Vermont Veterinary Medical Association

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Winter CE Conference

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Bovine Respiratory Disease Weaned Beef Calves

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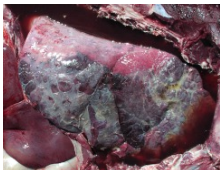
BRD in recently weaned beef calves: new developments



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  - Phibro
  - SAb Biotherapeutics
  - Zoetis

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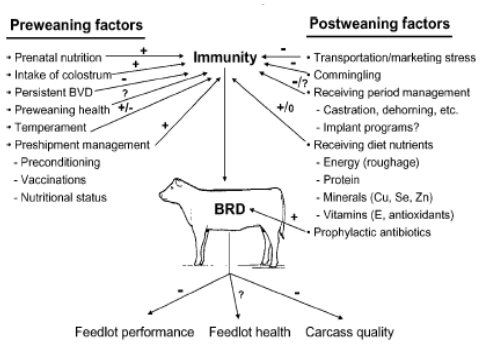

Duff and Galyean, 2007

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Impact of stress on immunity

- Stress: "Psychologically perturbing condition occurring in response to adverse external influences capable of affecting physical health."

  Aich, Potter, and Griebel, 2009

- In humans, social or psychological stress increases rate and severity of respiratory infections
  - Social support can overcome effects of mild but not severe stress

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- Negative effects of stress are not always mediated by cortisol
- Presumably stressful events don't always lead to measurable cortisol elevation
- Endogenous glucocorticoids are more **immunomodulatory** that immunosuppressive
  - Can induce a TH2-type bias in immune response
    - This may suppress cell-mediated immunity

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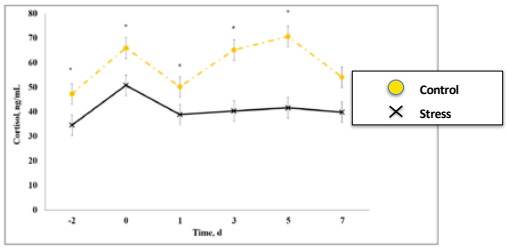
Serum cortisol concentrations the first week after receiving in single-source cattle weaned and transported 1 month (Control) or 3 days (Stress) before arrival and processing.



Hudson et al., 2020

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- Stress isn't always bad for immunity
  - Stress that is short and mild can improve immunity!
- Calves weaned, but without other stressors, may respond well to vaccination

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Antibody titers to BVDV2 in calves vaccinated the first time at weaning (black bars) or 3 weeks after weaning (hatched bars)

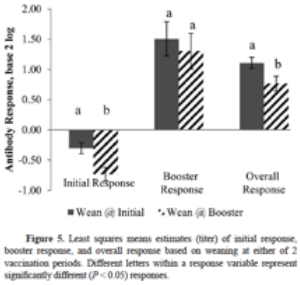

Figure 5. Least squares means estimates (titer) of initial response, booster response, and overall response based on weaning at either of 2 vaccination periods. Different letters within a response variable represent significantly different ($P < 0.05$) responses.

n = ≈ 500 per group

Downey et al., 2013

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Stress can cause the respiratory system to react excessively to inflammation

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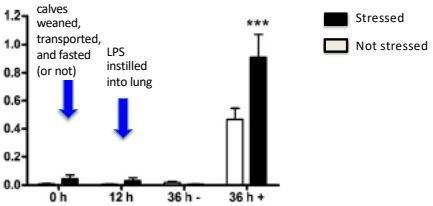
Neutrophil influx into lungs of calves after abrupt weaning and transport (stress), followed by LPS infusion into left lung 12 hours after transport



*** Significantly different, $p < 0.001$

Both L (+) and R (-) lungs were lavaged 24 hours after LPS infusion into L lung at 12 hours

Mitchell et al., 2008

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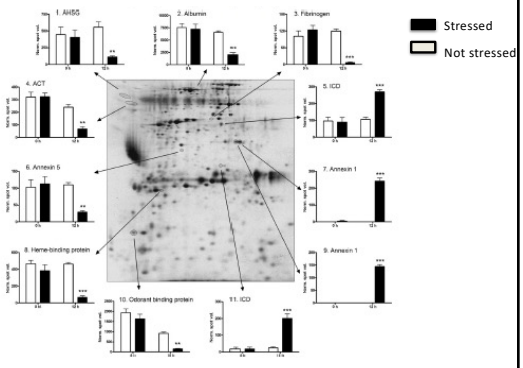
Changes in immune proteins in lung lavage fluid of stressed vs nonstressed calves



Significant differences in 11 of 372 proteins at 12 hours vs 0 hours

Mitchell et al., 2008

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Stress and health, summary

- The impact of "stress" depends on how you define stress
- Stressful events don't always make immune response worse
  - Depends on severity and duration of stress
- **The negative effects of stress may not be measurable until disease challenge occurs**

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Response of high-risk cattle to vaccination

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Antibody titers in cattle when they first arrive at a feedlot

Proportion of BRD cases/controls **seronegative** at arrival

IBRV	PIV3	BVDV	RSV
0.83/0.82	0.75/0.64	0.41/0.34	0.67/0.61

Martin et al., 1989

Proportion of calves **seronegative** at arrival

	Virus			
Dilution[a]	BVDV type 1	BVDV type 2	PI-3V	BRSV
0[b]	98 (81.7%)[c]	104 (86.7%)	86 (71.7%)	87 (72.5%)

Fulton et al., 2000

Proportion of calves **seronegative** to IBRV at arrival: 92%

Richeson et al., 2008

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Because cattle are likely seronegative when they first arrive at the feedlot, should we vaccinate them when they arrive?

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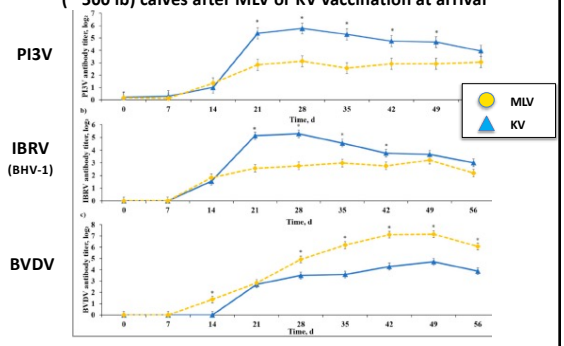
Serum neutralizing antibody titers in single source lightweight (~ 500 lb) calves after MLV or KV vaccination at arrival



Vaccines: MLV = Pyramid 5, KV = Triangle 5 KV boosted at d 14

Hudson et al., 2020

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Research trial at Mississippi State University: vaccination of high-risk steers and bulls immediately after purchase (at arrival)

- **Objective**: evaluate effect of vaccination at arrival on health, performance, and immune response to vaccination

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Study plan:

- Bulls and steers, bulls surgically castrated
- Average weight 205 kg (range 170 – 261 kg)
- 4 cattle per 2.5 acre (1 hectare) pasture, 20 pastures
- All cattle BVDV PI tested (none found)
- Day 0: cattle in 10 pastures vaccinated with
  - MLV-5 way containing BHV1, BVDV1+2, PI3V, BRSV (Express 5) + 7-way clostridial (Vision 7)
- Day 56: all cattle vaccinated
- Health and weight gain followed over 85 days
- Serum antibody titers to BHV-1 and BVDV1 measured on multiple days

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- Health outcomes after 84 days
  - Total BRD morbidity: 46% Total BRD mortality: 16%
  - vaccinated cattle were **more** likely to
    - be treated for BRD
    - die due to BRD

Griffin et al., Bov Pract 52:26-33, 2018

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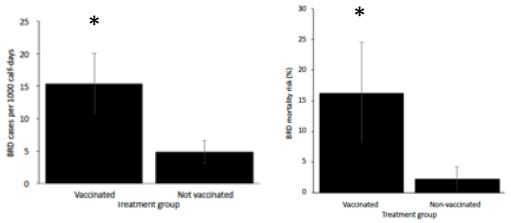
BRD incidence, vaccinated vs not vaccinated cattle

BRD mortality, vaccinated vs not vaccinated cattle



*significantly higher, P < 0.05

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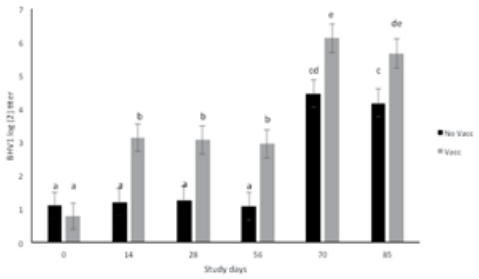
BHV-1 SN titers for Trial 1 stockers vaccinated or not vaccinated on d. 0. All cattle were vaccinated on d. 56

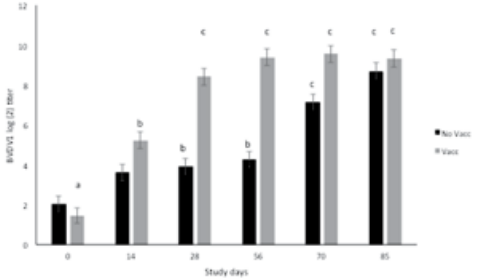


SN titers are model-adjusted. Bars = 1 standard error.
Values with different superscripts are significantly different (α = 0.05)

Griffin et al., 2018

21

BVDV-1 SN titers for Trial 1 stockers vaccinated or not vaccinated on d. 0. All cattle were vaccinated on d. 56



SN titers are model-adjusted. Bars = 1 standard error.
Values with different superscripts are significantly different (α = 0.05)

Griffin et al., 2018

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- Vaccination with viral respiratory + clostridial vaccines was associated with higher morbidity and mortality
- However, cattle were able to make an antibody response to vaccination on arrival
  - They were not too stressed to respond to vaccination
  - Antibody titers in non vaccinated cattle suggested cattle were exposed to BVDV, but not BHV-1, during the trial

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- Why would vaccination make BRD worse in these cattle?
  - Vaccination induced excessive inflammation?
    - Two vaccines given: 5-way viral + 7-way clostridial
    - Cattle were VERY high risk cattle
      - many bulls, which were also castrated at arrival
- We think the combined effects of these factors increased disease, but the exact mechanism is unknown
- **Vaccination was not associated with increased BRD in 2 subsequent replicate trials**
  - This suggests that negative outcomes to vaccination are not common, but possible

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A novel idea…

"You BRD researchers always study the cattle that get sick. Why don't you study the cattle that stay healthy?"

Dr. Del Miles

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BRD resistance and tolerance?

- Immunologic tolerance: lack of response to potentially immunogenic stimulus
  - Central tolerance: bone marrow and thymus
  - Peripheral tolerance: after initial selection
- Could a form of "tolerance" explain cattle that stay healthy??

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Host Tolerance to Infection with the Bacteria that Cause Bovine Respiratory Disease

Laura L. Bassel, DVM, MSc, Saeid Tabatabaei, DVM, PhD, Jeff L. Caswell, DVM, DVSc, PhD*

Vet Clin Food Anim 36:349-359, 2020

- Authors present hypothesis that some cattle stay healthy because they don't develop a severe inflammatory response to bacteria that reach the lung

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The evidence

- Uniform groups of Holstein calves:
  - Clean caught at birth and taken to isolation within hours
  - Same farm of origin
  - Same age
  - All seronegative
  - No *M haemolytica* isolated from respiratory tract
  - Challenged with same isolate of *M. haemolytica*
- **In repeated trials, substantial difference in pathology among challenged calves**

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- One example: 11 calves challenged
  - 4 calves had < 2% lung consolidation
  - 3 calves had 3% - 15% lung consolidation
  - 4 calves had 21% - 55% lung consolidation

Bassell et al., Vet Micro 234:34-43, 2019

- Other evidence: multiple researchers have found discordance between number of bacteria in lung and percent abnormal lung

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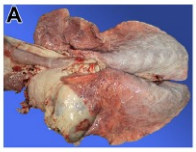
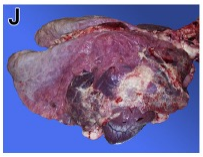
Two calves following *M. haemolytica* challenge



Calf 1: Essentially normal lung post challenge

R CV lobe: $10^{8.1}$ cfu *Mh*/100 mg lung
L CV lobe: $10^{3.5}$ cfu Mh/100 mg lung



Calf 2: Severe fibrinous pneumonia

R CV lobe: $10^{6.6}$ cfu *Mh*/100 mg lung
L CV lobe: $10^{6.5}$ cfu Mh/100 mg lung

Bassel et al., Vet Clin Food Anim 36:349-359, 2020

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- This variable pattern of response has been repeated across many research studies
- Similar findings in naturally occurring disease
  - In groups of cattle at high risk for BRD, some cattle never develop disease

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- How might this tolerance be mediated?
- In other species:
  - Airway epithelial cells produce compounds that keep alveolar macrophages from over-reacting to daily uptake of particulates
  - Mediators produced in airways can
    - Curtail neutrophil responses
    - Scavenge molecules that cause inflammation
  - Activation of inflammation is accompanied by inflammation-resolving activities

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Specific pro-resolving mediators (SPM)

- Lipid mediators similar to prostaglandins and leukotrienes that modulate inflammation and promote resolution
  - without causing immunosuppression
- Many families of SPM exist
  - Lipoxins, resolvins, maresins, protectins

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Lipoxin biosynthesis (looks a lot like prostaglandin biosynthesis)

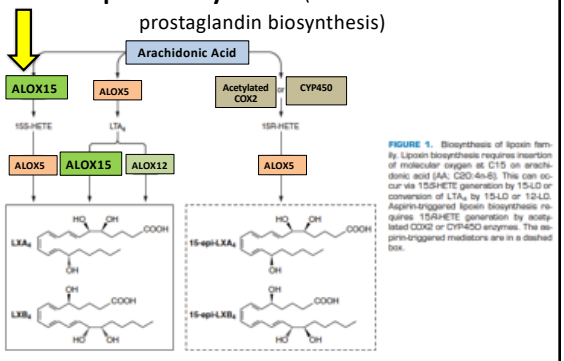

FIGURE 1. Biosynthesis of lipoxin family. Lipoxin biosynthesis requires insertion of molecular oxygen at C15 on arachidonic acid (AA; C20:4n-6). This can occur via 15-SHETE generation by 15-LO or conversion of LTA_4 by 15-LO or 12-LO. Aspirin-triggered lipoxin biosynthesis requires 15-RHETE generation by acetylated COX2 or CYP450 enzymes. The aspirin-triggered mediators are in a dashed box.

Krishnamoorthy et al., 2018

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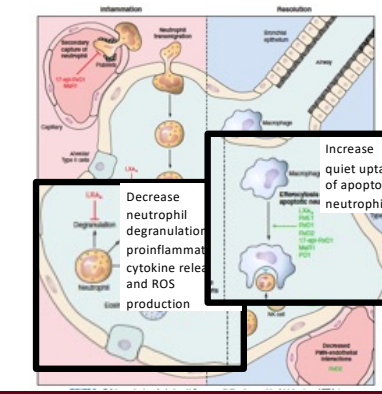

Some mechanisms of anti-inflammatory and pro-resolving actions of SPMs in the alveolar space

Krishnamoorthy et al., 2018

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Human lung diseases associated with decreased levels of SPM

SPM	Disease	Finding	Reference
Resolvin E1	Cystic Fibrosis	Decreased RvE1 in CF patients with lower lung function	Yang et al 2012
Protectin D1	Asthma Exacerbation	Decreased PD1 in uncontrolled asthma Decreased PD1 in eosinophils in severe asthma	Levy et al 2007 Miyata et al 2013
Lipoxin A4	Severe Asthma	Decreased LXA_4 biosynthesis in severe asthma (blood, sputum, BAL); Lower LXA_4 levels in exhaled breath condensates correlates with worse lung function	Levy et al 2005; Vachier et al 2005; Celik et al 2007; Planagumà et al 2008; Bhavsar et al 2010; Wu et al 2010; Fritscher et al 2012; Kazani et al 2013.
	Asthma Exacerbation	Decreased LXA_4 in exhaled breath condensates during exacerbation	Hasan et al 2012
	Exercise-induced Asthma	Decreased LXA_4 in plasma of children with exercise induced bronchospasm	Tahan et al 2008
	Aspirin-intolerant asthma	Decreased lipoxins in aspirin-intolerant asthmatics compared to aspirin tolerant asthmatics	Sanak et al 2000; Celik et al 2007; Yamaguchi et al 2011
	COPD	Reduced LXA_4 detected in exhaled breath condensates; serum amyloid A opposes LXA_4 at ALX	Fritscher et al 2012; Bozinovski et al 2012
	Cystic Fibrosis	Decreased LXA_4 production and defective lipoxin activity	Karp et al 2004; Chiron et al 2008; Mattoscio et al 2010; Yang et al 2012
	Pleural Effusions	LXA_4 present in exudative effusions and correlates with neutrophils	Levy et al 2001
	Lung Transplant	LXA_4 present in BAL fluid during rejection	Levy et al 2011
	Scleroderma	Decreased LXA_4 levels in BAL of patients with scleroderma lung disease	Kowal-Bielecka et al 2005

Duvall and Levy, 2016

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Do SPMs contribute to BRD resistance in cattle?

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Research trial: On-arrival blood transcriptome assessment to predict BRD in high-risk cattle

Hypothesis: Altered transcriptional profiles in the blood of stocker calves at arrival will reveal regulatory pathways responsible for resisting respiratory disease

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What is a transcriptome?

- Transcriptome:
  - All the transcripts (messenger RNAs) in a tissue
  - Indicates which genes are activated (expressed)
  - If a gene is expressed = more copies of that mRNA
- Transcriptome assessment: provides information regarding activation of 1000's of genes
- "Transcriptomics" is used to identify molecular pathways relevant to disease and health in numerous systems

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Cattle and sampling

- 80 commercial crossbred steers (n=16) and bulls (n=64)
  - 24 cattle randomly selected for d. 0 blood collection
- Followed for 84 days; production and treatment records recorded
- 12 animals (healthy n=6; BRD n=6) selected for blood RNA sequencing (RNA Seq)
  - 1 healthy sample removed (low read counts)

Scott et al., 2020; doi.org/10.1371/journal.pone.0227507

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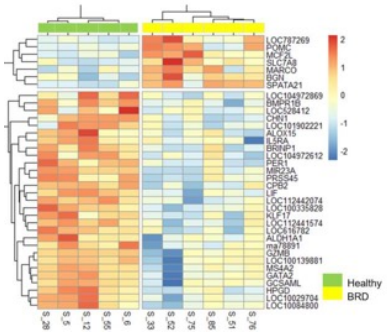
Genes differentially expressed at arrival in BRD vs Healthy



Scott et al., 2020; doi.org/10.1371/journal.pone.0227507

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Results

Significant Biological Pathways

Gene Set	Description	Size	P Value	FDR
R-HSA-9018896	Biosynthesis of E-series 18(S)-resolvins	5	1.40E-05	0.0209
R-HSA-9018679	Biosynthesis of EPA-derived SPMs	6	2.10E-05	0.0209
R-HSA-2022377	Metabolism of Angiotensinogen to Angiotensins	17	1.90E-04	0.0939
R-HSA-9018677	Biosynthesis of DHA-derived SPMs	17	1.90E-04	0.0939
R-HSA-9018678	Biosynthesis of specialized proresolving mediators (SPMs)	19	2.40E-04	0.0943

Scott et al., 2020; doi.org/10.1371/journal.pone.0227507

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Summary of Results

- DEGs increased at arrival in cattle that were eventually treated for BRD: antimicrobial activity
- DEGs increased at arrival in cattle that stayed healthy: SPM formation, and pro-inflammation resolving

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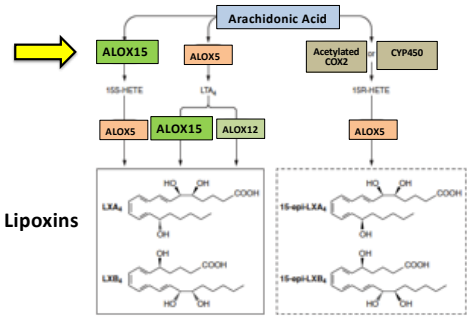
In multiple studies , ALOX15 has been increased at arrival in cattle never treated for BRD, or in healthy cattle compared to BRD cattle

Scott et al., 2020 - 2024



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Conclusions (so far):

- In groups of cattle from different times and locations, certain genes repeatedly differentially expressed at arrival
  - ALOX15: increased in Healthy
  - Complement Factor B: increased in BRD+
  - IFN-related genes: increased in BRD+
- In some cases, DEG are seen not at arrival, but at treatment
  - Gene expression may be indicating presence of BRD
- **These findings could eventually help predict or diagnose BRD more accurately**
  - And could lead to new prevention strategies

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Conclusions, and questions

- Adaptive immune responses induced by **vaccination at arrival** may not be the best way to prevent BRD in high-risk cattle
- **Hyperinflammation** more than immunosuppression may increase BRD in high risk cattle?
- Host responses that **modulate inflammation without causing immunosuppression** may have greater impact on BRD in high-risk beef cattle
  - Can we find ways to activate these?
  - Can we select cattle for these?

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Acknowledgements

At-arrival blood transcriptome in high-risk cattle

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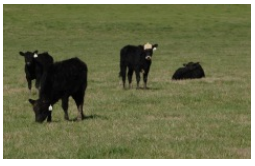

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