Keys to Effective Vaccination of Calves

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Vaccinating Calves: Questions

• Can immunity of calves be improved by vaccination?

• How early can you vaccinate calves effectively?

• What about maternal antibody interference?
Immune Development: Prenatal Calf

• Immune system begins developing before calf is born
  – Thymus (T cell development) evident at 40 days gestation
  – Response to some viruses possible at 70 days gestation
  – By third trimester, can respond to many different infections

• At birth, see serum antibody titers elevated before colostrum intake
Immune Development, Neonatal Calf

• At birth, calf has no antibody in serum
  – Unless infected before birth

• Other issues
  – Serum complement levels lower than adults
  – Cell functions lower than adults
    • neutrophils
    • macrophages
    • antigen presenting cells
    • T and B cells
• Immune response of neonatal calf is functional, but naïve and immature

• Colostrum is a solution to this problem
Response of calf lymphocytes to mitogenic (nonspecific) stimulation in first week of life

Data from Kehrli, in Cortese 2009
• Calves vaccinated at 8 hours old were protected against *Mycobacterium bovis* challenge 15 weeks later
  
  Buddle et al., 2003

• Colostrum-deprived calves exposed to coronavirus at 1 day of age were protected against challenge at 3 weeks

  Heckert et al., 1991

• Calves vaccinated with ovalbumin at 2 days of age: antibody at 4 weeks

• Calves vaccinated with PPD at 2 days of age: skin test positive at 7 weeks

  Nonnecke et al., 2012
• Numerous studies show diminished immune responses in 1 – 2 week old calves, compared to juveniles or adults

• BUT: calves within a week of life CAN mount meaningful immune responses

• Not clear when in first week is best time to vaccinate if vaccination is appropriate
Vaccination of calves and maternal antibody

- Vaccination in the face of maternal antibody (IFOMA) traditionally considered ineffective
Antibody titer

Time

Vaccination without maternal antibody

Antibody titer

Time

Primary response

Anamnestic (memory) response

Vaccination without maternal antibody
Vaccination with maternal antibody

Antibody titer

Time

No response
Calf vaccination IFOMA

• Several studies indicate calves CAN respond to vaccination IFOMA
  – Anamnestic response when maternal antibodies gone
  – Measures of T cell responsiveness in absence of seroconversion

– Protection against later challenge
Vaccination IFOMA and antibody responses

• 2-3 month old beef calves
  – Vaccinated with MLV IBRV + BVDV
    • IBRV SN titers 1:19
    • BVDV SN titers 1:35
• Control calves not vaccinated
• Both groups vaccinated again at 6-7 m.o.

Menanteau-Horta et al, 1985
• Calves vaccinated at 2-3 months seroconverted to BVDV
  – IBRV titers continued to fall

• At vaccination at 6-7 months, calves vaccinated IFOMA seroconverted rapidly to IBRV
  – Significantly higher titers than calves not vaccinated at 2-3 months
Vaccination IFOMA can prime for memory response when maternal antibodies are gone.
Vaccination IFOMA and antibody responses—inactivated vaccine

• 2 – 3 month old beef calves
  
  IBRV SN titers:  
  BVDV 1 SN titers:  
  BVDV 2 SN titers:  

  – Inactivated IBRV/BVDV/PI3/BRSV
    • Vira Shield® 5
    • ELITE® 4
    • Triangle® 4
  
  – Control group, no vaccine
  – Boosted 1 month later  

  Kaeberle et al, 1998
• At 6-7 months of age, calves in Vira-Shield group had significantly higher titers to IBRV, BVDV 1, and BVDV 2 than control calves

• Administration of some inactivated vaccines IFOMA induces persistence of serum antibody
  – Boosting may be important
Vaccination IFOMA can prolong titers
Vaccination IFOMA and antibody responses—effect of age

- Dairy calves vaccinated with *M. haemolytica* vaccine (Presponse®)
  - 2 and 4 weeks old
  - 6 and 8 weeks old
  - Control group not vaccinated
- No difference in titers at 2 weeks of age

Hodgins and Shewen, 1998
• At 10 weeks of age, leukotoxin neutralizing titers significantly higher in calves vaccinated at 6 and 8 weeks
  – Not significantly higher in calves vaccinated at 2 and 4 weeks

• Magnitude of titer and age may impact efficacy of vaccination IFOMA in very young calves
Vaccination IFOMA and T cell responses

• Beef calves vaccinated IFOMA at 10 days old
  – MLV/inactivated 4-way (CattleMaster 4®)
  – Control group not vaccinated

• At 22 days old
  – No difference antibody titers
  – Significantly higher lymphocyte responses to IBRV and BRSV in vaccinates

Ellis et al, 1996
• Vaccination IFOMA stimulated specific T cells, even though no apparent effect on antibody production
Summary

• Vaccination of calves IFOMA can:
  – Prime for a memory response after maternal antibodies are gone
  – Increase the half-life of serum antibodies
  – Stimulate T cell responses

• Not as reliable in calves < 1 month old
Vaccination IFOMA and resistance to disease

- Increased resistance to disease: best measure of value of vaccination IFOMA

- Effect has been measured in response to
  - Experimental challenge
  - Naturally-occurring disease
Vaccination IFOMA and resistance to disease

• 4 to 6 week old Holsteins
  – SN titers 1:4 – 1:64
  – “Vaccinated” IN once with MLV (hi pass) BRSV
  – Challenged on d. 30 with virulent BRSV
  – Clinical signs evaluated for 7 days
  – BRSV-specific IFN-γ production in several sites evaluated

Woolums et al, 2004
Rectal Temperatures

Woolums et al., 2004
• A single dose of MLV BRSV IN given IFOMA protected calves from virulent challenge one month later

• Protection was associated with virus-specific IFN-γ production in respiratory lymph nodes and pharyngeal tonsil
• Duration of protection following IN vaccination IFOMA may not be long

• This may be particularly true for BRSV
Disease in calves challenged with BRSV after IN vaccination IFOMA at 3 – 8 days of age

Ellis et al., 2013
Vaccination IFOMA and resistance to disease: BHV-1

• Three separate but related trials: effect if IN vaccination on disease due to BHV-1 challenge
  – 3 – 8 day old calves
  – Trial A and B: calves had no maternal antibody
  – Trial C: calves had maternal antibody
• Calves vac IN once with INFORCE 3 (BHV-1, BRSV, PI3V)
• Control calves: same vaccine but no BHV-1

Mahan et al., 2016
Rectal temperatures measured after IBRV challenge

Calves vac IN at 3-8 days of age
A and B: no maternal antibody
C: maternal antibody
Challenged at
  1 month after vac (A)
  6 months after vac (B)
  3 months after vac (C)

Mahan et al., 2016
BHV-1 shedding after BHV-1 challenge

Mahan et al., 2016
Vaccination IFOMA and resistance to disease: BVDV

- 5 week old calves
- Fed colostrum with or without BVDV antibody
- Vaccinated MLV adjuvantad 5-way (Pyramid® 5)
- BVDV 2 SN titers at vaccination 1:128 – 1:2048
- Control group: no antibody, no vaccine
- Challenged with BVDV2 at 3.5 months

Zimmerman et al, 2006
Zimmerman et al., 2006

rectal temperature (°F)

-3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

study day

• NO antibody, NO vac

□ NO antibody, vac

△ antibody, vac

Zimmerman et al., 2006
• Calves in the no vac group were positive for virus in buffy coats after challenge
  – no calves in either vaccinated group was positive for virus

• 3 of 7 calves in no vac group died after challenge
  – No calves in vaccinated groups died
Maternal antibody did not prevent the development of a protective response to vaccination.

– Also: vaccination of 3 – 5 week old seronegative calves was safe and effective.
• Summary, BVDV studies
  – maternal antibody can protect calves from virulent BVDV challenge
  – calves vaccinated IFOMA develop immunity that is protective
    • even after maternal antibodies are gone

• Other research: T cells mediate the immunity associated with vaccination when maternal antibodies are gone

  Endsley et al., 2004
Case #1, preweaning beef calves

- 65 head cow-calf operation
- BRD in nursing calves 3 to 4 months old
Case #1, preweaning beef calves

- 30% of calves have signs, 2 have died
  - Necropsy of 1 calf: BRSV and *Mannheimia*
- Three pregnant heifers purchased from neighbor 2 months ago
Case #1

• Herd evaluation
  – Dam body condition and nutrition acceptable
  – Calving season lasts 5 months
  – Cows not vaccinated or dewormed regularly
    • vaccinated once 2 years ago with killed 5-way
  – Calves not handled until weaning
• Plan to help limit disease in calves now:
  – Consider treating all calves in herd with long-acting antibiotic
  – OR increase surveillance and treat calves with signs of diminished activity
  – Vaccination in face of outbreak?
    • Often done
    • Evidence for benefit anecdotal
    • BRSV vac can be harmful in BRSV outbreaks
• Plan to prevent this problem in future:
  – Improve maternal antibody to respiratory viruses in calves?
    • Get cows on annual program of 5-way vaccination

• What about boosting cows late in pregnancy?
  – Can increase antibodies in calves
    • Studies have most often tested 2 doses to cows
  – Little evidence for decreased disease in calves
Effect of cow vaccination on preweaning calf BRD
- 430 cows randomly allocated to receive either
  - inactivated 5-way viral respiratory
  - no vaccine
- cows vaccinated 40 days (mean) from calving

BRD diagnosed in 12% of calves before weaning

Incidence of calf BRD not different between groups (OR = 0.8, p = 0.54)
- 13% in calves from unvaccinated dams
- 10% in calves from vaccinated dams

Trend toward a gender effect seen; heifers from vaccinated dams had less BRD (p = 0.07)

Smith et al., 2013
• What about vaccinating the calves?
  – MLV best for this application
    • Must be safe for use in contact with pregnant cows
    • If killed, look for data showing efficacy in animals with maternal antibody
  – TWO doses ideal
    • Consider giving at 2 months and 3 months
  – Viral vaccine
    • Consider IN first dose, IM second dose
  – *M. haemolytica* vaccine may also help
Case #2: Dairy calves

- Dairy milking 1600 cows
- Pneumonia in calves after they leave hutches and go to group pens at 14 days of age
  - 18 – 25 calves per group pen
  - group pens ≈ 15 feet wide x 30 feet long
  - automatic feeder (CF1000, DeLaval)
- Calves are given intranasal IBR/PI3 vaccine at 2 days of age
- Given IM MLV 5-way vaccine immediately before being turned into group pens
Case #2: Dairy calves

- 50% of calves treated for pneumonia in past month
- 5 calves out of 200 have died
- Necropsy of 2 calves: pure culture of *Histophilus somni*
Case #2: Management issues to consider

- In hutches
  - colostrum delivery
  - body condition

- In groups
  - group sizes
  - group age range
  - function of automatic feeder

- In both
  - timely identification and treatment of BRD cases
  - consistent adherence to treatment protocols
Case #2: use of vaccines

• Intranasal IBR/PI3 at 1 day of age
• IM 5-way at move to group pens

• Could this approach be improved?
• What might be better?
Take home messages: calf vaccination

• Young calves can respond to immune stimulation
  – As early as 1 day of life
  – Reliability of response inversely correlated with age
    • Especially in calves with good passive transfer

• Adult immune responses present by 5 – 8 months
Take home messages: calf vaccination

• Passive antibody blocks immune responses sometimes but not always
  – Blocking greatest in first month of life
  – Calves 2 – 3 months old: blocking not much problem
  – Really need more research confirming effect on disease
Take home messages: calf vaccination

• If vaccinating in first 6 months of life, 2 doses advised
  – 1 – 2 months between doses
  – Try to time second dose 1 month before expected challenge
Take home messages: BRD vaccination

• BRD vaccines must show efficacy in challenge studies to be licensed
  – But challenge studies are relatively artificial

• Clinical trial evidence supports vaccines for:
  – *Mannheimia haemolytica*
  – BRSV

• We need more clinical trials to know how BRD vaccines work in “real life”
Take home messages: BRD vaccination

• When BRD vaccines appear to fail, review factors related to
  – vaccine handling
  – timing of vaccination
  – agents in vaccine vs agents infecting cattle
  – ability of host to respond

• Help producers remember that vaccines are just one of many management tools needed to prevent BRD