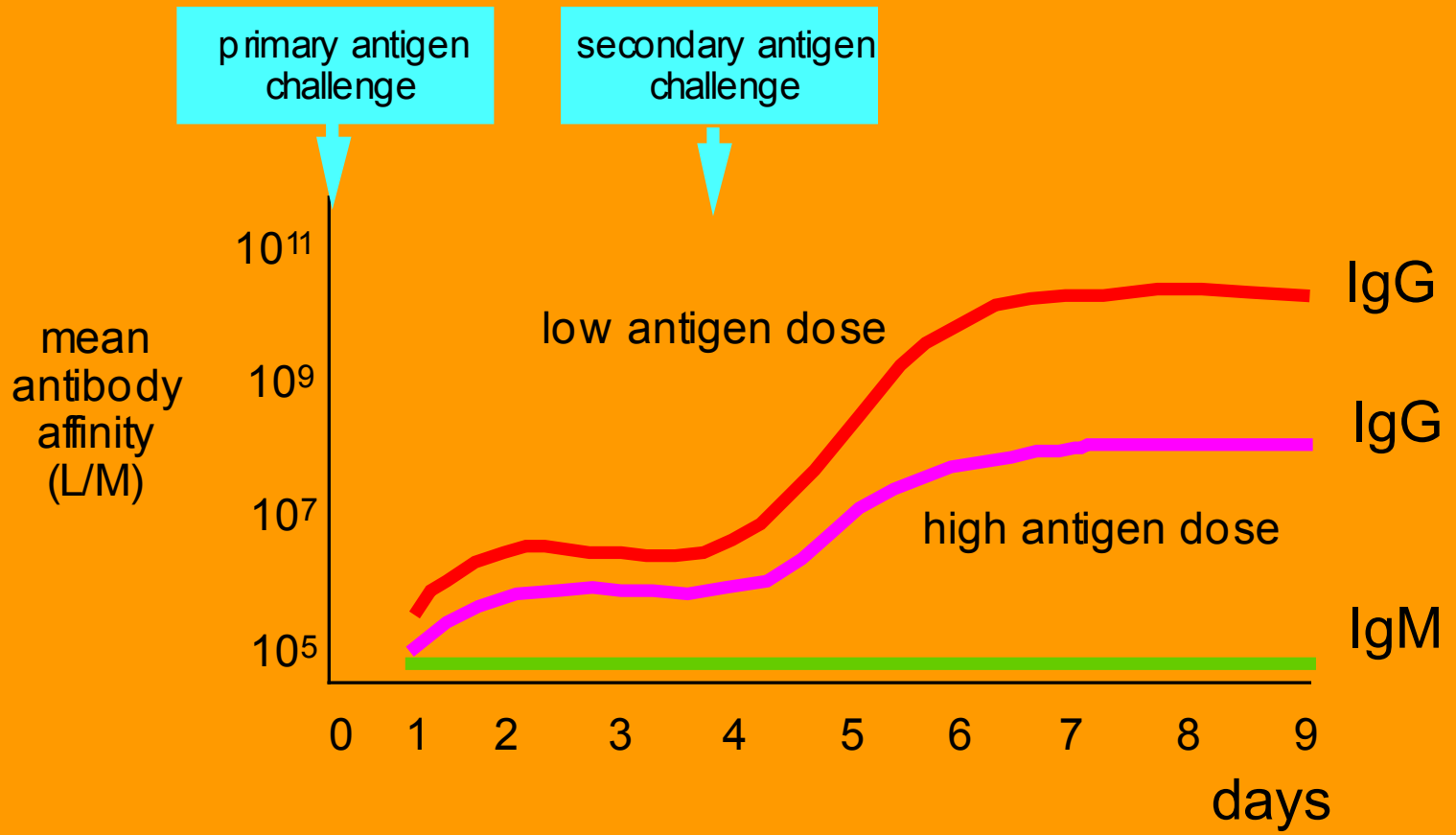
Low Dose Vaccine	High Dose Vaccine
Pro	Pro
Produces higher affinity antibodies (strong immune response to antigen challenge)	Induces active immune response even in the presence of maternal antibodies
Con	Con
May be too low to induce active immune response in the presence of maternal antibodies	Produces lower affinity antibodies (weak to moderate immune response to antigen challenge)

Effects of vaccine dose on antibody affinity



Low antigen doses bind to and trigger only those B cells with high affinity receptors, whereas high antigen doses allow triggering of more B cell clones and produce antibody responses with lower average affinity.

Dose-Dependent Affinity Maturation of Antibodies



Factors that Interfere with Effective Immunization in the Young Dog

- **Maternal Antibody Interference**
- **Immature Immune Function (specifically impaired T-cell function)**

Influence of Age at Time of Vaccination on Duration of Rabies Antibody Titer

	Age at Time of Vaccination (years)					
	< 1	1	2-3	4-5	>6	Total
# Dogs	14	15	16	18	15	78
Antibody Titer* = 0.5 IU/ml (% of Dogs)	8 (57)	10 (67)	10 (63)	11 (61)	12 (80)	51 (65)
Average Titer/group (IU/ml)	1.53	1.72	10.6	5.71	20.4	11.0

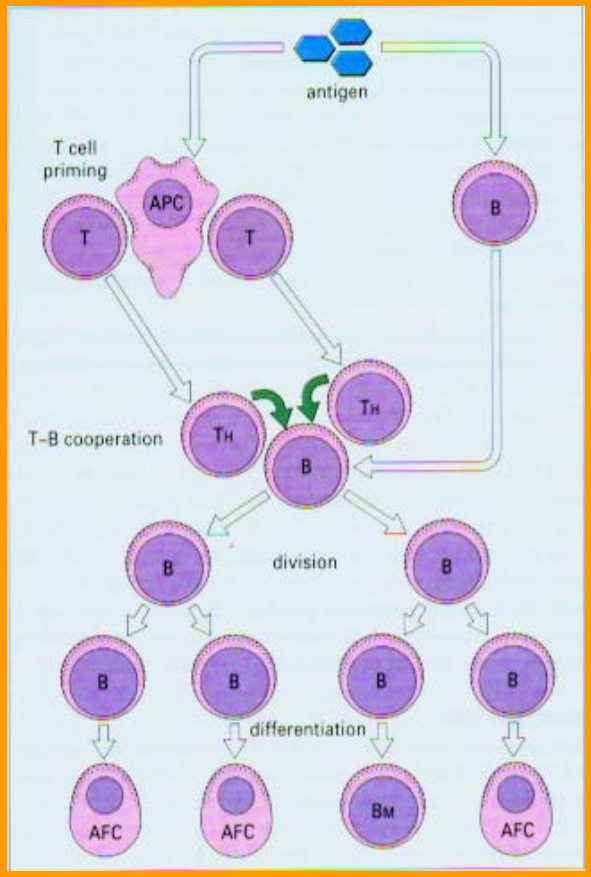
* Titer results at 1 year following vaccination.

Y. Shimazaki et al., J Vet Med B, 2003

Maternal antibodies do not interfere with T cell activation and thus early vaccination serves as effective priming for T cells

Cell Cooperation in the Antibody Response

Antibodies are presented to virgin T cells by Antigen Presenting Cells (APCs). B cells also take up antigen and present it to the T cells, receiving signals from the T cells to divide and differentiate into antibody forming cells (AFCs) and memory B cells (BM).



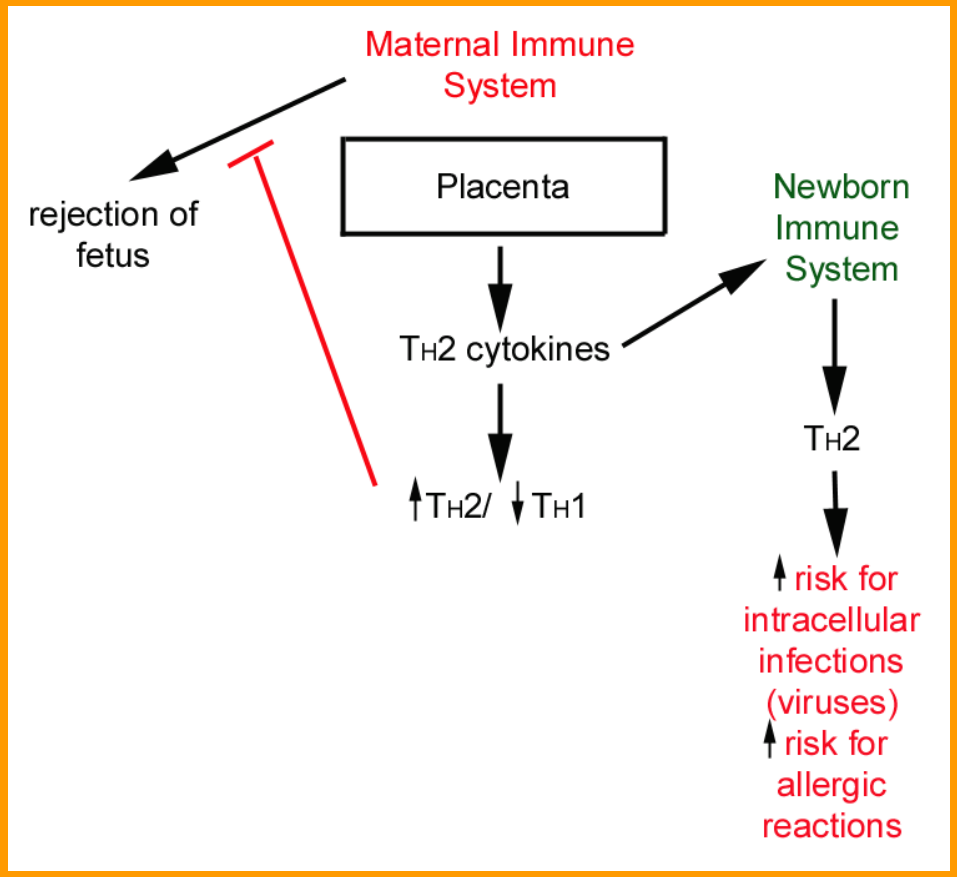
IgM

IgG

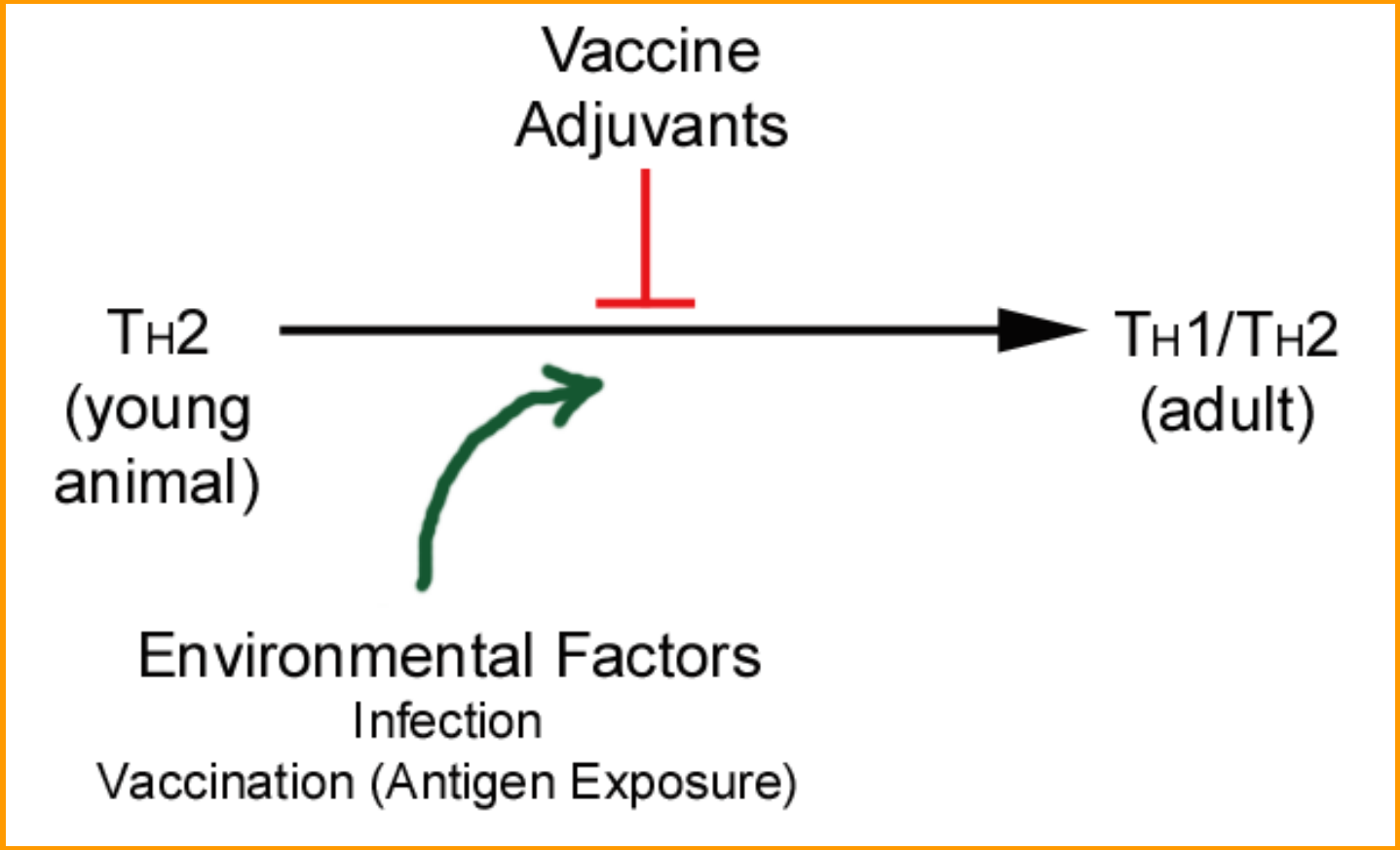
Characteristics of T_H Cell Types

T_H1 Cells	T_H2 Cells
Cell-mediated Immunity (directed at pathogens that get into the cells; i.e. viruses)	Humoral (antibody) Immunity (directed at pathogens living in the blood and body fluids outside the cells; i.e. bacteria)
Direct Cytotoxic T cells and Natural Killer (NK) Cells	Direct eosinophils, neutrophils, and antibody secreting cells

Maternal Influences on the Offspring Immune System



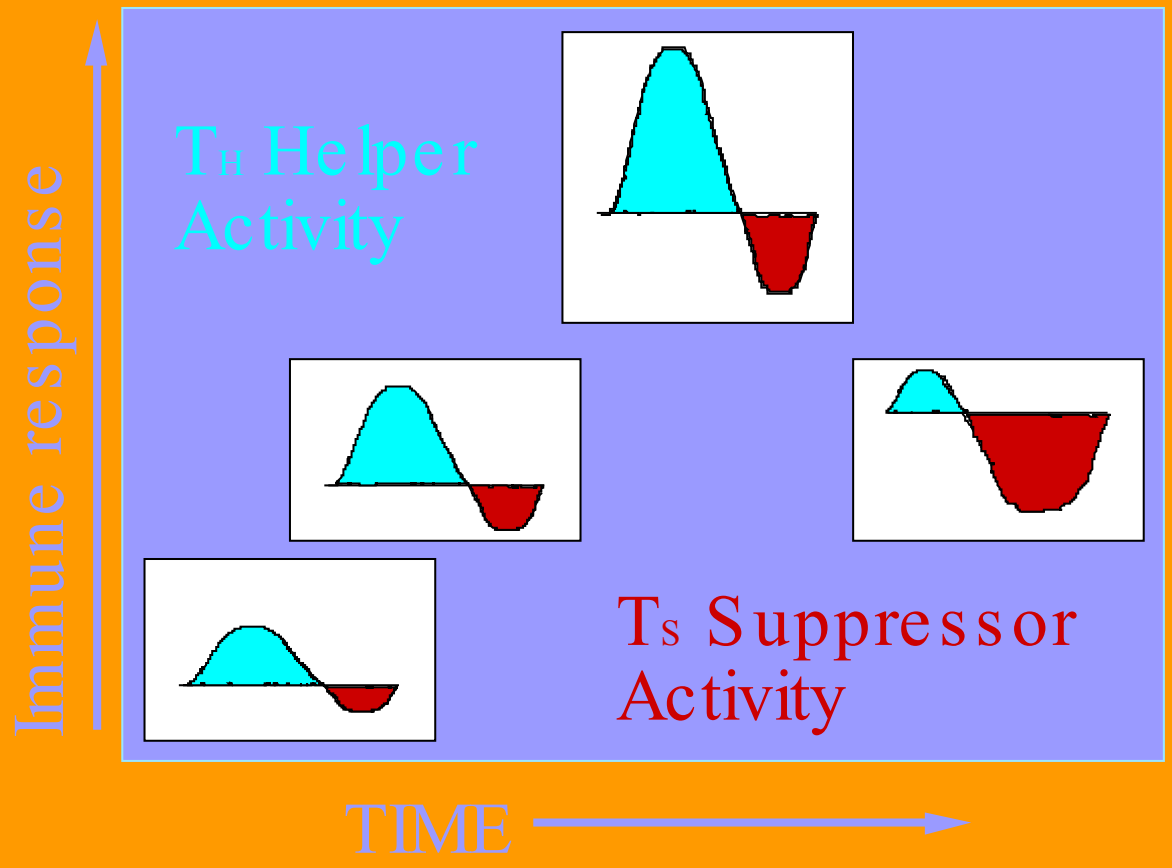
Immune Maturation



Some vaccines induce immunosuppression

- **Antigen Overload**
  when the amount of antigen introduced into the dog exceeds the ability of the immune system to respond
- **Vaccine Interference**
  when one antigen component of the vaccine prevents the immune system from responding to another antigen component of the multivalent vaccine
- **Vaccine Tolerance**
  Antigens administered orally induce tolerance by activating suppressor T cells

Repeated antigen stimulation and the immune response



Are Vaccines Dangerous?

Immune Complex Diseases

- **Type III Hypersensitivity**
- **Binding of antibodies to vaccine antigens create large molecules that may be deposited in certain organs of the body and result in inflammation of local tissue**

Examples of Immune Complex Disease:

- **Blue-Eye (Caused by Early CAV-1 Vaccines)**
- **Vaccine-Induced Vasculitis**

Vaccine-Induced Vasculitis

- **Rare Disorder**
- **Cause: T cell dysfunction (genetic or age-related)**
- **Disease Process: Immune Complexes bind to blood vessels and subsequent immune processes damage vessels while targeting the antigen for destruction**
- **Symptoms: behavioral disturbances, tremors, muscle weakness, seizures; abdominal bloating, pain, bloody stools; difficulty breathing, coughing, exercise intolerance, heart enlargement; loss of vision**
- **Treatment: glucocorticoids (anti-inflammatory steroids)**
- **Complications: Pulmonary emboli**

Epilepsy and Acute Disseminated Encephalomyelitis

- Type III Hypersensitivity
- Most often associated with ML-CDV vaccine
- Cause: Immunosuppression or immune dysfunction
- Disease Process: Antigens gain access to the CNS and replication of attenuated virus in brain tissue causes inflammatory lesions
- Symptoms: fever, depression, nausea and vomiting motor weakness, loss of coordination, difficulty breathing and/or epileptic seizures
- Treatment: anti-inflammatories

Vaccine-induced Hypertrophic Osteodystrophy

- **Most often associated with CDV multivalent vaccines**
- **Cause: vaccine-induced IL-6**
- **Disease Process: Vaccine components induce IL-6 that cause defects in osteoclasts**
- **Symptoms: Sudden lameness, reluctance to move, fever, lethargy, loss of appetite, bone swelling, bone deformities**
- **Treatment: glucocorticoids (anti-inflammatory steroids) and antibiotics**

Autoimmune Disease

- **Type II Hypersensitivity**
- **Cause: Cross-reactive antigens (vaccine or components) stimulate autoreactive B and T cells (molecular mimicry); T cell dysregulation; target organ defects**
- **Disease Process: Antibodies target host tissues and organs (ex. Autoimmune thyroiditis, immune-mediated hemolytic anemia, vaccine-induced arthritis [Lyme disease])**
- **Symptoms: Dependent upon organ or tissues involved**
- **Treatment: Immunosuppressive therapy**

Vaccine Anaphylaxis

- Type I (immediate) hypersensitivity
- Cause: Vaccine triggers IgE binding to mast cells
- Disease Process: IgE-sensitized mast cells produce an acute inflammatory reaction ranging from mild to severe
- Symptoms: local swelling and redness; vomiting and bloody diarrhea, followed by collapse, convulsions, coma and eventually death indicate a state of anaphylactic shock secondary to systemic anaphylaxis
- Treatment: Antihistamine administration; for systemic anaphylaxis: fluid therapy to replace blood volume and epinephrine to increase blood flow as well as inactivate mast cell response

Nosodes as Vaccine Alternatives

- **Homeopathic vaccines prepared using high, serially agitated dilutions of infectious body fluids, vomitus, feces, or other tissue and administered to the dog orally for the purpose of protecting against later infection with the respective pathogen**
- **controlled clinical studies indicate that nosodes are not effective for protecting against disease challenge**
- **Reports of nosode efficacy are most likely attributed to herd-immunity**

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Distemper Virus Vaccines

Vaccine	Initial Puppy Vaccine	Initial Adult Vaccine	Revaccination	Comments
CDV-MLV	One dose at 6-8 wks, 9-11 wks, 12-14 wks	One dose	Manufacturer: Annually AAHA: Booster at 1 yr, then every 3 yrs	Highly recommended
rCDV	One dose at 6-8 wks, 9-11 wks, 12-14 wks, >16 wks	Two doses 2-4 wks apart	Manufacturer: Annually AAHA: Annually	Suitable alternative to the CDV-MLV. Does not routinely provide sterile immunity in immunologically naïve dogs. Not recommended for puppies with high risk for CDV. If used following immunization with CDV-MLV, boosters every 3 yrs are acceptable.

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Parvo Virus Vaccines

Vaccine	Initial Puppy Vaccine	Initial Adult Vaccine	Revaccination	Comments
CPV-2-MLV	One dose at 6-8 wks, 9-11 wks, 12-14 wks	Two doses, 3-4 wks apart (one dose is protective and acceptable)	Manufacturer: Annually AAHA: Booster at 1 yr, then every 3 yrs	Highly recommended
CPV-2 (killed)	One dose at 6-8 wks, 9-11 wks, 12-14 wks, and 15-17 wks	Two doses 2-4 wks apart	Manufacturer: Annually AAHA: Annually, if MLV used in puppy series and 1 yr booster, killed CPV-2 could be used every 3 yrs to booster	Suitable alternative to the CPV-2-MLV. Does not routinely provide sterile immunity in immunologically naïve dogs. Not recommended for puppies with high risk for CDV. Maternal antibody interference up to 16-18 wks.

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Adenovirus Vaccines				
Vaccine	**Initial Puppy Vaccine**	**Initial Adult Vaccine**	**Revaccination**	**Comments**
CAV-2 (MLV, killed, or MLV-topical)	One dose at 6-8 wks, 9-11 wks, 12-14 wks	One dose (MLV); Two doses, 2-4 wks apart (killed)	Manufacturer: Annually AAHA: Booster at 1 yr, then every 3 yrs	Recommended

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Rabies Vaccines

Vaccine	Initial Puppy Vaccine	Initial Adult Vaccine	Revaccination	Comments
Rabies 1-yr (killed)	One dose as early as 12 weeks of age	One dose	Annually. Follow state laws; may be used as a booster vaccine when annual vaccines are required	Required; note that 1 yr vaccines do not present fewer adverse reactions than 3 yr vaccines.
Rabies 3-yr (killed)	One dose as early as 12 wks of age; may be used in place of the 1-yr vaccine	One dose	The second rabies vaccination is recommended 1 yr following the initial dose regardless of the animal's age at the time of the first dose, then every 3 yrs or as required by state law	Required; note that the rabies 1-yr vaccine is often administered as the initial dose followed one year later by the 3-yr vaccine

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Vaccines				
Vaccine	**Initial Puppy Vaccine**	**Initial Adult Vaccine**	**Revaccination**	**Comments**
Parainfluenza Virus (Parenteral or Topical)	One dose at 6-8 weeks, 9-11 wks, and 12-14 wks	One dose	Manufacturer: Annually AAHA: Booster at 1 yr, then revaccinate every 3 yrs	Recommended: Parenteral vaccine is less effective than topical (intranasal) vaccine
Leptospira interrogans (canicola, icterohaemorrhagiae, grippotyphosa, Pomona)	One dose at 12 wks, then 14-16 wks. (Do not administer to dogs less than 12 wks	Two doses, 2-4 wks apart	Manufacturer: Annually AAHA: Annually unless severe incidence of leptospirosis, then every 6 months.	Disease prevalence is likely to vary for each serovar. This product carries a high risk for adverse vaccine events.

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Bordetella Vaccines				
Vaccine	**Initial Puppy Vaccine**	**Initial Adult Vaccine**	**Revaccination**	**Comments**
Bordetella bronchiseptica (killed, parenteral)	One dose at 6-8 weeks and 10-12 wks	Two doses, 2-4 weeks apart	Manufacturer: Annually AAHA: Annually or more often dependent upon risk	Recommended; DOI is about 9-12 months
Bordetella bronchiseptica (live avirulent, intranasal)	Single dose as early as 3-4 wks, then at 5-6 wks	Single dose recommended by the manufacturer	Manufacturer: Annually AAHA: Booster recommended within 6 months of boarding	Recommended; DOI is about 10 months; provides superior local immunity compared to parenterally administered vaccine

Report of the AAHA Canine Vaccine Task Force 2003

AAHA 2003 Guidelines and Recommendations for Canine Lyme Vaccines

Vaccine	Initial Puppy Vaccine	Initial Adult Vaccine	Revaccination	Comments
Borrelia burgdorferi (killed whole bacterin)	One dose at 9 or 12 wks and a second dose 2-4 weeks later	Two doses, 2-4 weeks apart	Manufacturer: Annually AAHA: Revaccinate just prior to tick season	Recommended only for use in endemic regions; DOI is about 12 months
Borrelia burgdorferi (r OspA)	One dose at 9 and then 2-4 wks later. Optimal age for initial dose is > 3 months, with a second dose 2-4 wks later	Two doses, 2-4 wks apart	Manufacturer: Annually AAHA: Revaccinate just prior to tick season	Recommended only for use in endemic regions; believed to be associated with fewer adverse reactions than whole bacterin; minimal DOI is 12 months

Summary

- **For the general dog population, vaccines are safe and a beneficial procedure that prevents diseases**

- **The efficacy of vaccines to induce protective immunity and the duration of that immunity are dependent on several factors including the route of administration, the immune status of the dog, the age of the dog, the immunogenicity of the vaccine, and the dose and degree of attenuation of the vaccine**

Summary

- **There are dogs who, after vaccination, have developed diseases that they may have not developed had they not been vaccinated**
- **There is currently no way to identify those dogs that will develop vaccine adverse side-effects, though certain conditions may be viewed as increasing risk**

Conclusions

- **Vaccine schedules should be modified for the individual dog with consideration to the following:**
  - **the efficacy of the vaccine**
  - **the likelihood of the dog being exposed to the disease-causing agent**
  - **the age and underlying health of the animal**
  - **and the probability of side-effects**