Recognizing and Treating Adverse Effects of Vaccines in Animals

Chris Chase
Overview

- Peracute
- Acute
- Reproductive
- Episodic - Veterinary Version of “Autism and Vaccination”
Adverse Events-Cats

- Between 2002-2005 more than 1.25 million doses of various vaccines administered to 0.5 million cats (Banfield Study).

- Adverse reactions within 30 days of vaccination of 51.6/10,000 cats vaccinated (0.52%), with 92% of these reactions occurring within the first 3 days.

- Clinical signs with vaccination-associated adverse events
  - lethargy (± pyrexia) in 54%,
  - local pain or swelling at the vaccine site (25%)
  - vomiting (10%)
  - facial or periorbital edema (6%)
  - generalized pruritus (2%).

- Death was reported in four cats

- At least two of these it was attributed to anaphylaxis.
Adverse Events - Small Dogs

- Adverse events in 1.2 million dogs that received 3.4 million doses of vaccine. 38.2/10,000 vaccinations (AE 0.38%)

- Administration of multiple vaccine doses to small breed dogs at the same appointment.

- Young adult small-breed neutered dogs at highest risk

- History of a vaccine AE in a small breed dog is not predictive of future risk. Any dog, regardless of size, breed, gender, or age, can experience a vaccine AE.

- Mitigating risk in small dogs (puppies and small breeds) by reducing the volume of vaccine is not recommended. Doing so may result in a suboptimal response to the vaccine and may not eliminate risk associated with hypersensitivity to one or more vaccine constituents.
Vaccine Example: Rabies

- Rabies vaccine causes adverse reactions in 1 out of 60,000 dogs.
- In the United States, rabies in domestic animals (like dogs, cats, and cattle) has declined dramatically since the 1950s. This decrease is mainly due to rabies vaccinations.
- The benefits of giving rabies vaccines for protection against disease far outweigh the risks of occurrence of adverse reactions.
Peracute Reactions
Adverse Reactions to Vaccines

- Peracute vaccine reactions are uncommon, but they are important to watch out for because some of these rare reactions can be fatal. **It is recommended that animals be monitored for vaccine reactions for 24 hours following vaccinations.**
Anaphylaxis

- **Anaphylaxis** is a rare, life-threatening, immediate allergic reaction. The most common symptoms are the sudden onset of diarrhea, vomiting, seizures, coma, and shock. The animals' gums will be very pale, and the limbs will feel cold.

- Immune-mediated hypersensitivity (type I) reaction to vaccination, but it is rare (approximately 1–5/10,000 vaccines).
Acute Reactions
Inflammatory Response

BLOOD
- Monocyte
  - VAL-4
  - VCAM-1
- Neutrophil
  - PSGL-1
  - P-selectin
  - IL-8
- Lymphocyte
  - LFA-1
  - ICAM-1

TISSUES
- Histamine
- Prostaglandins Leukotrienes
- Mast cell
  - C3a
  - C5a
  - C5b67
- Chemokines
  - IL-1, IL-6, TNF-α
- Prostaglandins Leukotrienes
- Activated macrophage
  - Bradykinin
  - Fibrin Fibrinopeptides
- Complement activation
- Alternative or classical pathways
- Bacteria
- Endothelial damage
- Plasmin
- Tissue damage
Inflammatory Response

Systemic response

- Local acute inflammatory response
  - IL-1, TNF-α, IL-6
  - IL-6, LIF, OSM

- Hypothalamus (via pituitary)
  - ACTH
  - Adrenal cortex (Corticosteroids)

- Liver
  - IL-1, TNF-α
  - IL-6, LIF, OSM

- Bone marrow
  - Leukocytosis (↑ white blood cells)
  - Bone marrow (↑ CSF by stromal cells and macrophages)

- Prostaglandins
  - Fever

- Acute-phase proteins:
  - C-reactive protein (CRP)
  - Serum amyloid A (SAA)
  - Fibrinogen
  - Mannose-binding protein
  - Complement components
Primary Immune Response - Animal Doesn't Lie

- Immune response
  - Proinflammatory response necessary
    - Expect Some Side effects
    - No side effects - no response
  - Without response - Higher disease
    - Poorer immunity (active response)
When you Vaccinate, if Nothing Happens, Nothing Happened

- Droopy ear - OK
- Listless - OK
- Down and out - Not OK

- Lactating Cow - drop test and/or production
Not Enough of A Good Thing

LEVEL

TIME

- Green: Immune Response
- Purple: Disease Challenge
Too Much of A Good Thing

LEVEL

TIME

- Immune Response
- Disease Challenge
Macrophages are the Immune System’s Eyes and First Responder

Normal Macrophage
CD 14 receptor and Toll-like receptor binding

Stress Proinflammatory Response

Activated “Angry” Macrophages
CD 14 receptor and Toll-like receptor binding
Activated Macrophages Recruit and Activate Neutrophils as First Responder in Response to Pathogens

Gram Negative bacteria
- M. Haemolytica
- H. Somni
- P. multicida

Activated “Angry” Macrophages

Innate Cytokines
- IL-1β
- IL-6
- IL-8

Produce Proinflammatory Cytokines

Recruits Neutrophils
Macrophage effector mechanisms against extracellular pathogens

Activated "Angry" Macrophages

Gram Negative bacteria
- M. Haemolytica
- H. Somni
- P. multicida

Innate Cytokines
- IL-1β
- IL-6
- IL-8

Recruits Neutrophils
Controlled Response

TNFalpha ELISA

- TNFalpha Level (pg/ml)
- Hours p.i.

- 0 ug/ml
- 3.75 ug/ml
- 7.5 ul/ml
- 15 ul/ml
- 25 ug/ml
- LPS Control
Table 1  Vaccines used in the experiments and their endotoxin content

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No. of vaccines being tested</th>
<th>Range of endotoxin concentration IU x 10^6/dose</th>
<th>No. of vaccinated animals (no. of controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>4</td>
<td>0.24–2.4</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Actinobacillosis</td>
<td>4</td>
<td>0.12–4.8</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Multi-component</td>
<td>3</td>
<td>0.48–4.8</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Live</td>
<td>2</td>
<td>0.30–3.0</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

Endotoxin- Reactions-Swine

Fig 1  Body temperature (A), white blood cell count (B) and concentration of plasma endotoxin (C) after injection of vaccines containing less (n = 44) or more (n = 25) than 1 x 10^6 IU/dose endotoxin.
### Table 2: Clinical signs after injection of vaccines containing endotoxin less ($n=44$) or more ($n=25$) than $1 \times 10^6$ IU/dose

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Criteria</th>
<th>Vaccine endotoxin conc. IU/dose</th>
<th>% showing signs after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Restless, trembling</td>
<td>$&lt;1 \times 10^6$</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;1 \times 10^6$</td>
<td>36</td>
</tr>
<tr>
<td>Activity</td>
<td>Reluctant to move, recumbent</td>
<td>$&lt;1 \times 10^6$</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;1 \times 10^6$</td>
<td>12</td>
</tr>
<tr>
<td>Food intake</td>
<td>Refused</td>
<td>$&lt;1 \times 10^6$</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;1 \times 10^6$</td>
<td>16</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Accelerated</td>
<td>$&lt;1 \times 10^6$</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>respiratory rate</td>
<td>$&gt;1 \times 10^6$</td>
<td>32</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Pale mucous, blue ears</td>
<td>$&lt;1 \times 10^6$</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;1 \times 10^6$</td>
<td>16</td>
</tr>
</tbody>
</table>
What About Bacterins in Cattle?- Endotoxin Stacking

- Endotoxin Stacking and Vaccines (ranked most reactive to least reactive)
  - E.coli Mastitis vaccines
  - Pinkeye (Moraxella bovis)- Whole cell LOS very reactive
  - Histophilus somnus Whole cell LOS very reactive
  - Salmonella-Whole cell LPS
  - Scour vaccines E.coli-Whole cell LPS
  - Mannheimia hemolytica- Whole cell LPS
  - Pasteurella multicida

- Subunit vaccines- no issues, leukotoxin, fimbriae, OMP

- Leptospira DOES NOT contribute to ENDOTOXIN STACKING-leptospiral LPS does not have potent endotoxigenic properties

- If need to use more than one- administer on other side of the neck
Inflammatory Response

Cytokines produced by macrophages cause dilation of local small blood vessels

Leukocytes move to periphery of blood vessel as a result of increased expression of adhesion molecules

Leukocytes extravasate at site of infection

Blood clotting occurs in the microvessels

Figure 2-8 Immunobiology, 6/e. (© Garland Science 2005)
Tissue Damage - Overactive Immune System
Brain-Gut-Microbiota axis
Inflammation and Obesity - Overconditioned Weaned Calves, Fat Cattle, Transition Cow

Cytokine Storm

- High Temps- 104˚-106˚F
- Respiratory Disease-
  - Acute Lung Injury
  - Acute Respiratory Disease Syndrome
- Is BRSV???
- Is Vaccination or Aspirin the Answer?
Cytokine Storm

Controlling Inflammation During Times of Stress

- Avoid practices that increase inflammation
  - Vaccination - with gram negatives
  - Too hot a ration too fast
  - Animals properly hydrated
Reproductive Interactions
Vaccine Induced Abortions

- Endotoxin-Systemic response
- Virus- MLV- Naive
  - Classic Swine Fever Virus
  - PRRSV-swine
  - Pseudorabies virus-Swine herpesvirus
  - Equine Herpesvirus-horses
  - Bovine herpesvirus 1
Pregnant Cows and MLV Vaccination
Misuse- Opening Pandora’s Box

• Safe in pregnant animals vaccinated with the same product prior to breeding (within 12 months)

• NOT without recent vaccination
Duration of Safety Claim is now called an EXEMPTION

New Label

However, if an exemption is granted, the label must include the following statement concerning residual risk:

“Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian.”
31 IBR Vaccine Cases

- From 9 states - CO, IN, MN, MT, NE ND, SD, WI, WY
- From 2009-2016
- Not all histories are complete
- Most were given during pregnancy. Some were properly vaccinated.
- An additional two cases occurred following the administration of an oil adjuvanted vaccine during pregnancy
<table>
<thead>
<tr>
<th>Year</th>
<th>Case Received and Case #</th>
<th>State of affected herd</th>
<th>Number of animals affected</th>
<th>Number of animals in affected group</th>
<th>Prior Herd Vaccinated On label with MLV</th>
<th>Vaccination during Pregnancy with MLV</th>
<th>When did the first abortion occur following vaccination</th>
<th>Results of Genomic analysis</th>
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<tbody>
<tr>
<td>2009</td>
<td>SD</td>
<td>2</td>
<td>70</td>
<td>4 abortions, 5 stillbirths, 1 weak calf</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Group 3</td>
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<tr>
<td>2009</td>
<td>SD</td>
<td>10</td>
<td>250</td>
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<td>2009</td>
<td>SD</td>
<td>6</td>
<td>60</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
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<td>2010</td>
<td>SD</td>
<td>4</td>
<td>60</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Group 3</td>
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<tr>
<td>2010</td>
<td>SD</td>
<td>6</td>
<td>60</td>
<td></td>
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<td>2010</td>
<td>WY</td>
<td>17</td>
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<td>Group 3</td>
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<td>2010</td>
<td>WY</td>
<td>12</td>
<td>165</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>32-55 days</td>
<td>Group 3</td>
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<td>2011</td>
<td>SD</td>
<td>3</td>
<td>3</td>
<td></td>
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<td>31-38 days</td>
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<td>No</td>
<td>Yes</td>
<td></td>
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<tr>
<td>2012</td>
<td>SD</td>
<td>2</td>
<td>2</td>
<td></td>
<td>Yes</td>
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<td></td>
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<td>2013</td>
<td>WY</td>
<td>3</td>
<td>45</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Group 3</td>
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<tr>
<td>2013</td>
<td>WY</td>
<td>2</td>
<td>3</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Group 3</td>
</tr>
<tr>
<td>2013</td>
<td>NE</td>
<td>1</td>
<td>4</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>2014 #1</td>
<td>ND</td>
<td>44</td>
<td>106</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>6 days</td>
<td>Group 2</td>
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<td>2014</td>
<td>MN</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Group 3</td>
</tr>
<tr>
<td>2014</td>
<td>SD</td>
<td>16</td>
<td>160</td>
<td></td>
<td>Yes</td>
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<td>2014</td>
<td>WY</td>
<td>25</td>
<td>200</td>
<td></td>
<td>Yes</td>
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<td>WY</td>
<td>30</td>
<td>300</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Group 3</td>
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<tr>
<td>2014</td>
<td>MT</td>
<td>15</td>
<td>30</td>
<td></td>
<td>Yes</td>
<td></td>
<td>~30 days</td>
<td>Group 3</td>
</tr>
<tr>
<td>2015 #2</td>
<td>MN</td>
<td>15-20</td>
<td>220</td>
<td></td>
<td>Yes, (Group 2 &amp; Group 3)</td>
<td></td>
<td>~90 days</td>
<td>Group 3</td>
</tr>
<tr>
<td>2015 #3</td>
<td>ND</td>
<td>13</td>
<td>48</td>
<td></td>
<td>No, calves vaccinated with MLV</td>
<td></td>
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<td>Group 3</td>
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<tr>
<td>2015 #4</td>
<td>IN</td>
<td>3 heifers, 1 cow</td>
<td>71 heifers, 35 cows</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>20-30 days</td>
<td>Group 3</td>
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<tr>
<td>2015</td>
<td>ND</td>
<td>25</td>
<td>75</td>
<td></td>
<td>Yes</td>
<td></td>
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<td>Group 3</td>
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<tr>
<td>2015</td>
<td>WI</td>
<td>3</td>
<td>3</td>
<td></td>
<td>Yes</td>
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<td></td>
<td>Group 3</td>
</tr>
<tr>
<td>2016</td>
<td>CO</td>
<td>3</td>
<td>200</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>~80 days</td>
<td>Group 3</td>
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<tr>
<td>2016</td>
<td>CO</td>
<td>3</td>
<td>500</td>
<td></td>
<td>Yes</td>
<td></td>
<td>~70 days</td>
<td>Group 3</td>
</tr>
<tr>
<td>2016</td>
<td>WI</td>
<td>9</td>
<td>500</td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Group 3</td>
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</table>
Take Aways-Case Studies

- Heifers were most susceptible in all 4 cases
- Calves can shed vaccine virus that can cause abortion
- MLV BHV-1 vaccines must be used judiciously following label directions. In spite of the following the label, reproductive issues can still occur.
Summary

- Pregnant cow claim was not the original intent

- Safety- not efficacy
  - Definition of Safety never causes abortion- NOT
  - Definition of Safety rarely causes abortion- YES
  - Dependent on having a solid defense to stop the offense (MLV) –Works in Football not in Cows
  - If defense stops MLV growth then no antigenic mass- vaccine efficacy??

- Pregnant cow is immunosuppressed

- Herpesvirus vaccines are abortifacient (non-temperature sensitive)
Vaccinating the Postpartum Cow
Postpartum Cow

- Postpartum immunosuppression
- Energy Drain
- Ketosis immunosuppression
- Lose the opportunity to boost colostrum
Immunosuppression

- Placenta and Uterine cytokines
- Progesterone
- Cortisol
- Bovine Pregnancy associated glycoprotein
Proinflammatory Response in Fresh Cow

Cytokine Storm

Fresh Cows-Cytokine Storm

- High Temps- 104°-106°F
- Respiratory Disease-
  - Acute Lung Injury
  - Acute Respiratory Disease Syndrome
- Is it Really BRSV in Cattle???
- Is Vaccination or Aspirin the Answer?
Periparturient Immunosuppression

- Elevated incidence of new Inter-mammary infections 2 wk prepartum to 3 wk post-partum
- Elevated incidence of infectious disease postpartum Clinical Johne's, Salmonellosis
- Impaired native defenses around calving time

INNATE Immunity

Days Relative to Parturition

Percent of Controls

-21 -14 -7 0 7 14 21

Mastectomy (n=6)

Intact (n=6)
“Episodic” Reactions
Feline Sarcomas and Vaccines

- Reports indicate that Sarcomas occur at a rate of about 1 case per 10,000 to 30,000 vaccinations.

- Vaccine-associated sarcoma was first recognized as an issue in cats in the early 1990s.
Feline Sarcomas and Vaccines

While initial studies suggested a risk of sarcoma development in around 2/10,000 doses of vaccine administered which increased to 13–36/10,000 doses in other studies.

Current estimates based on larger epidemiologic studies (published between 2002 and 2007) suggest that the risk of sarcoma development following vaccination is actually very low (probably well below 1/10,000 doses of vaccine).

Although initial reports linked development of sarcomas at vaccination sites with the use of inactivated rabies or Feline Leukemia Virus vaccines and aluminum-based adjuvants,

Latest studies show no relationship between Feline vaccines and alums and Sarcomas.
Feline Sarcomas and Vaccines

Figure 10  Regions indicated in green are recommended. Those in red are key sites that should be avoided. Image ©iStockphoto.com/GlobalP
Summary

- Anaphylaxis
- Acute Reactions - Endotoxin
- Reproductive issues
- Feline Sarcoma