Development of the immune system in the newborn calf and its impact on inducing active immunity following vaccination.

Robert Tremblay, DVM, DVSc, Dipl ACVIM
Boehringer-Ingelheim (Canada) Ltd
• Outline:
  – How does the immune system develop in calves
  – How does passive immunity influence the calf’s immune response
  – Can vaccination protect young calves
  – How could you use this knowledge
• How do calves respond immunologically:
  – The bovine fetus in mid-late gestation (>190 days) can respond following exposure to some antigens but the ability to respond is antigen dependent. Barrington and Parish, 2001
  – new-born calves have lower numbers of circulating B lymphocytes than adults;
  – circulating B lymphocytes are similar to adults by 20 days of age. Senogles et al, 1978
• How do calves respond immunologically:
  – T cell responses in calves are similar to those in adults by 2 weeks of age;
    Osburn et al, 1974
  – local immune responses (e.g. GALT, BALT) reach levels observed in adults when calves are 3 to 5 weeks old.
    Husband, 1980
• How do calves respond immunologically:
  – the first time a calf is infected, its immune responses will differ from the adult response:
    • each first exposure is a primary response;
    • Primary responses usually develop more slowly than a secondary response;
    • the primary response develops to a lower level than a secondary response;
    • **even though their immune system is developed, it may not work as efficiently as an adult’s.**
• How do calves respond immunologically:
  – Numerous studies have demonstrated that calves vaccinated with any of several antigens, will fail to generate a detectable serological response......this should not be equated with a failure to become actively immunized.
• Influence of colostrum feeding:
  – Passive colostral immunity can influence a calf’s ability to mount an active immune response:
    • colostrum-deprived calves have earlier and higher active antibody production than colostrum-replete calves;

  Husband & Lascelles, 1975
• Influence of colostrum feeding:
  – colostrum-fed calves had no IgG$_1$ nor IgG$_2$ positive cells in lymphoid tissues compared to colostrum-deprived calves.
    Aldridge, McGuirk, Lunn, 1998
  – colostrum-fed calves had lower lymphocyte responses to 3 mitogens than colostrum-deprived calves.
    Clover & Zarkower, 1980
• Should you vaccinate young calves?
  – The labels of vaccines marketed in Canada recommend vaccination of calves on either the basis of age (3 to 6 months) or stage of life (“weaning”). If calves are vaccinated earlier, they should be re-vaccinated with a primary series later in life.
Objectives in vaccinating calves:

1. To provide protection against infectious disease in the calves themselves;
2. To provide a foundation for subsequent vaccination when calves later enter the herd;
3. To produce a detectable antibody or cell mediated immune response.
• How do calves respond immunologically:
  – most studies evaluating the results of vaccinating young calves have often used indirect measures of protection (e.g. serologic responses) or protection following challenge. Few studies evaluate the affect of vaccination on treatment rates or death losses from naturally-occurring disease.
• How do calves respond immunologically:
  – the relative importance of passive and active immunity differs depending on the risk of disease.
  – Poor passive or active immunity has greater consequences in herds with a relatively high incidence (or risk) of disease.
Parainfluenza type 3 virus
Parainfluenza type 3 virus

• How do calves respond immunologically:
  – colostrum-fed calves were vaccinated intranasally with MLV PI3 vaccine or placebo at 1 week and 5 weeks of age;
  – following experimental challenge, vaccinated calves had lower clinical scores, fewer lung lesions, lower nasal shedding and less PI3 antigen in lung tissue.

Bryson et al, 1999
Parainfluenza type 3 virus

- How do calves respond immunologically:
  - colostrum-fed calves were vaccinated intranasally with MLV PI3 vaccine or placebo at 1 week and 5 weeks of age;
  - following experimental challenge, vaccinated calves had more rapid clearance of PI3 from lung tissue and greater alveolar macrophage function than placebo-vaccinated calves.

Adair et al, 2000
Bovine viral diarrhea virus
Bovine viral diarrhea virus

• How do calves respond immunologically:
  – calves fed colostrum with or without anti-BVDV antibody were vaccinated at 10-14 days of age with a MLV BVDV1 vaccine;
  – following intranasal challenge with a virulent BVDV2 3 weeks after vaccination, only BVDV seronegative, unvaccinated calves developed severe disease.

Cortese et al, 1998
Bovine viral diarrhea virus

- calves that were either colostrum deprived or fed colostrum with low or high anti-BVDV antibody were vaccinated with an MLV BVDV1 vaccine at 10-14 days of age;

- calves with high anti-BVDV antibody developed more severe disease when challenged with a virulent type 2 BVD virus 5 months later.  

Ellis et al, 2001
Bovine viral diarrhea virus

• How do calves respond immunologically:
  – colostrum deprived and colostrum fed calves were challenged with a virulent BVDV2;
  – calves with passively acquired immunity were protected when challenged at 2-5 weeks of age and when subsequently repeat challenged at 7-9 months of age, even though they did not seroconvert to the first challenge.

Bovine viral diarrhea virus

• How do calves respond immunologically:
  – calves vaccinated in the presence of passive immunity developed antigen specific T-cell responses to BVD following vaccination with an MLV but not with an inactivated vaccine;
  – calves vaccinated in the presence of passive immunity with an MLV (1x) or inactivated (2x) vaccine developed an anamnestic antibody response following boosting.  

  Endsley et al, 2003
Bovine viral diarrhea virus

• How do calves respond immunologically:
  – Calves fed either colostrum with or without BVDV antibodies were vaccinated with a 5-way MLV vaccine at 5 weeks of age and challenged with virulent BVDV3 14 weeks later.
  – Both groups of vaccinated calves had significantly less disease than unvaccinated control calves that had received BVDV antibody-free colostrum.

Zimmerman et al, 2006
Bovine viral diarrhea virus

• How do calves respond immunologically:
  – colostrum-replete calves were vaccinated with MLV BVD and IBR virus vaccine at 84 and 196 or at 196 days of age;
  – BVDV titre increased even in the presence of high (>1:32) passive tires;

Menanteau-Horta et al, 1985
Bovine viral diarrhea virus

• How do calves respond immunologically:
  – heifer calves were vaccinated with an inactivated BVD vaccine at 15 days of age and with an MLV BVD at 45 days of age or left unvaccinated;
  – vaccinates had lower rate of spread of BVD virus following grouping but no significant differences in morbidity or mortality.

Thurmond, Munoz-Zanzi, Hietala, 2001
Infectious bovine rhinotracheitis virus
IBR virus

• How do calves respond immunologically:
  – cows were vaccinated twice in late gestation and their calves were vaccinated at 10 days with an MLV IBR/BRSV vaccine;
  – at weaning, vaccinated calves exhibited significantly higher virus-specific lymphocyte proliferation than unvaccinated calves (memory was induced).

Ellis et al, 1996
IBR virus

• How do calves respond immunologically:
  – colostrum-replete calves were vaccinated with MLV BVD and IBR virus vaccine at 84 and 196 or at 196 days of age;
  – calves that had been vaccinated at 84 days did not have an increase in titre in the face of passive immunity (>1:16) but had a greater response to boosting that did calves vaccinated once at 196 days.

Menanteau-Horta, 1985
Bovine respiratory syncytial virus
BRSV

• How do calves respond immunologically:
  – cows were vaccinated twice in late gestation and calves were vaccinated at 10 days of age with an MLV IBR/BRSV vaccine;
  – at weaning, vaccinated calves exhibited significantly higher virus-specific lymphocyte proliferation than unvaccinated calves (memory was induced).

Ellis et al, 1996
BRSV

• How do calves respond immunologically:
  – calves were vaccinated at 3 weeks of age *in* or *im* with live or inactivated BRSV in the presence and absence of maternal antibody;
  – calves with maternal antibody failed to respond serologically but calves vaccinated *in* with live BRSV shed less BRSV when challenged 9 weeks later.

  Kimman et al, 1989
BRSV

• How do calves respond immunologically:
  – beef calves were vaccinated against *M hemolytica/H somnus* and/or BRSV (MLV) at 3 and 5 weeks of age;
  – vaccinated calves had a trend (p=0.13) to lower risk of treatment;
  – vaccinated calves had no significantly change in titre to BRSV following either vaccination.

Van Donkersgoed et al, 1994
BRSV

• How do calves respond immunologically:
  – calves with maternal antibody were vaccinated *im* with an inactivated BVSV/PI3/ *M haem* vaccine at 2 and 6 weeks of age and challenged 4 weeks later or vaccinated at 2, 6 and 18 weeks or at 14 and 18 weeks and challenged 25 weeks later.
  – The challenge was mild but vaccination reduced virus shedding.

Patel and Didlick, 2004
BRSV

• How do calves respond immunologically:
  – Seropositive calves were vaccinated with either a placebo, MLV BRSV vaccine or inactivated BVSV/PI3/ M haem vaccine then challenged 3 weeks later.
  – Clinical signs in the controls were mild but fewer calves receiving the inactivated vaccine shed virus following challenge.

Mawhinney and Burrows, 2005
Bacteria associated with respiratory disease
Respiratory bacteria

- How do calves respond immunologically:
  - calves vaccinated at 1 and 2 months of age with inactivated *Mannheimia hemolytica* and *Hemophilus somnus* vaccine in the presence of passively acquired antibody had higher titres to both organisms at 4 and 6 months of age than unvaccinated calves.

  Van Donkersgoed et al, 1995
Respiratory bacteria

- How do calves respond immunologically:
  - 2 to 3 week old calves were vaccinated with a *M hemolytica/Pasteurella multocida* vaccine twice with a 2 week booster interval;
  - vaccinated calves had a significantly greater rise in antibody titre but no significant difference in average daily gain, age of first or last treatment, number nor duration of treatment.

Aubry et al, 2001
Respiratory bacteria

• How do calves respond immunologically:
  – Colostrum-fed calves were vaccinated with a *M haemolytica* vaccine at either 2 and 4 or 6 and 8 weeks of age.
  – Serology of samples collected at 10 weeks of age suggested that calves vaccinated at 6 and 8 weeks of age had a greater probability of being protected.

Hodgins and Shewen, 1998
Respiratory bacteria

• How do calves respond immunologically:
  – beef calves were vaccinated against *M. hemolytica/H somnus* and/or BRSV (MLV) at 3 and 5 weeks of age;
  – vaccinated calves had a trend (p=0.13) to lower risk of treatment;
  – vaccinated calves had significantly high titre to *M. hemolytica* but not *H somnus* or BRSV.

Van Donkersgoed et al, 1994
Leptospirosis
Leptospirosis

• How do calves respond immunologically:
  – calves from dams that were vaccinated in late pregnancy against *L. hardjo* and *L. pomona* were vaccinated with the same vaccine at either 4, 6, 8 or 16 weeks of age;
  – all vaccinated calves were protected against subsequent challenge with virulent *L. hardjobovis* (no contemporaneous controls)

Palit et al 1991
• If you vaccinate young calves, how long will the memory last?
  • this has practical implications in knowing when to give the next booster vaccination.
  • research in trying to protect against acute BVD suggested that memory doesn’t last as long in calves vaccinated when they have high passive immunity.  

  Ellis et al, 2001
• If you vaccinate young calves, how long will the memory last?
  – How long will the memory last?
  • other trials suggest that memory of vaccination with BVD lasts at least 7 months even in the absence of seroconversion.

If you vaccinate young calves, how long will the memory last?

- How long will the memory last?

- 3 groups of 3 to 10 week old beef heifer calves were vaccinated with 1 of 3 protocols:
  - M1 and boosted 120 days later with M1;
  - M1 and boosted 120 days later with M2;
  - IBR-PI3 (NV) only and boosted 120 days later with M1.
The graph shows the GM BVD 1 titre levels post-vaccination over different days. The titre levels are measured in arbitrary units. The x-axis represents the day post-vaccination, ranging from 0 to 310 days. The y-axis shows the GM BVD 1 titre levels, ranging from 0 to 3000.

Three different groups are compared:
- **M1-M1** (represented by light blue bars)
- **M1-M2** (represented by dark red bars)
- **NV-M1** (represented by yellow bars)

- **Day 0**: All groups show similar titre levels, with **M1-M1** and **NV-M1** slightly higher than **M1-M2**.
- **Day 120**: The titre levels for **M1-M1** and **NV-M1** are still comparable, with **M1-M1** being slightly higher. **M1-M2** shows a significantly lower titre level.
- **Day 160**: The titre levels for **M1-M1** and **NV-M1** drop significantly, with **M1-M1** being higher than **NV-M1**. **M1-M2** shows the lowest titre level.
- **Day 310**: The titre levels for **M1-M1** and **NV-M1** remain low, with **M1-M1** being marginally higher. **M1-M2** shows a very low titre level.

The graph indicates a decrease in titre levels over time, with **M1-M1** and **NV-M1** maintaining higher titres compared to **M1-M2**.
• Should you vaccinate young calves?
  – the relative importance of passive and active immunity differs depending on the risk of disease and when disease occurs.
  – low passive or active immunity has greater consequences in herds with a relatively high incidence (or risk) of disease.
  – passive immunity is more likely to be effective in disease that occurs when calves are <6 weeks old.
• Should you vaccinate young calves?
  – vaccines can only protect if they induce immunity to the microbes causing the disease of concern;
  – not all farms will have the microbes that cause disease (for example, BVD, IBR and *Mycoplasma*) although many of the microbes are present on most farms (PI3, BRSV, *Mannheimia*);
  – farms with calves from many sources are more likely to have numerous microbes (and to get a benefit from vaccination).
• Conclusions:
  – there are large gaps in knowledge about the clinical efficacy (or efficiency) of vaccinating young calves;
  – current research suggests that vaccination of calves against BVD, BRSV (?). \( M \) \textit{haemolytica}, \( H \) \textit{somnus} and leptospirosis may be justified especially in high risk situations;
• Conclusions:
  – evidence suggests that vaccination of young calves against IBR, BVD, PI3, BRSV (?), *M. haemolytica* and leptospirosis will result in induction of a memory cell response;
  – in instances of suspected or proven failure of passive transfer, the response to vaccination may be greater.
• Conclusions:
  – available research suggests that MLV vaccines be used in calves;
  – MLV vaccines should be avoided until the calf is at least 5 days old;
  – there is only limited data on when is best time to vaccinate, on how long protection or on how long memory lasts following vaccination of calves. Protection or memory may not last as long as in adults.
Thank you

Questions?