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Vaccination and Immunity in Calves

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Vaccination and Immunity in Calves


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  - Merck
  - Phibro
  - SAb Biotherapeutics
  - Zoetis

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Calf immunity, questions

- Is the young calf immunodeficient?
- What can be done to help calves resist infections?
- When is vaccination useful to stimulate immunity in calves?

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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, fetus can respond to many different infections
    - If infection occurs, serum antibody titers are elevated before colostrum intake

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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

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Immune Development, Neonatal Calf

- Immune response of neonatal calf is functional, but naïve and immature
- Colostrum is a solution to this problem

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Failure of transfer of passive antibody in beef calves

Study	Cutoff	Percent FPT
Perino et al., 1995	Serum IgG < 800 mg/dl	23%
Filteau et al., 2003	Serum IgG1 < 1000 mg/dl	19%
Dewell et al., 2006	Serum IgG1 < 800 mg/dl	14%
Waldner and Rosengren, 2009	Serum IgG < 800 mg/dl	6%

- Dewell et al. (2006) recommended cutoff of 2400 mg/dl
  - Calves with serum IgG1 < 2400 mg/dl:
    - 1.6 times as likely to become sick
    - 2.7 times as likely to die
  - **41% (631/1556) of calves had IgG1 < 2400 mg/dl**

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Suboptimal transfer of passive antibody, beef calves

- In 601 beef calves sampled at 2 – 8 days old
  - If serum IgG < 2400 mg/dl:
    - Odds of treatment for any disease 1.5x greater ($P = 0.07$)
    - Odds of death 1.6x greater ($P = 0.02$)
    - **33% of calves had serum IgG < 2400 mg/dl**

Waldner and Rosengren, 2009

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Percent of U.S. dairy heifers with failure of passive transfer

d. Percentage of tested heifer calves by IgG level and passive transfer status

IgG Level (mg/mL)	Passive Transfer Status	Percent Calves	Standard Error
More than 20.0	Excellent	52.4	(2.4)
15.0 to 20.0		14.3	(1.2)
10.0 to 14.9	Adequate	14.1	(1.4)
6.2 to 9.9	Failure	8.0	(0.9)
Less than 6.2		11.2	(1.2)
Total		100.0	

NAHMS 2007

19%

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Amount of colostrum fed to heifer calves on U.S. dairies

Percent Heifer Calves

Herd Size (number of cows)

	Small (30–99)		Medium (100–499)		Large (500 or more)		All operations	
Amount (qt)	Pct.	Std. error	Pct.	Std. error	Pct.	Std. error	Pct.	Std. error
Total in the first 24 h								
Less than 4	12.3	(1.9)	10.5	(1.8)	8.1	(1.4)	9.2	(1.0)
4	53.4	(2.9)	39.0	(3.2)	30.6	(2.9)	35.5	(2.1)
5	8.1	(1.6)	6.8	(1.6)	5.7	(1.3)	6.3	(0.9)
6 or more	26.2	(2.5)	43.7	(3.3)	55.6	(3.1)	49.0	(2.2)
Total	100.0		100.0		100.0		100.0	

NAHMS, 2014

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Percent of operations that routinely monitor serum total protein as a measure of passive transfer status of heifer calves

Herd Size (number of cows)

	Very small (fewer than 30)		Small (30–99)		Medium (100–499)		Large (500 or more)		All operations	
Parameter	Pct.	Std. error	Pct.	Std. error	Pct.	Std. error	Pct.	Std. error	Pct.	Std. error
Operations	4.9	(2.8)	1.2	(0.6)	5.5	(1.2)	38.3	(2.3)	6.2	(0.6)
Heifer calves	3.6	(2.6)	1.0	(0.6)	6.8	(1.7)	53.9	(3.0)	35.3	(2.1)

NAHMS, 2014

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New recommendations, passive antibody cutoffs for dairy calves:

≥ 2500 mg/dl	excellent
2499 – 1800 mg/dl	good
1799 – 1000 mg/dl	fair
< 1000 mg/dl	poor

Serum total solids of 6.2 recommended cutoff for excellent passive transfer

Lombard et al., 2020

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- Optimal transfer of passive immunity can improve health, vs adequate transfer
- If aiming for optimal passive transfer, there is room for improvement U.S. operations

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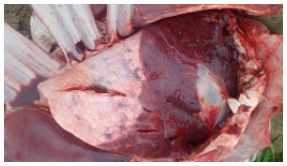
A brief aside: respiratory disease in dairy calves



- Respiratory disease is (still) the second leading cause of death in preweaned dairy calves, and the leading cause of death in postweaned dairy heifers

Photo: Dr. S. Cornejo

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Calf respiratory disease: new developments

- In the past, we thought diagnosing respiratory disease in calves was obvious
- Calves with respiratory disease…
  - cough
  - have a snotty nose
  - breathe hard
  - fail to thrive

Photo: Dr. J. Van Donkersgoed

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Calf respiratory disease: new developments

- Recently, we've learned something new
- Calves can look completely normal, and still have respiratory disease
- On some dairies and calf rearing operations, this can be 20% or more of the **preweaned** calves

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Use of ultrasound to diagnose BRD

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Transthoracic ultrasound

- Transthoracic ultrasound can be used to identify consolidated lung, pleural effusion, or lung abscesses
- Easily performed on farm (1 – 2 min/calf)
- Limitation: cannot identify abnormalities covered by normal lung
  - Not a problem in most calf respiratory disease

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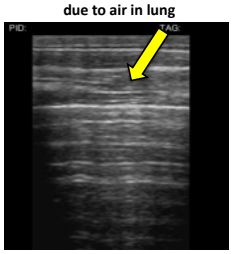
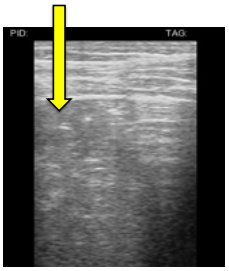
Normal lung, as seen with ultrasound

Consolidated lung next to normal lung

Parallel horizontal lines: reverberation artifact due to air in lung





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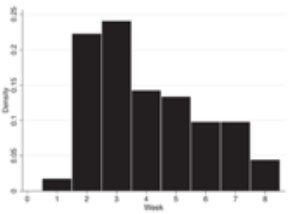
Percent of calves with consolidated lung in each week of the first 8 weeks of life
(215 calves from 3 Ontario dairies)



57% of calves had consolidation (≥ 3 cm) at least once

14% of these never showed clinical signs of disease

Calves with consolidated lung had, on average, 1155 lb less milk in first lactation 305ME production

Dunn et al., 2018

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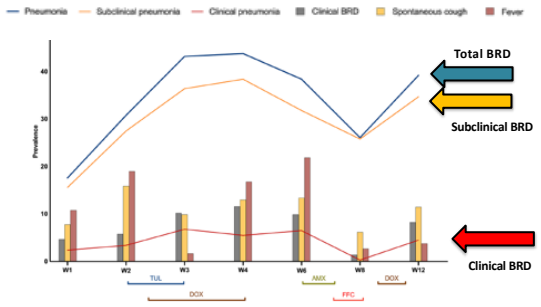
Clinical and subclinical BRD in 295 male dairy calves examined repeatedly over 12 weeks after arrival to Belgian facility



Clinical disease: California score ≥ 5 and consolidation ≥ 1 cm
Subclinical disease: California score < 5, consolidation ≥ 1 cm

Jourquin et al., 2022

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- 95 calves on 11 dairies in Quebec
  - 10 oldest preweaned calves examined
  - Wisconsin clinical score: abnormal if ≥ 7
  - Thoracic ultrasound: abnormal if ≥ 1 cm consolidation
- 49/95 calves (52%) had lung consolidation
  - 32 of these calves (65%) had normal clinical scores

Francoz et al., 2015

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Calf BRD identified by ultrasound: negative effects

- In preweaned calves, lung consolidation identified by ultrasound has been associated with:
  - Increased mortality by 30 days of age

    Buczinski et al., 2015
  - Increased risk of being culled before first calving

    Adams and Buczinski, 2015; Texeira et al., 2017
  - Delayed time to first calving

    Texeira et al, 2017
  - Decreased likelihood of insemination and achieving first calving

    Abuelo et al., 2021

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Guidelines to limit lung consolidation and its negative effects in calves

Developed by Dr. Terri Ollivett and collaborators, University of Wisconsin

https://thedairylandinitiative.vetmed.wisc.edu/home/calf-health-module/

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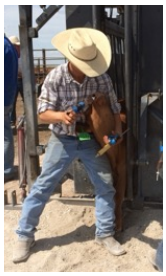
Vaccinating Calves: Questions

- How early can you vaccinate calves effectively?
- How much can calf immunity be improved by vaccination?
- What about maternal antibody interference?



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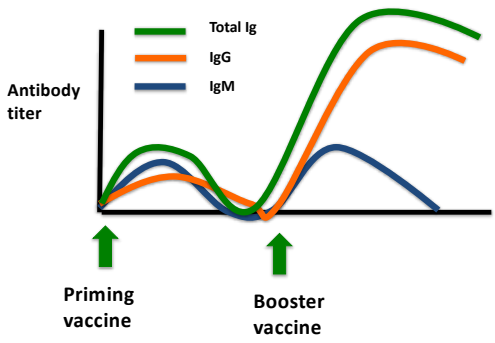
Why We Vaccinate



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- 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

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Vaccination of calves that have maternal antibody

- Vaccination of calves with maternal antibody historically considered ineffective

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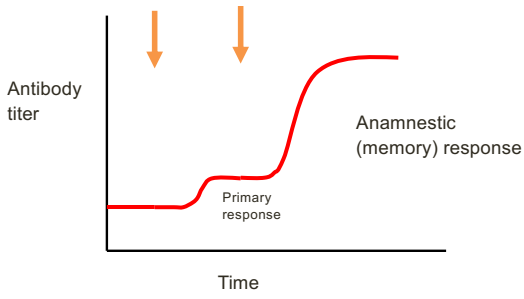

Vaccination without maternal antibody

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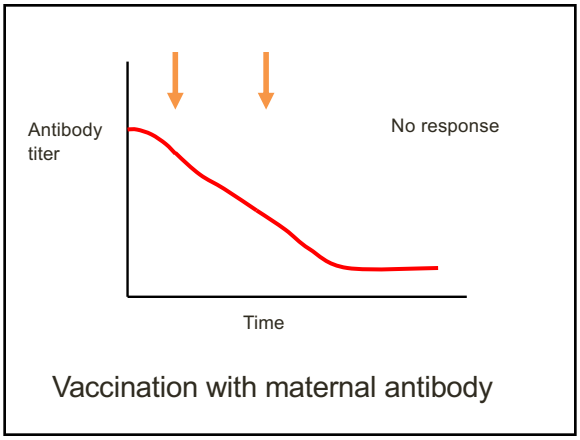

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- In spite of this thinking, research studies indicate calves CAN respond to vaccination even when they have maternal antibody
  - Anamnestic response when maternal antibodies gone
  - Measures of T cell responsiveness in absence of seroconversion
  - **Protection against later challenge**

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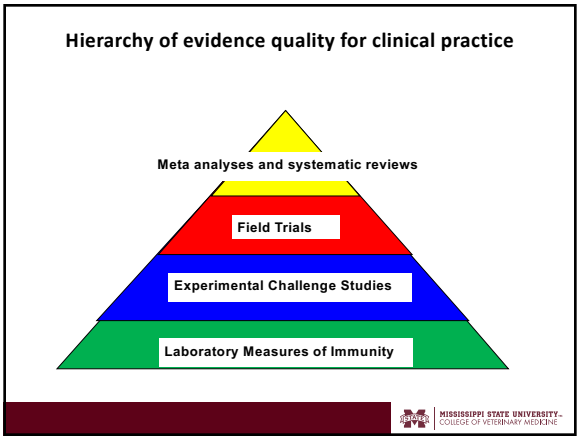

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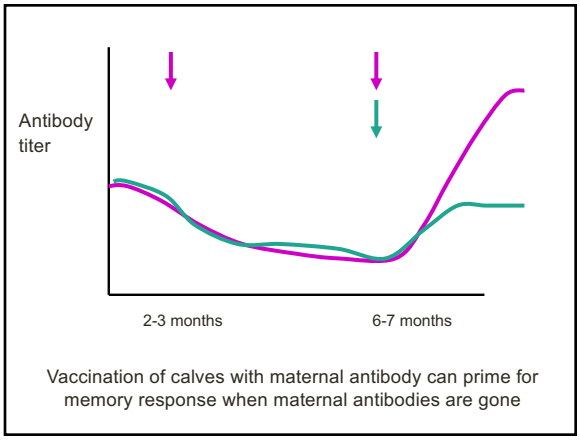

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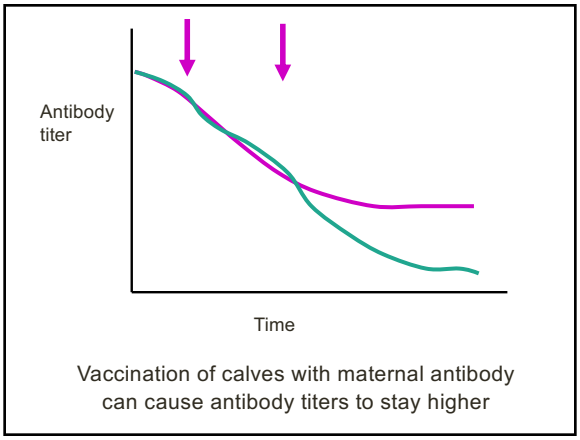

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- Vaccination stimulated specific T cells, even though no apparent effect on antibody production

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Calf vaccination: population implications

- 2834 Angus calves vaccinated with MLV 5-way (Bovishield Gold 5)
  - 3 weeks before weaning and at weaning
  - At weaning and 3 weeks later
  - Antibody titers measured at vaccination, 3 weeks, and 6 weeks later

Kramer et al., 2017

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- Better antibody response to BVDV1 and BVDV for calves vaccinated **first at weaning**
- Better antibody response to BVH-1 and BRSV for calves first vaccinated **3 weeks before weaning**
  - Possibly due to suppression of response due to higher maternal BVDV titers 3 weeks before weaning?
- Small number of calves never seroconverted
  - At all time points
    - 107 calves had BVDV1 titer of 0
    - 9 calves had BVDV2 titer of 0
    - 227 calves had BHV-1 titer of 0

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- Time of vaccination leading to highest antibody response varied for different viruses
- Some individuals in a population may never respond to vaccination
- Later study indicated that multiple genes were likely responsible for antibody response in these calves
  - Heritability of response moderate to low
  - Other calf-related factors had larger response

Kramer et al., 2019

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Summary

- Vaccination of calves that have maternal antibody can:
  - Prime for a memory response after maternal antibodies are gone
  - Keep calf serum antibodies higher longer
  - Stimulate T cell responses
- Response not as reliable in calves vaccinated when < 1 month old
- Individuals in a vaccinated group don't all respond the same

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Vaccination of calves that have maternal antibody: resistance to disease

- Increased resistance to disease: best measure of value of vaccination
- Effect has been measured in response to
  - Experimental challenge
  - Naturally-occurring disease

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Vaccination and resistance to disease: one example

- 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-g production in several sites evaluated

Woolums et al, 2004

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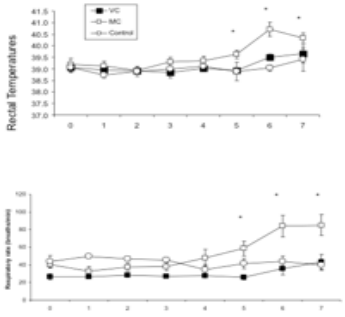

Woolums et al., 2004

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- Duration of protection following intranasal vaccination may not be long
- This may be particularly true for BRSV

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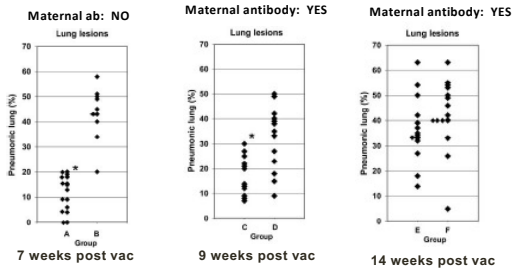
Disease in calves challenged with BRSV after IN vaccination at 3 – 8 days of age



Ellis et al., 2013

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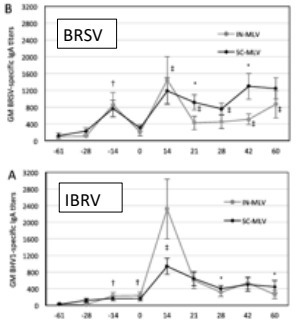
IN vs SC vac: surprising findings?

- Young beef calves primed IN at 1 – 5 weeks old (Inforce 3), then boosted 60 d later IN or SC
- **SC boost** 60 days later
  - nasal IgA higher **after IN boost** for IBRV
  - nasal IgA higher **after SC boost** for BRSV



Palomares et al., 2021

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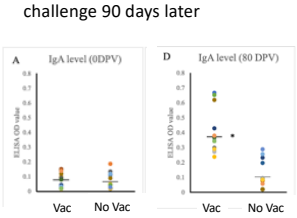
IN vs SC vac: surprising findings?

- MLV SC vaccination (Pyramid 5) of 1-month-old colostrum fed dairy calves induced nasal IgA and decreased shedding post BRSV challenge 90 days later



Nasal BRSV-specific IgA before vac and challenge

Nasal BRSV shedding post challenge
No Vac: green line
Vac: orange line

Kolb et al., Vaccine 38:298, 2020

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Parenteral vaccination and maternal antibody: BVDV

- 3 groups of Holstein calves
  - no maternal antibody, no vac (n = 6)
  - maternal antibody, no vac (n = 8)
  - maternal antibody, vac (n = 8)
- Vaccinated (Pyramid 5) at 4.5 weeks of age
  - Calves with antibody: BVDV1 + 2 SN $\geq$ 256 at vaccination
- Challenged 7 months after vaccination
  - All calves had very low to negative titers at challenge

Zimmerman et al., 2009

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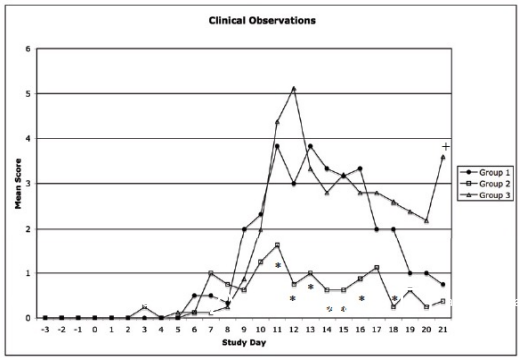

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- Summary:
  - Calves vaccinated in the face of maternal antibodies develop immunity that is protective
    - Even if serum antibodies don't go up after vaccination
    - Even after maternal antibodies are gone
- Other research: T cells mediate the immunity associated with vaccination when maternal antibodies are gone

Endsley et al., 2004

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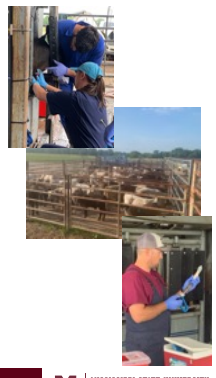
Vaccination of Calves: Field Trials



- Most relevant measure of vaccine efficacy
- Expensive and logistically challenging to conduct

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Field Trial Example #1

- 2882 dairy calves at 19 dairies in Minnesota and Ontario
- Calves vaccinated with MLV 5-way IM (Bovishield)
  - 2 weeks of age
  - 5 weeks of age
  - 2 and 5 weeks of age
  - Not vaccinated (control group)
- Producers recorded whether calves developed respiratory disease

Windeyer et al., 2010

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- Overall, 19% of calves treated for BRD
  - Range of calves treated by herd: 0% - 37%
- BRD first seen
  - In 6% of calves < 2 weeks old
  - In 7% of calves between 2-5 weeks old
  - In 7% between 5 weeks and 4 months of age
- Rate of failure of passive transfer was low
- Results: **no difference** in rate of BRD for any vaccine groups

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Field Trial #1, Key Points

- Important amount of disease already occurring before vaccines had time to take effect
  - But would have been hard to vaccinated calves much earlier!
- Low rate of FPT: maternal antibodies may have interfered with vaccine
  - Perhaps intranasal vaccine would have been more effective?
- Vaccinating part of calves in each herd decreased chance of seeing effect of vaccine (herd immunity)

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Field Trial Example #2

- Cow-calf herd with history of nursing calf pneumonia
  - 80% of calves treated for BRD in previous year
  - BRSV and *M. haemolytica* isolated from fatal cases
- Calves divided into 4 groups
- Vaccinated at 3 and 5 weeks of age
  - No vaccine
  - *M. haemolytica/H. somnus* vaccine (Somnu-Star Ph)
  - MLV BRSV (BRSV Vac)
  - Both vaccines

Van Donkersgoed et al, 1994

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- Maternal antibodies to BRSV, *Mannheimia*, and *Haemophilus* confirmed present at vaccination
- Risk of treatment for respiratory disease prior to weaning (producer defined)
  - 34% in nonvaccinates
  - 15% in calves receiving both vaccines (p = 0.13)
    - Low numbers of calves (26-29/group) may have decreased study power

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Field Trial #2, Key Points

- Calves vaccinated at young age in face of maternal antibody
- 2 doses given
  - Labor intensive
- Vaccination with both vaccines (but not either one alone) associated with trend toward decreased respiratory disease
  - "Herd immunity" decreased chance of significant difference between groups

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Field Trial, Example #3

- 468 calves from 3 dairies in Ontario
  - Within each herd, calves randomly assigned to receive
    - IN MLV 3-way vac (Inforce) at 3 – 6 d of age and again at 6 weeks (n = 215)
    - SC MLV 5-way vac (Bovishield Gold 5) at 6 weeks (n = 211)
    - Control: saline IN both IN and SC at 3 – 6 d and 6 weeks (n = 42)
- Treatment groups housed in different areas to prevent transfer of vaccine between groups
- Calves examined by a veterinarian twice a week for 12 wk
  - Wisconsin respiratory score
  - Thoracic ultrasound Ollivett et al., 2018

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- 54% of calves had respiratory score ≥ 4 at least once
  - Rate of BRD for each group
    - IN vac: 53%
    - SC vac: 59%
    - Control: 33%
      - controls less likely to have BRD than IN or SC ($P < 0.05$)
      - no difference between vac groups ($P > 0.05$)
- 54% of calves had lung consolidation on ultrasound
  - **Agreement between clinical signs and US only fair: k = 0.38**

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- Accounting for herd, dystocia, and rib fractures:
  - Odds of consolidation:
    - For SC:
      1.6 that of IN ($P = 0.03$) 0.38 times Control ($P = 0.03$)
    - For IN
      0.23 times Control ($P = 0.03$)
- In summary
  - Vaccination had no effect on clinical signs of disease, but decreased risk of lung consolidation
    - IN vac 2x decreased lung consolidation more than SC vac 1x

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Field Trial #3, Key Points

- Ultrasound was needed to identify effect of vaccination
  - Also needed to control for farm, dystocia, rib fractures
- Calves got 2 doses of IN vac vs 1 dose of SC
- Can't separate effect of vaccination from location
- Relatively high rate of FPT (TP < 5.2 mg/dL)
  - IN: 48% SC: 31% Control: 21%
  - BUT analysis did not reveal effect of FPT on response to vaccination

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Take home messages

- Young calves can respond to vaccination
  - As early as 1 day of life
- Responses diminished relative to adults
  - Adult responses present by 5 – 8 months of age
- Passive antibody interferes with immune responses sometimes but not always
  - Antibody interference greatest in first month of life

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Take home messages

- Booster vaccines are especially important in calves
  - Booster 1 to 2 months after the initial vaccination
  - Last dose: aim for 1 month before disease is expected

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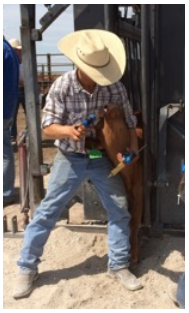
Take home messages

- Vaccination is less reliable in the first month of life
  - IN vaccines (might be) better than parenteral at this time
    - Really need more research testing side-by-side
  - Immunity from early life IN vaccines may not last long (weeks)



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Take home messages

- It might be possible to vaccinate TOO much
  - We need more research on this issue in dairy calves
- Periodically review vaccine protocols to update, address protocol drift

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Vaccinating Calves: Persisting Questions

- Does it help to vaccinate 1-day-old calves?
  - If so, for how long is protection afforded?
- How often should calves be vaccinated?
- Can you vaccinate calves too much?
- **Do the answers to these questions differ for calves in different housing situations?**
- Large dairies and heifer rearing operations could answer these questions with properly designed trials

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Questions?

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