Mucosal Immunity in Newborn Calves: Implications for Vaccination

Dr. Philip Griebel
Vaccine & Infectious Disease Organization
School of Public Health
University of Saskatchewan
Saskatoon, Saskatchewan
Canada
philip.griebel@usask.ca
Overview

- Perceived barriers to neonatal immunization
- Immune system development in newborn calves
- Maternal antibody at mucosal surfaces
- Response of newborn calves to mucosal vaccines
- Duration of immunity following neonatal vaccination
- Conclusions
Why Vaccinate Newborn Calves…

- Cows fail to receive booster vaccinations within 60 days of parturition
- Suboptimal transfer of maternal antibody
- Immune status of dam is unknown
- Purchase newborn calves with unknown history
- Respiratory or enteric disease outbreaks in newborn calves
- Prepare calves for critical transition periods (group housing/weaning)
Perceived Barriers to Neonatal Immunization

- Failure to detect altered decay in maternal antibody and immune memory following parenteral vaccination of newborn (Ellis et al. 2001)

- MLV vaccine neutralization by maternal antibody but CMI responses detected after neonatal vaccination (Endsley et al. 2004)

- Immature immune system may respond but responses are not protective (Chattha et al. 2009; Pihlgren et al. 2004)

- Can problems with parenteral vaccines be circumvented with mucosal vaccine delivery?
Mucosal Immune System

- Over 70% of immune system associated with respiratory, gastro-intestinal, reproductive tract, and eyes (MUCOSAL IMMUNE SYSTEM)

- Over 90% of pathogens (respiratory and enteric) enter at mucosal surfaces

- Mucosal surfaces of newborn calf rapidly colonized by a wide variety of commensal microflora (Malmuthuge al. FEMS Microbiology Ecology, 2012)

- Mucosal immune system provides an effective barrier (IgA) to both commensal microflora and pathogens (Mantis et al. Mucosal Immunol, 2011)
Mucosal Immune Development in the Newborn Calf

No apparent activation of systemic immune system

10-fold increase in intestinal MALT within the first week of life
Nasaopharyngeal Tonsil in Newborn Calves

Fetus

Day 7

Day 21

GC

GC

GC
Endogenous IgA Production at 21 Days

IgM

Epithelial Surface

GC

IgA

Epithelial Surface

sIgA

PCs
Summary

- Rapid development of mucosal immune system in gut and upper respiratory tract during the first 2 to 3 weeks of life

- Maturation of mucosa-associated lymphoid tissues (MALT) in the newborn involves GC development and expression of enzymes for IgA isotype-switching and somatic mutation of Ig V genes

- Maturation of MALT occurs some time between 1 to 2 weeks of age with active production of IgA at mucosal surfaces in healthy calves

- What is the optimum time to deliver intranasal vaccines in the newborn?
Response to Mucosal Vaccination of Newborn Calves

Experimental Design

- Newborn calves fed colostrum from cows immunized with multivalent MLV vaccine (BHV-1, BVDV1, BVDV2, PI3, BRSV)

- Three groups (n = 7) of calves:
  A) No vaccine (naïve controls)
  B) IN vaccination between 3-8 days of age (single vaccination)
  C) IN vaccination between 3-8 days and 35 days of age (booster)

- Monitor specific antibody levels in serum and nasal secretions
Transfer of Maternal IgG

**Serum Antibody Levels**

**Nasal IgG Levels**

Transfer of maternal IgG to serum but not nasal secretions

IN vaccination has no effect on maternal antibody decline in blood

Hill et al. JAVMA, 2012
Transfer of Maternal IgA

- Maternal IgA transferred to nasal secretions
- Rapid decay in maternal IgA
- Rapid increase in endogenous IgA production within 10 days following IN vaccination
- Endogenous IgA doesn’t block immune response following secondary immunization at 5 weeks

Hill et al. JAVMA, 2012
Mucosal Vaccination of Newborn Calves

- IN vaccination of newborn calves with MLV vaccine induces local IgA production within 10-14 days that can replace depleted maternal IgA.

- Endogenous IgA production raises the threshold of disease resistance to significantly enhance health in calves receiving limited or no colostral antibody.

- Re-vaccination at 5-6 weeks of age induces a memory response that prolongs local IgA production.

- IN vaccination of newborn calves provides a strategy to avoid disease susceptibility that occurs as maternal antibody wanes.
Optimal Strategy to Induce Immune Memory IFOMA

Intramuscular  versus  Intranasal

(Hill et al. Manuscript in Preparation)

VIDO
“Solutions through research”
Immune Memory in Newborn Calves: IN Versus IM Vaccination

<table>
<thead>
<tr>
<th>Group (n = 20)</th>
<th>First Vaccination (3-6 weeks)</th>
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<tbody>
<tr>
<td>A</td>
<td>Diluent</td>
</tr>
<tr>
<td>B</td>
<td>IM-Bovishield (MLV)</td>
</tr>
<tr>
<td>C</td>
<td>IM-Bovishield (MLV)</td>
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<tr>
<td>D</td>
<td>IN-Nasalgen-IP (MLV)</td>
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<tr>
<td>E</td>
<td>IM-Virashield (KV)</td>
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<tr>
<td>F</td>
<td>IM-Virashield (KV)</td>
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June 16, 2014
Branding: 3-6 weeks old
Angus-cross calves

October 08, 2014
Collect serum
Select seronegative calves
(n = 10/group)

October 16, 2014
Wean/transport Vaccinate

October 20, 2014
BHV-1 challenge

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Prevention of Clinical Disease: Following Primary Immunization IFOMA and Booster at Weaning

- Naive Controls
- Once Bovishield
- Twice Bovishield
- Twice Nasalgen
- Once Virashield
- Twice Virashield

Body temperature (°C)

- Naive Controls
- Once Bovishield
- Twice Bovishield
- Twice Nasalgen
- Once Virashield
- Twice Virashield

Change in BW (Kg)

- Naive Controls
- Once Bovishield
- Twice Bovishield
- Twice Nasalgen
- Once Virashield
- Twice Virashield
Prevention of Virus Shedding: Following Primary Immunization IFOMA and Booster at Weaning

![Graph showing BHV-1 Shedding (pfu/ml) vs Day Post-BHV-1 Challenge for different groups: Naive Controls, Once Bovishield (MLV IM vaccine at branding), Twice Bovishield (MLV IM vaccine boosted at weaning), Twice Nasalgen-IP (MLV IN vaccine boosted at weaning), Once Virashield (KV IM vaccine at branding), Twice Virashield (KV IM vaccine boosted at weaning).]
Conclusions

- IN vaccine at 3 to 6 weeks is the only strategy to induce sufficient immune memory to reduce clinical disease and virus shedding following a secondary vaccination at 5 to 6 months and 4 days prior to respiratory infection.

- IM MLV vaccine at 3 to 6 weeks IFOMA with a booster at 5 to 6 months significantly reduced clinical disease but not viral shedding.

- IM KV vaccine at 3 to 6 weeks IFOMA with a booster at 5 to 6 months failed to reduce clinical disease or virus shedding.

- IN vaccination at 3 to 6 weeks combined with a booster at 5 to 6 months provides a strategy that protects both individual animals and limit disease transmission (herd immunity).
Health Management Implications

- IN mucosal vaccination IFOMA circumvents the vaccine interference associated with parenteral vaccination of newborn calves

- Primary IN vaccination of newborn calves induces an IgA response that can prevent infection as maternal antibody rapidly wanes

- IN vaccination of newborn calves induces immune memory that lasts at least 5 to 6 months

- Primary IN vaccination of newborn calves combined with a booster vaccination within 4 to 5 months provides a vaccination strategy that reduces both infection and clinical disease with 4 days
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