Can we be good stewards of antimicrobials when battling bovine respiratory disease?

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3rd Annual TVMDL Amarillo
BOVINE RESPIRATORY DISEASE
Conference
July 7, 2018

Societal issues associated with food animal production

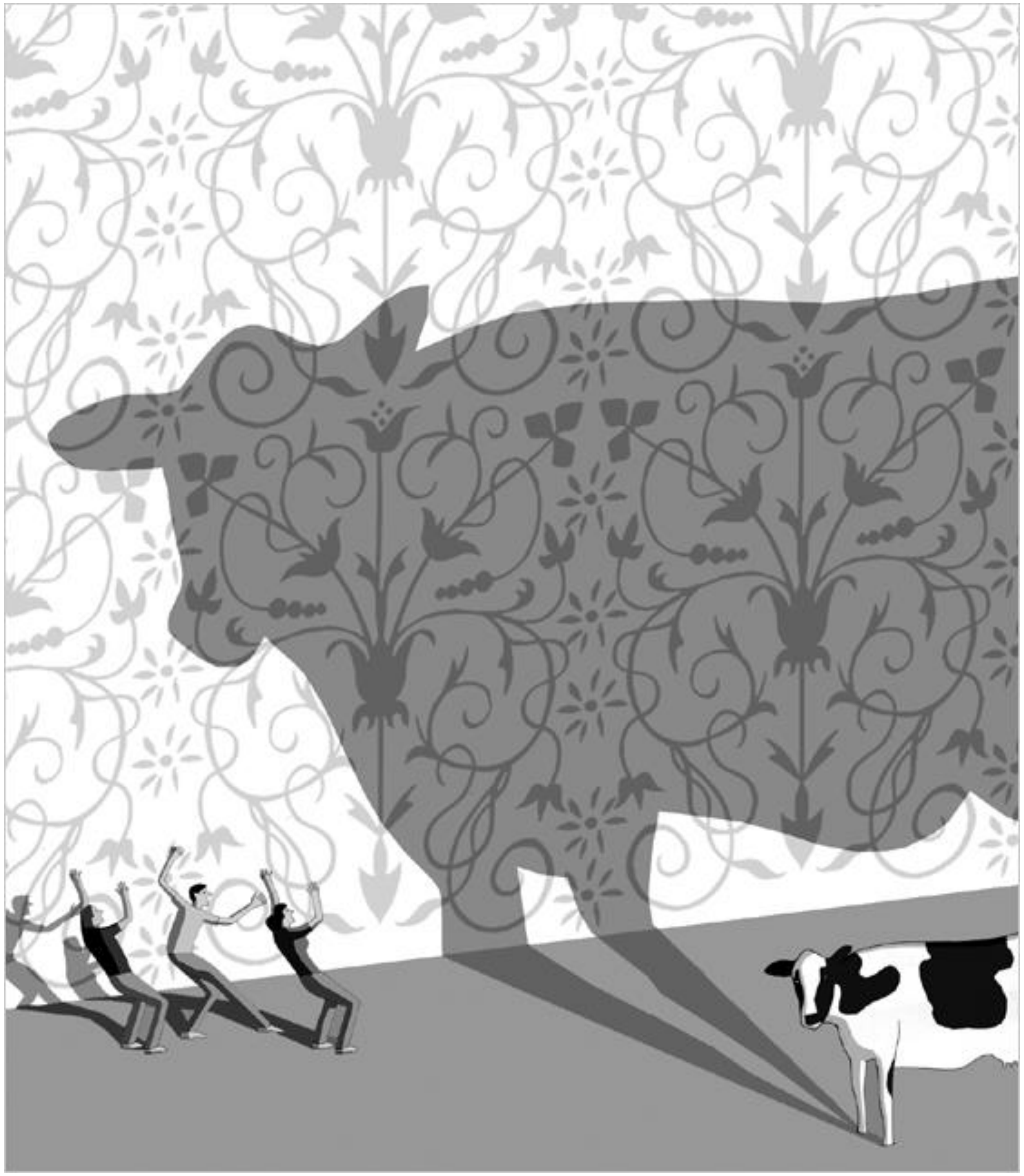
Food security

Public health and food safety

Animal well-being

Environmental health

Antimicrobial resistance



Outline

- What is antibiotic stewardship
- Is antibiotic resistance a real problem?
- A systems look at BRD
- What do we do?

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Antibiotic stewardship

"Antimicrobial stewardship refers to the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health."

(AVMA, 2018)

Antibiotic Stewardship

The American Veterinary Medical Association has defined five principles of antibiotic stewardship:

- ***Commit to stewardship***
- ***Advocate for a system of care to prevent common diseases***
- ***Select and use antimicrobial drugs judiciously***
- ***Evaluate antimicrobial drug use practices***
- ***Educate and build expertise***

(ref: https://www.avma.org/KB/Policies/Pages/Antimicrobial-Stewardship-Definition-and-Core-Principles.aspx. Accessed June 11, 2018)

Antibiotic stewardship has been around for a long time…

"Of course, the sulfa drugs and penicillin, like all new drugs, should be used only as prescribed by a veterinarian; their indiscriminate use may be wasteful and actually harmful to the animal patients."

USDA Yearbook of agriculture 1943-1947

Antibiotic stewardship has been around for a long time…

"A disturbing and increasingly dangerous practice of giving antibiotics promiscuously for almost any and all kinds of sickness has become increasingly common in recent years when many antibiotics became generally available. Some susceptible strains of disease-producing bacteria, especially staphylococci, may develop a total resistance because the antibiotics are improperly used. It has become apparent that when an antibiotic is used promiscuously in any given community or hospital, resistant strains of staphylococcic bacteria can be found in a significant portion of the animal or human population."

Dr. L. Meyer Jones, 1956 USDA Yearbook of Agriculture

Antibiotic stewardship has been around for a long time…

"Many persons have relied too much on antibiotics to control diseases. Under such conditions it is natural that there should be concurrent laxness of hygiene and management of animal patients.

"Antibiotics must be used cautiously, or their value will be lost. On the other hand, no patient should be deprived of the benefit of antibiotic therapy solely because of the fear of inducing resistance in the disease germ."

Dr. L. Meyer Jones, 1956 USDA Yearbook of Agriculture

Is Antimicrobial Resistance a Real Problem?

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

"Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections"

http://www.cdc.gov/drugresistance/

World Health Organization

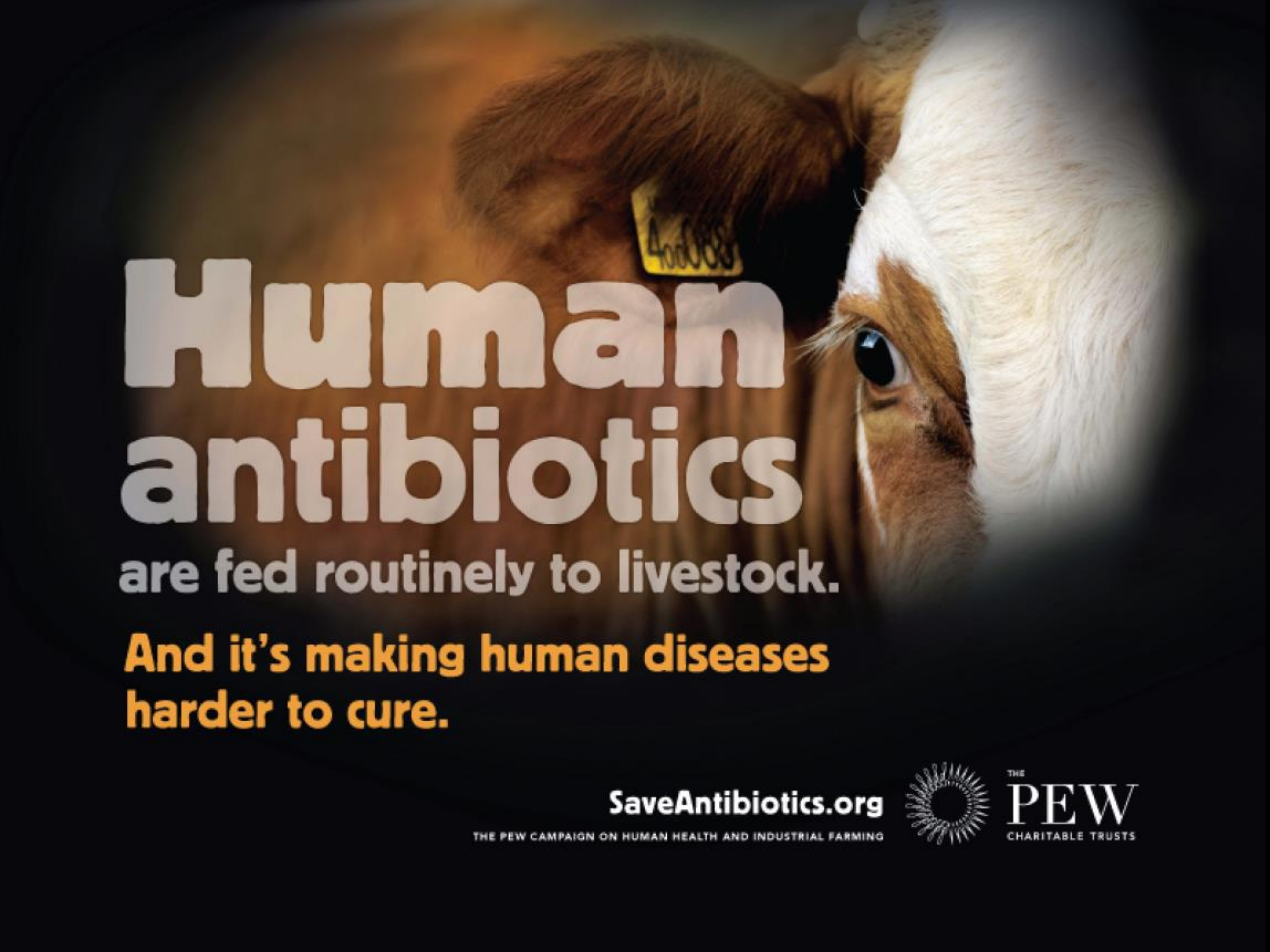
http://www.who.int/mediacentre/factsheets/fs194/en/
October 18, 2011

What drives antimicrobial resistance?

Inappropriate and irrational use of medicines provides favourable conditions for resistant microorganisms to emerge and spread. For example, when patients do not take the full course of a prescribed antimicrobial or when poor quality antimicrobials are used, resistant microorganisms can emerge and spread.

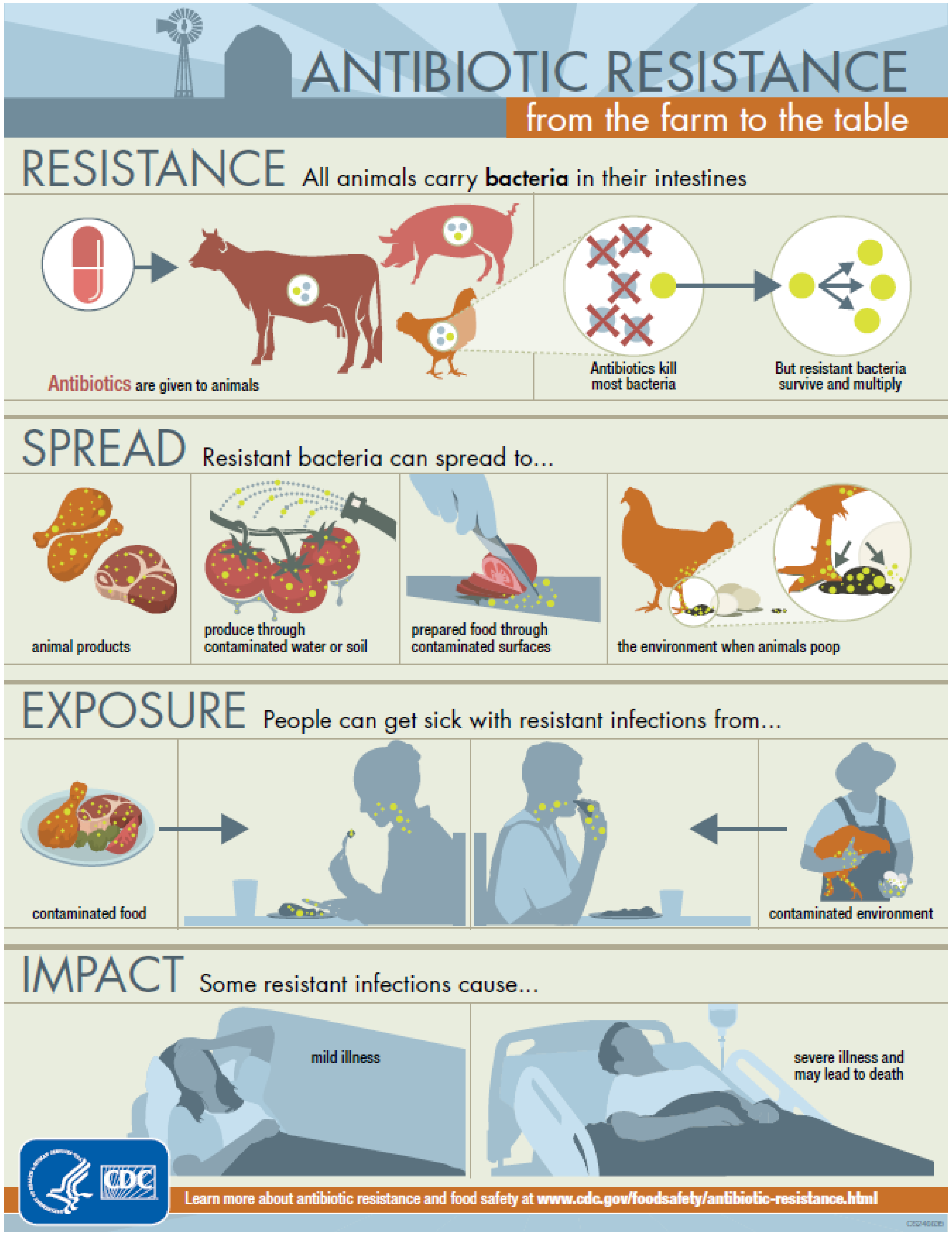
Underlying factors that drive AMR include:

- inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities;
- weak or absent surveillance and monitoring systems;
- inadequate systems to ensure quality and uninterrupted supply of medicines
- inappropriate and irrational use of medicines, including in animal husbandry;
- poor infection prevention and control practices;
- depleted arsenals of diagnostics, medicines and vaccines as well as insufficient research and development on new products.


Human antibiotics
are fed routinely to livestock.
And it's making human diseases harder to cure.
SaveAntibiotics.org
THE PEW CAMPAIGN ON HUMAN HEALTH AND INDUSTRIAL FARMING
THE PEW CHARITABLE TRUSTS

Centers for Disease Control and Prevention

- Resistance to important antibiotics for human health is <u>increasing</u>
- In the US over 400,000 people are sickened with resistant *Salmonella* or *Campylobacter* every year



TOP 5 Salmonella subtypes in the NARMS database

28,003 human clinical samples

- 4,490 Enteritidis
- **4,449 Typhimurium**
- 2,583 Newport
- 1,346 Javiana
- 1,034 Heidelberg

27,026 beef carcass samples

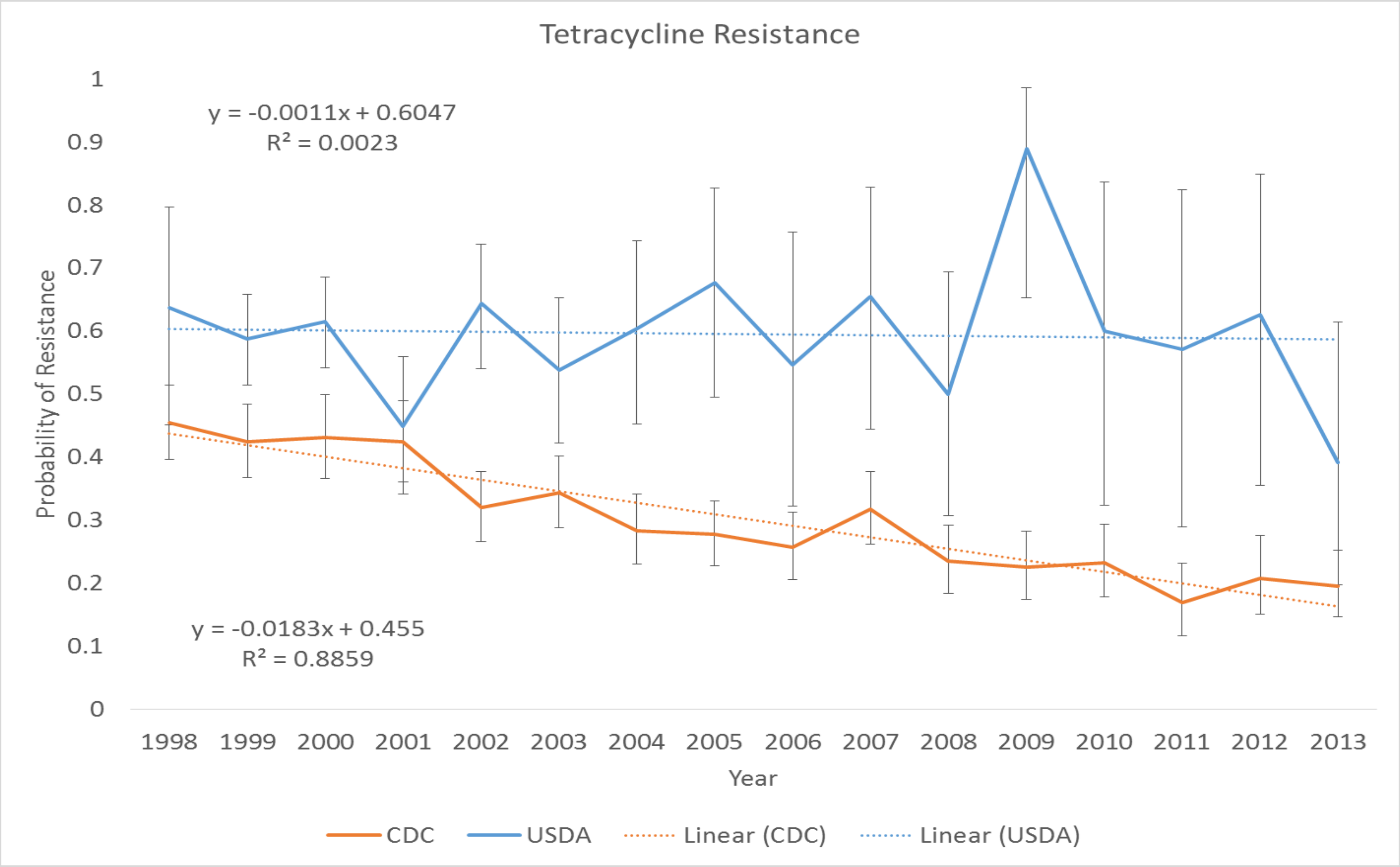
1997-2005:

- 948 Montevideo
- **755 Typhimurium**
- 627 Anatum
- 517 Newport
- 488 Muenster

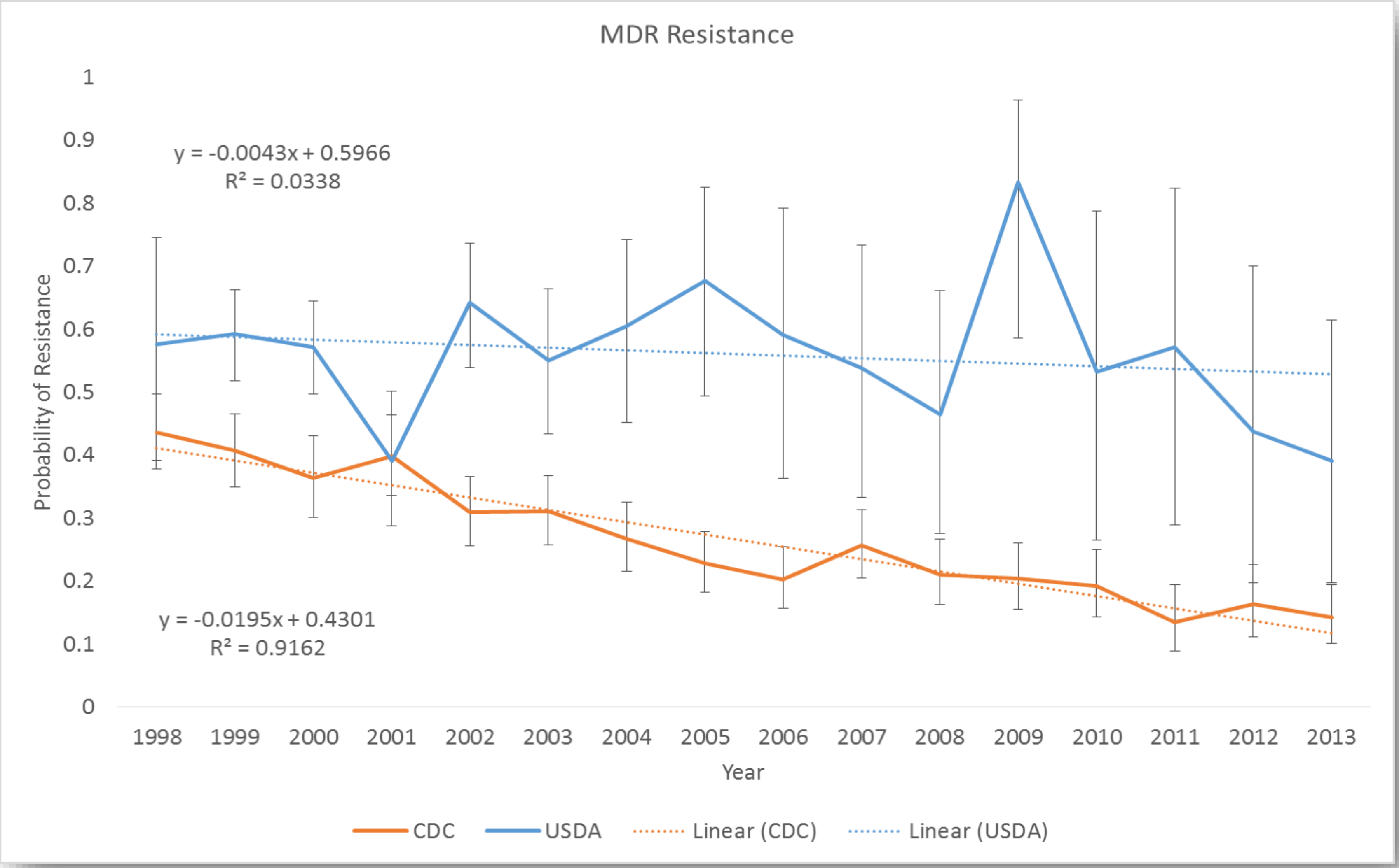
2006-2013:

- 654 Montevideo,
- 263 Dublin
- **162 Typhimurium**
- 158 Anatum
- 145 Newport

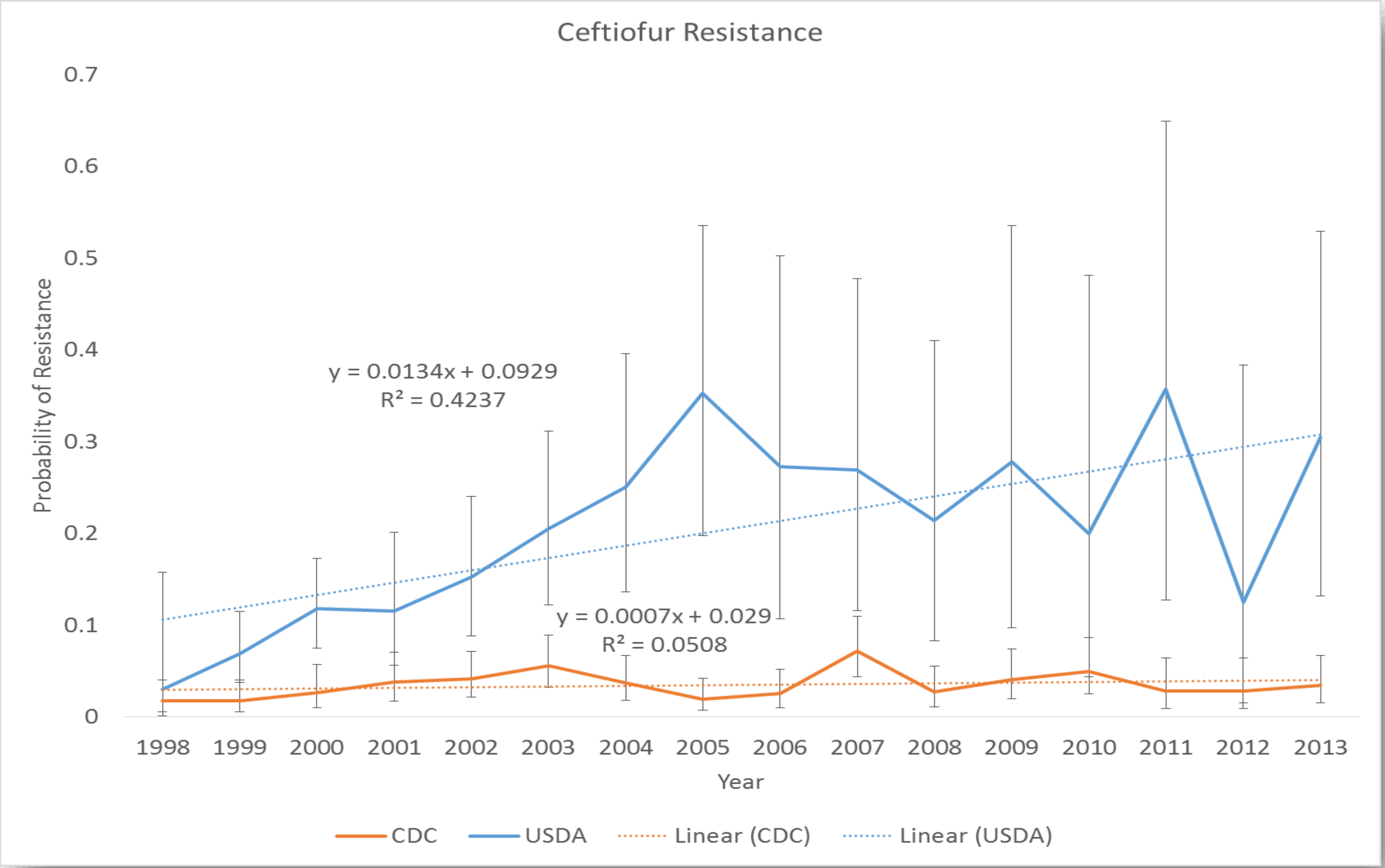
Salmonella typhimurium



Salmonella typhimurium



Salmonella typhimurium



Antibiotic resistance of BRD pathogens

ELSEVIER

Veterinary Microbiology

Volume 221, July 2018, Pages 143-152

Multidrug resistant *Mannheimia haemolytica* isolated from high-risk beef stocker cattle after antimicrobial metaphylaxis and treatment for bovine respiratory disease

Amelia R. Woolums [a,1], Brandi B. Karisch [b,1], Jonathan G. Frye [d,1], William Epperson [a], David R. Smith [a], John Blanton Jr. [b], Frank Austin [a], Ray Kaplan [c], Lari Hiott [d], Tiffanie Woodley [d], Sushim K. Gupta [d], Charlene R. Jackson [d], Michael McClelland [e]

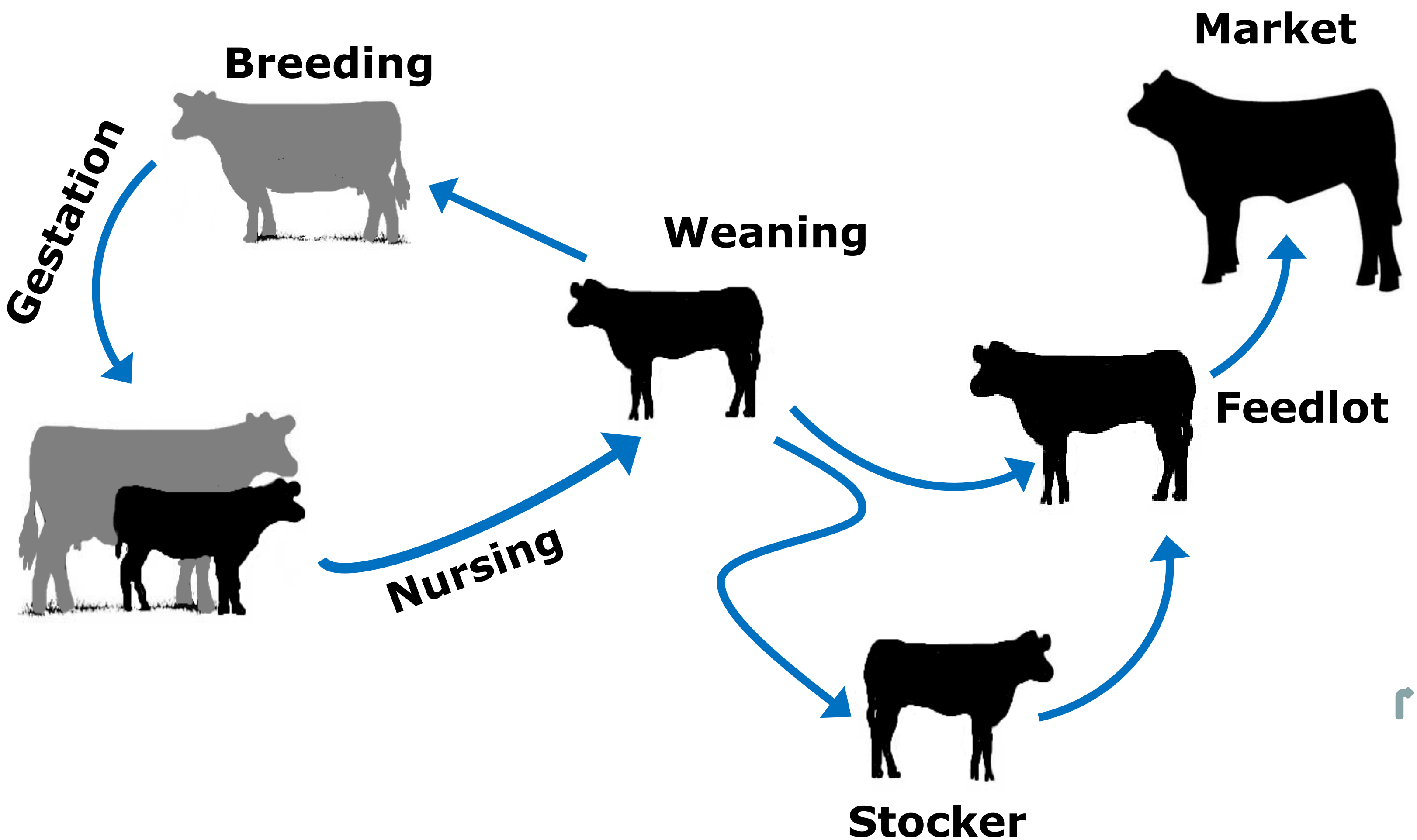
E. Snyder, B. Credille, R. Berghaus, S. Giguere. **Prevalence of multi drug antimicrobial resistance in *Mannheimia haemolytica* isolated from high-risk stocker cattle at arrival and two weeks after processing.** J. Anim. Sci., 95 (2017), pp. 1124-1131

B.V. Lubbers, G.A. Hanzlicek. **Antimicrobial multidrug resistance and coresistance patterns of *Mannheimia haemolytica* isolated from bovine respiratory disease cases–a three-year (2009–2011) retrospective analysis.** J. Vet. Diag. Invest., 25 (2013), pp. 413-417

C.L. Klima, R. Zaheer, S.R. Cook, C.W. Booker, S. Hendrick, T.W. Alexander, T.A. McAllister. **Pathogens of bovine respiratory disease in North American feedlots conferring multidrug resistance via integrative conjugative elements.** J. Clin. Micro., 52 (2014), pp. 438-448


Do your part to
CONSERVE
WATER!

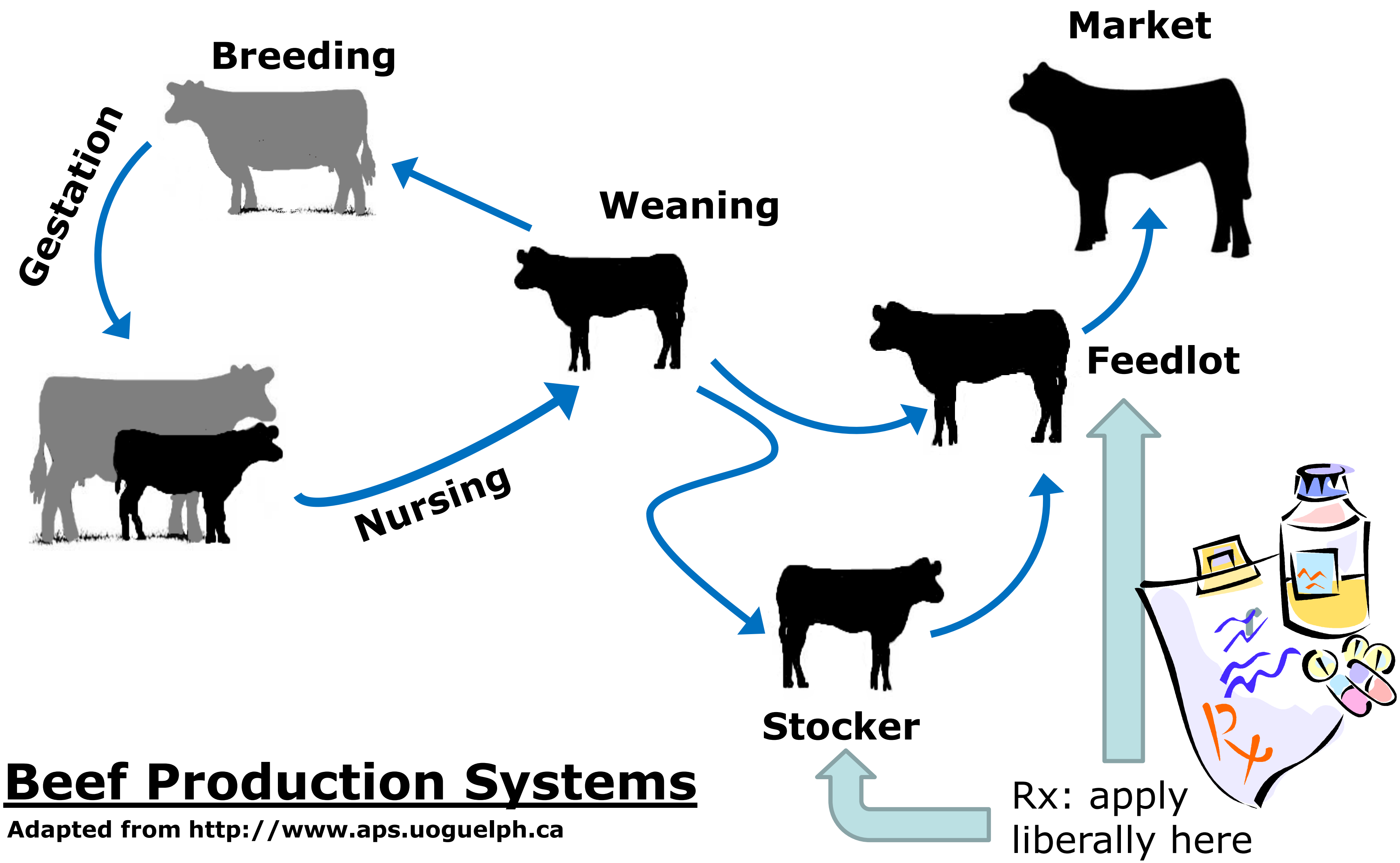
A systems look at BRD



Beef Production Systems

Adapted from http://www.aps.uoguelph.ca

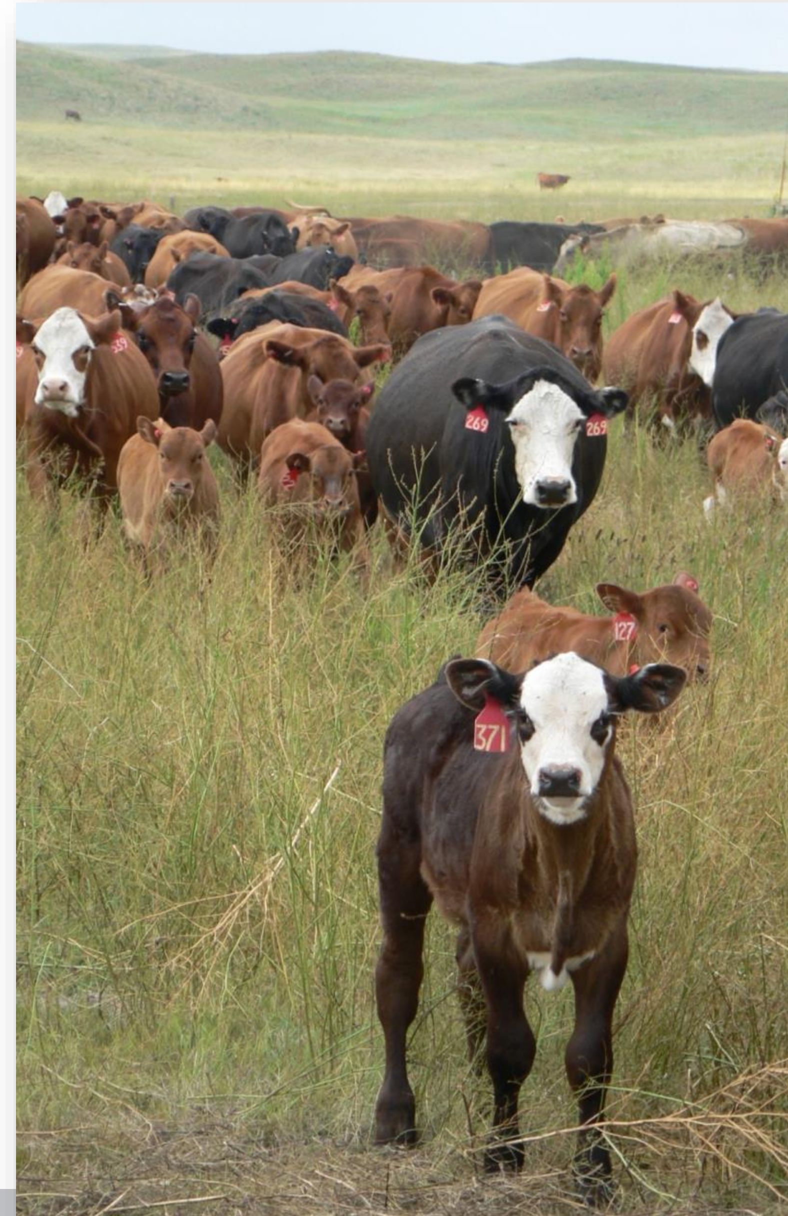
A systems look at BRD



Beef Production Systems

Adapted from http://www.aps.uoguelph.ca

Pre-Weaning Pneumonia in Beef Calves



Pneumonia is <u>the leading cause of death</u> in calves 3 weeks of age and older

Total cost of BRD in US beef calves prior to weaning, 2011–2015

Cost of BRD mortality

Treatment cost

Losses from lost weaning weight from BRD

Materials and Methods

Data

- USDA reports
  - NAHMS 2007-2008, NASS 2011-2015, and AMS 2011-2015
- Survey
  - 43 beef cow-calf ranchers from Nebraska, South Dakota, and North Dakota
- Peer-reviewed papers
  - Data directly from the paper
  - Simulation of the data from the paper

Materials and Methods

Monte Carlo Simulation Model

Risk analysis to estimate the uncertainty and variation of the cost of BRD in pre-weaning calves

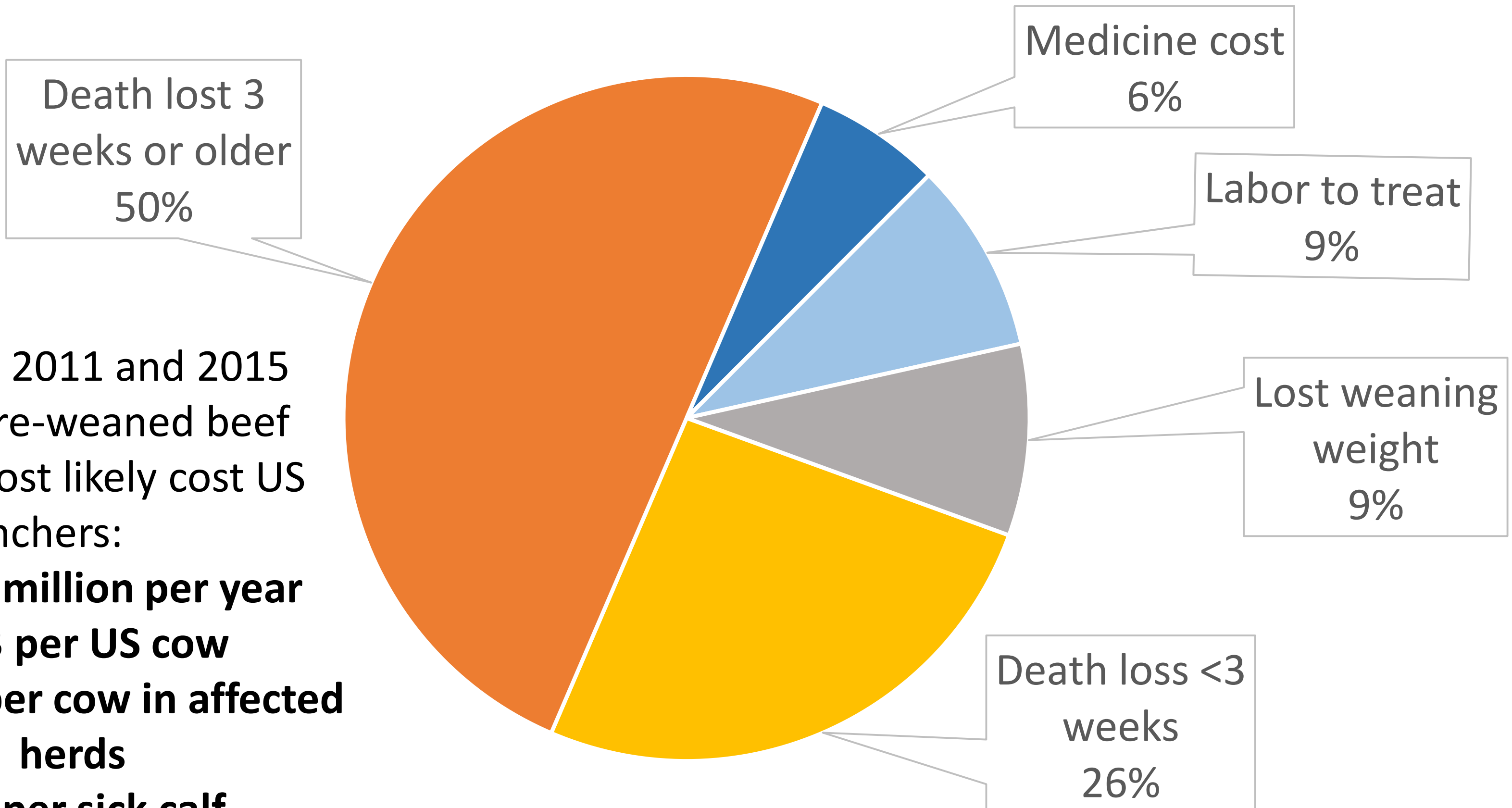
- 10,000 iterations
- Sensitivity analysis

@RISK
Advanced Risk Analysis for Spreadsheets

Excel

$165 million per year

Total cost of BRD in US beef calves prior to weaning*

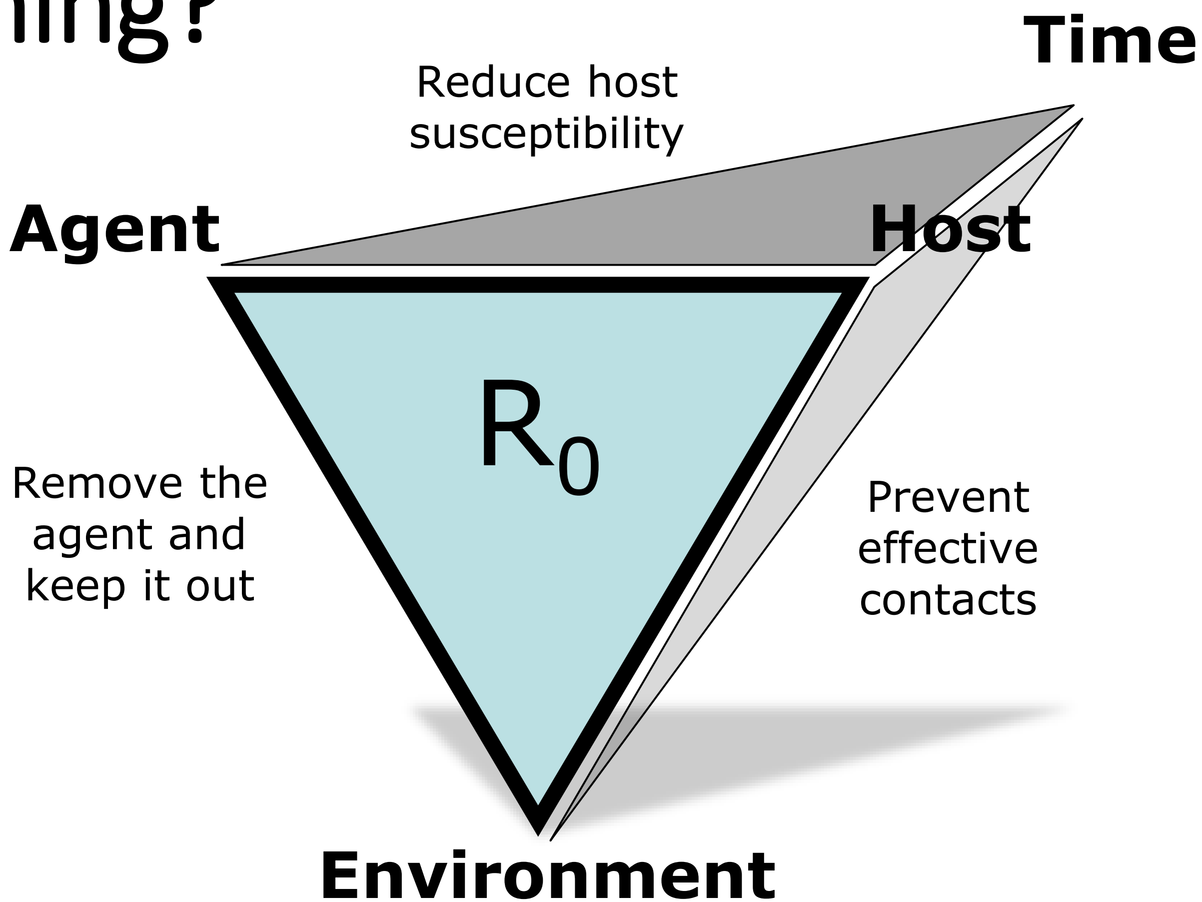


Between 2011 and 2015 BRD in pre-weaned beef calves most likely cost US cattle ranchers:

- **$165 million per year**
- **$5.63 per US cow**
- **$28 per cow in affected herds**
- **$216 per sick calf**

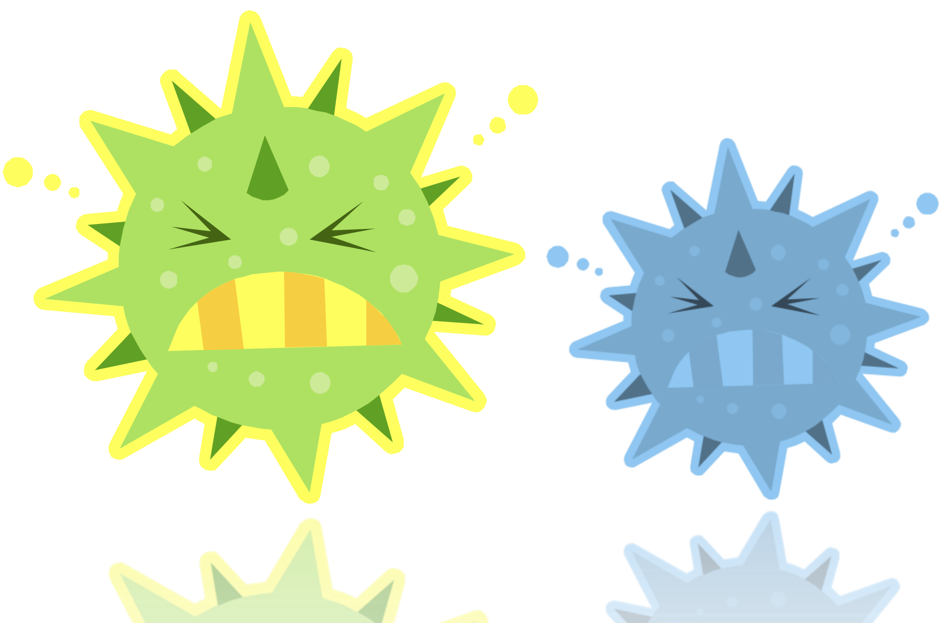
***Not** including the cost of vaccines or other prevention practices

Why do calves get BRD prior to weaning?



Agent factors

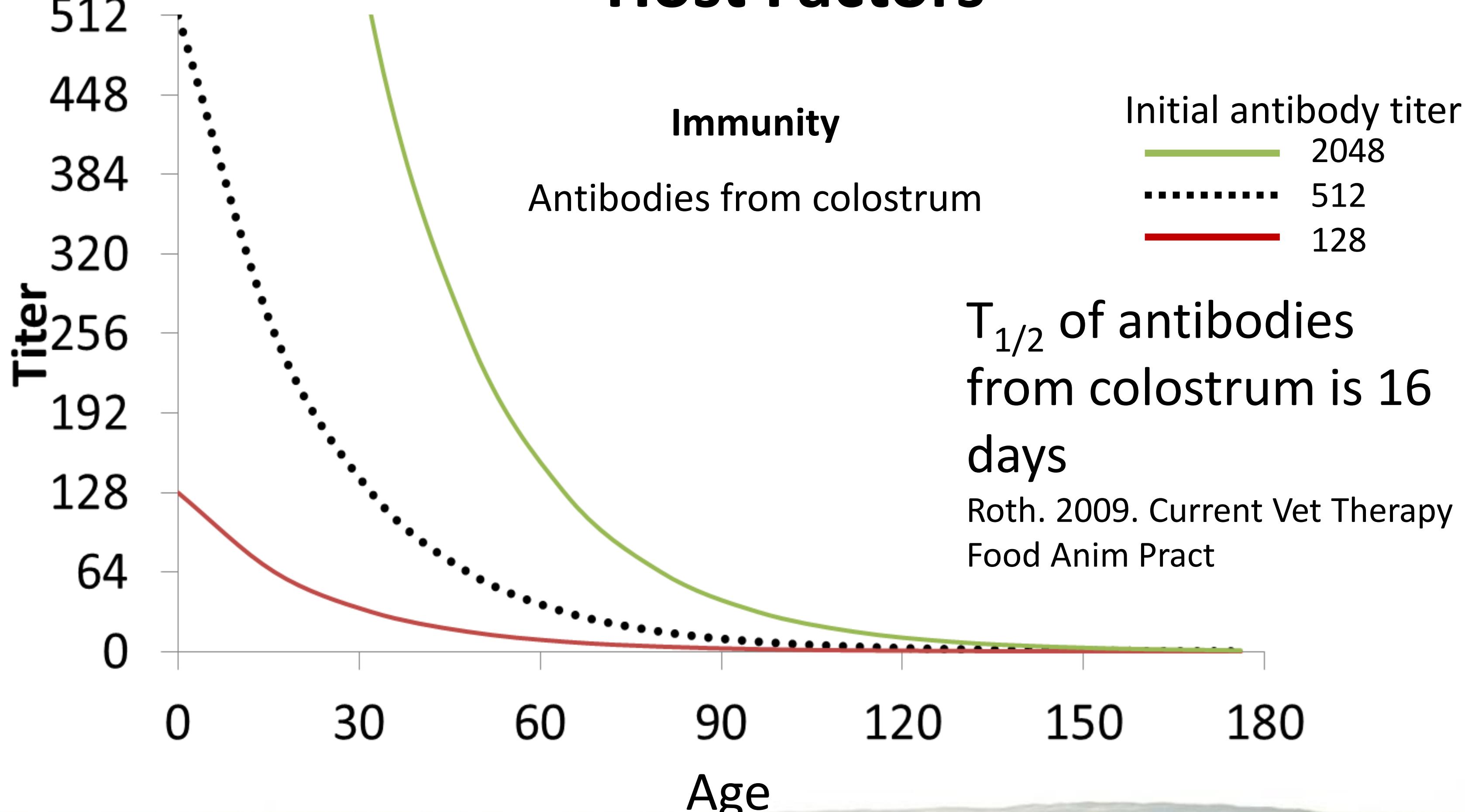
population dynamics of BRD pathogens in cow-calf systems are poorly understood



Host Factors

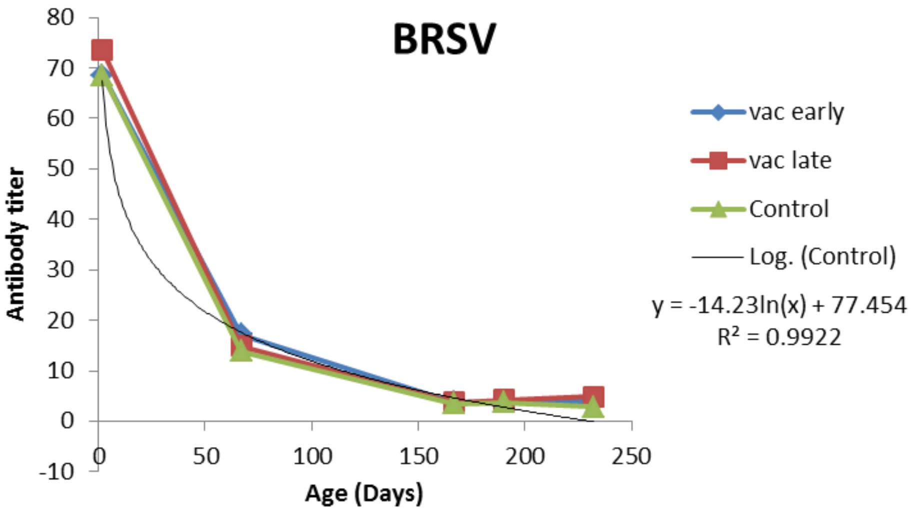
Immunity

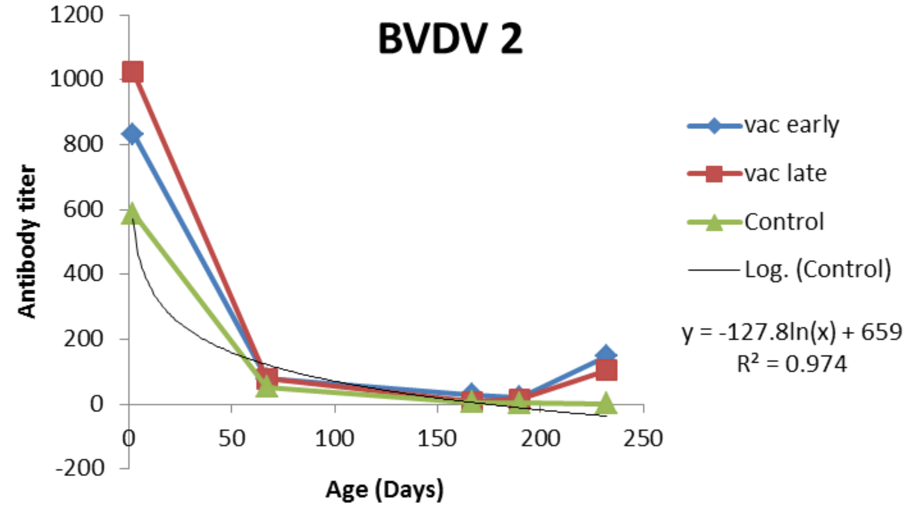
Antibodies from colostrum

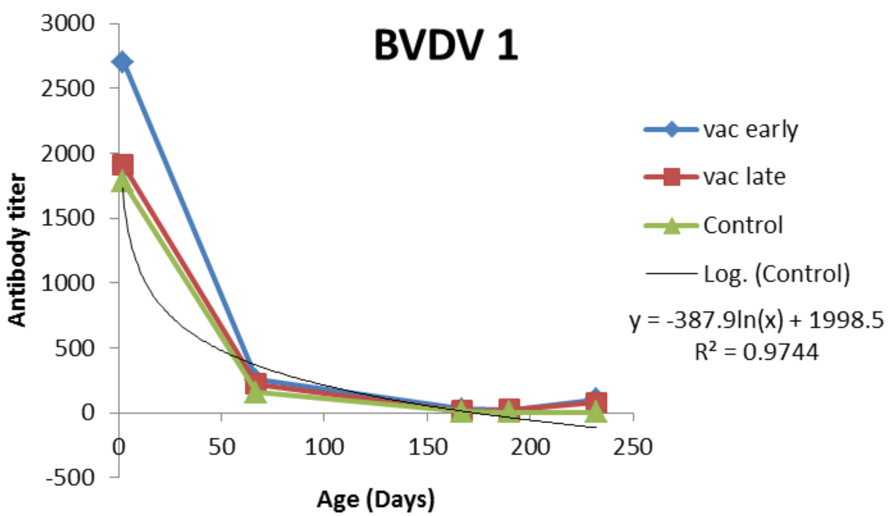


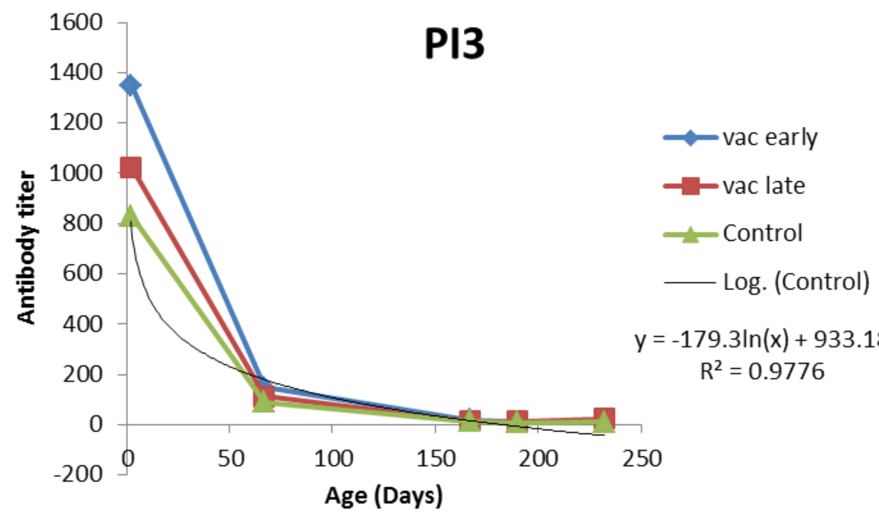
$T_{1/2}$ of antibodies from colostrum is 16 days

Roth. 2009. Current Vet Therapy Food Anim Pract



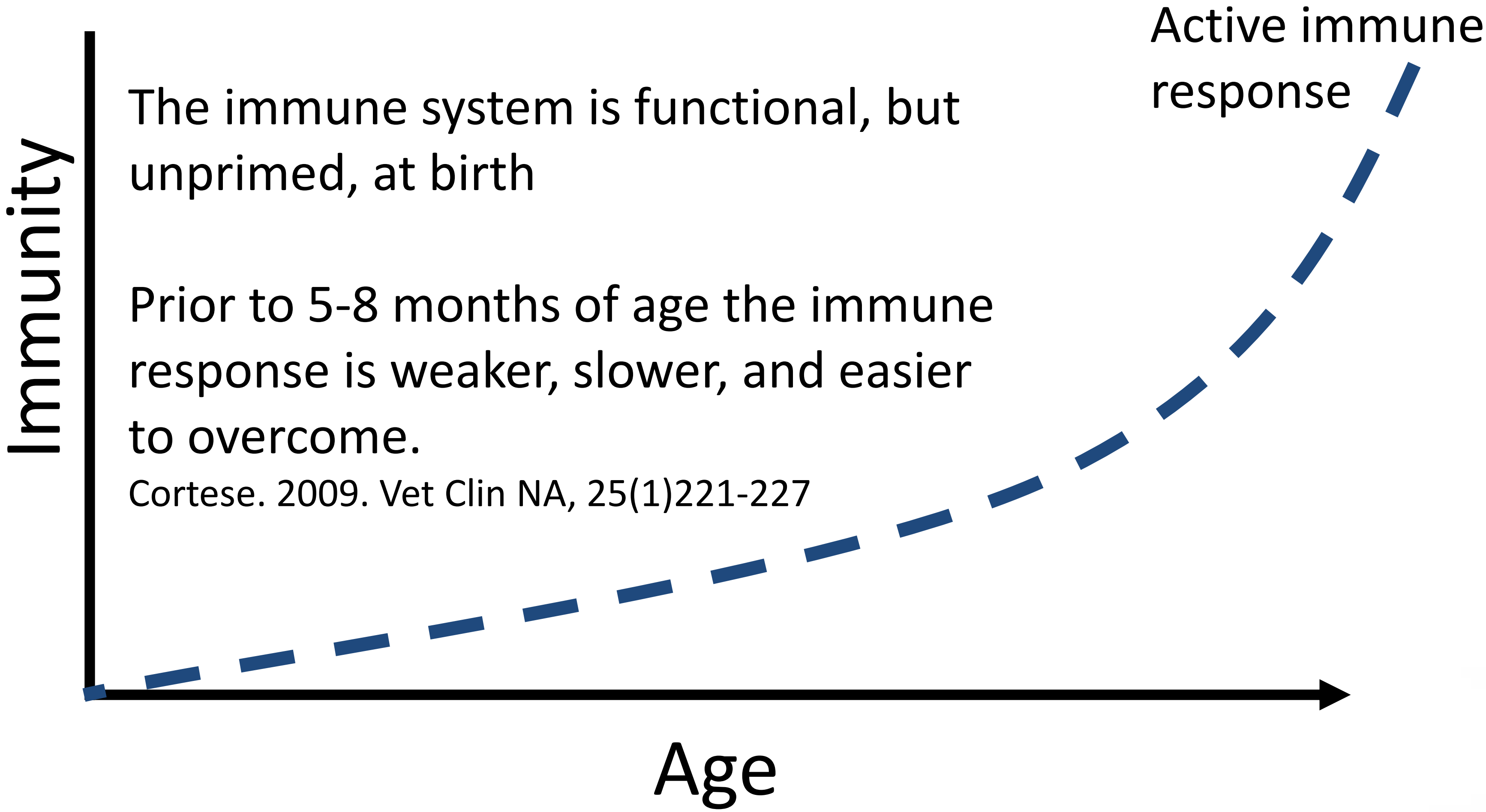






Early: 67d, 190d
Late: 167d, 190d

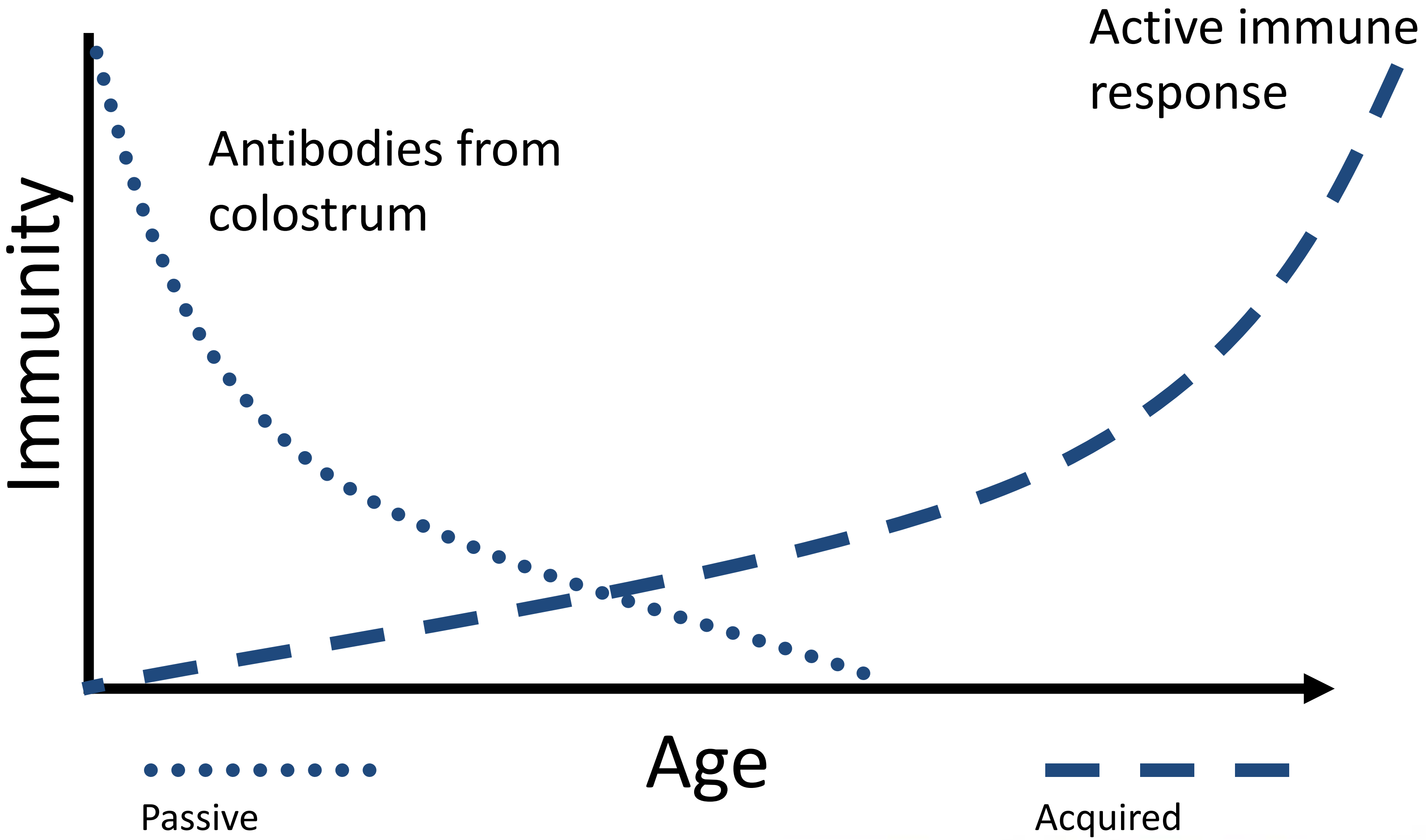
Kirkpatrick et al. JAVMA, Vol 233, No. 1, July 1, 2008

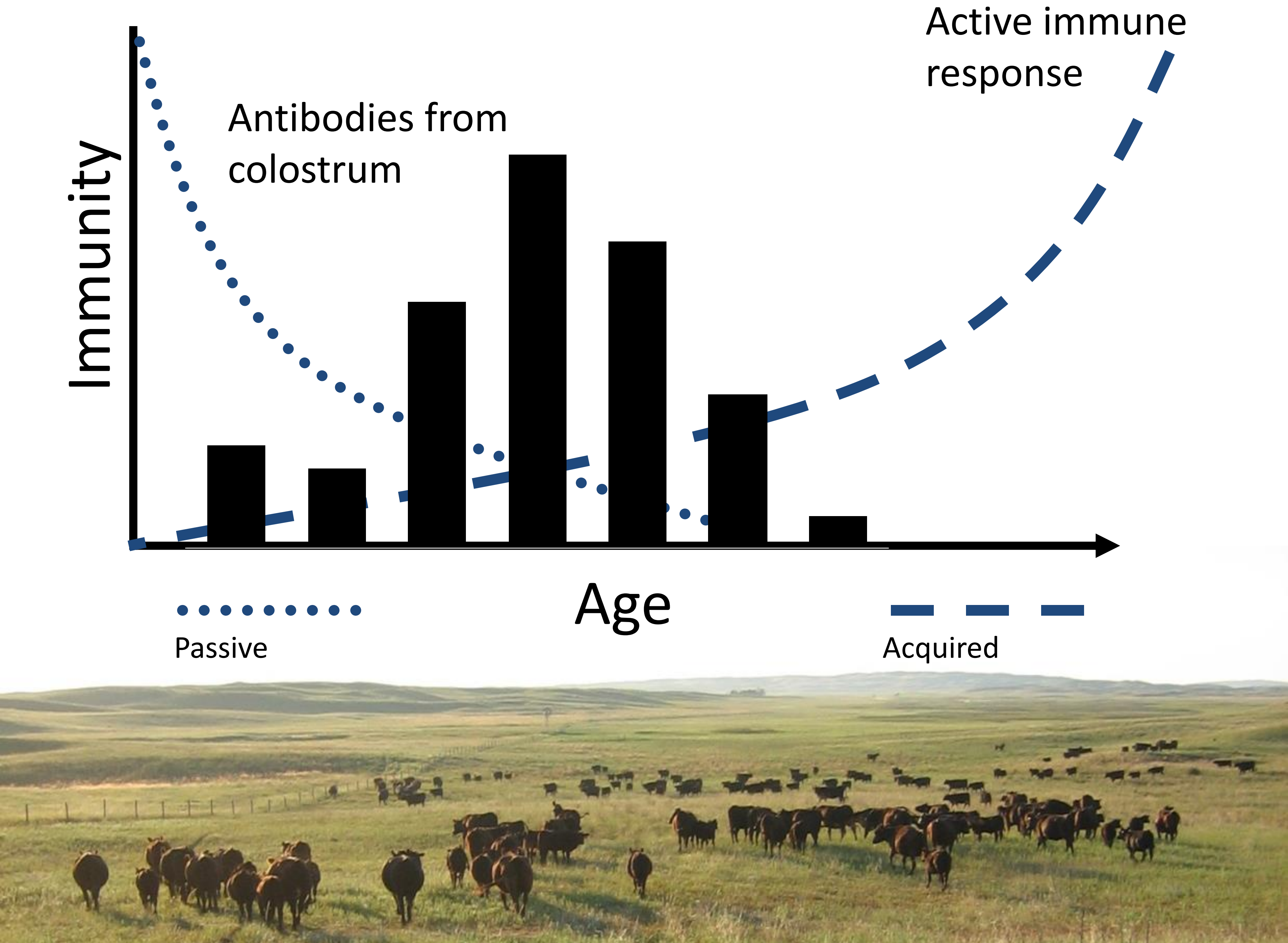


The immune system is functional, but unprimed, at birth

Prior to 5-8 months of age the immune response is weaker, slower, and easier to overcome.

Cortese. 2009. Vet Clin NA, 25(1)221-227


Active immune response
Antibodies from colostrum
Immunity
Age
Passive
Acquired


Active immune response
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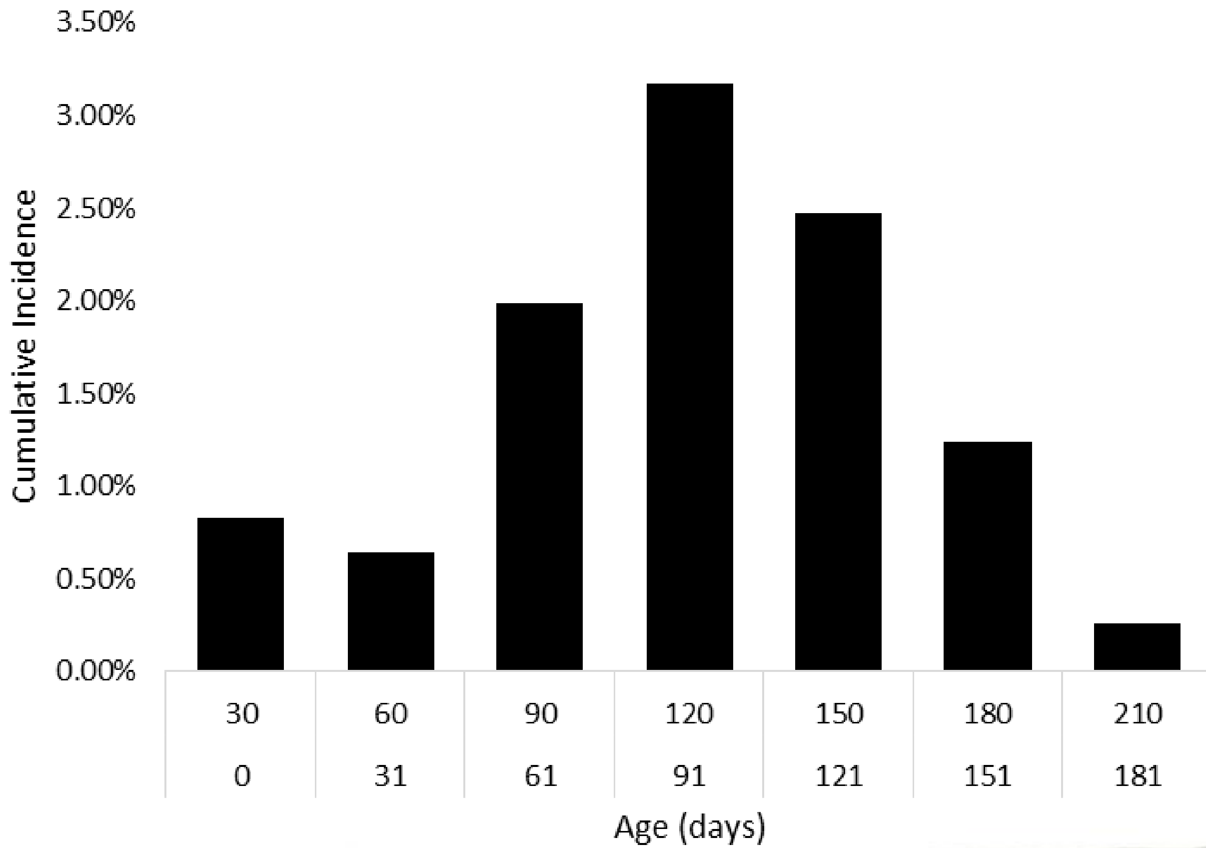
Acquired

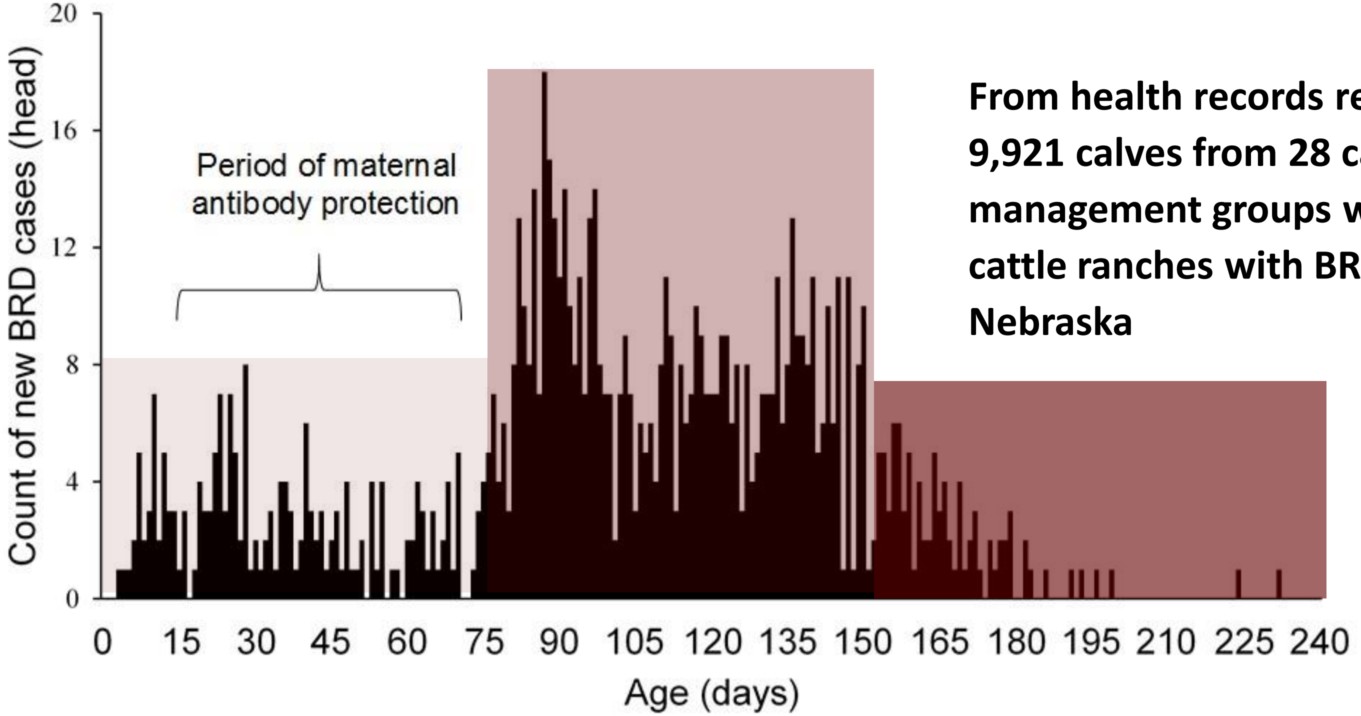
Age and immunity to BRD



- 9,921 calves
- 28 management groups
- 7 Nebraska ranches
- 1,031 recorded BRD cases (10.4%)

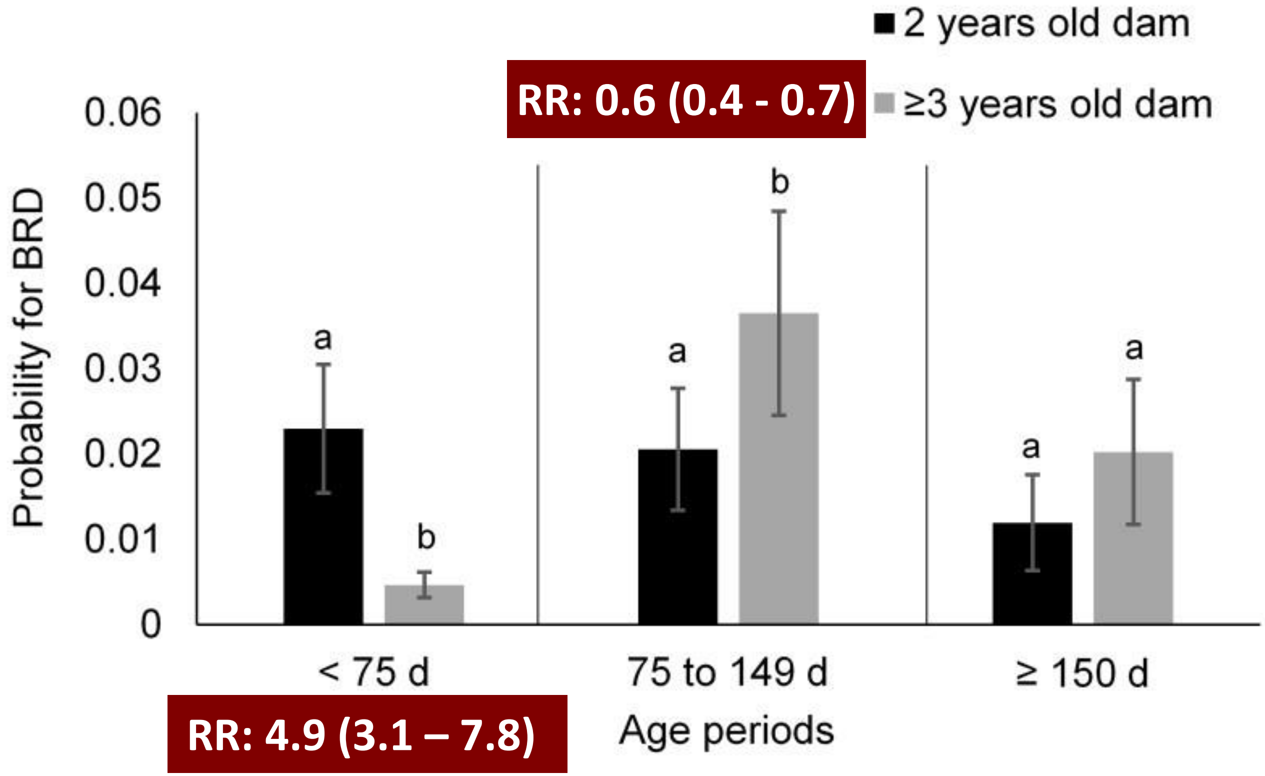
Different risk periods?

Age distribution for 877 of 9,582 calves with BRD



From health records representing 9,921 calves from 28 cattle management groups within 7 beef cattle ranches with BRD in Nebraska

Risk factors for BRD by age group



Adjusted probability for BRD by age of dam. Separate models for different age periods
(Differing superscripts within age periods are significantly different)

Passive transfer of maternal antibodies

1,671 calves with health records from a single ranch with 4 management groups

56 recorded cases of BRD (3%)

- 384 calves from 3 management groups tested for IgG passive transfer
  - Radial immunodiffusion (adequate ≥ 1,600 mg/dl)
- 36 of 384 calves (9%) had inadequate passive transfer

Passive transfer of maternal antibodies

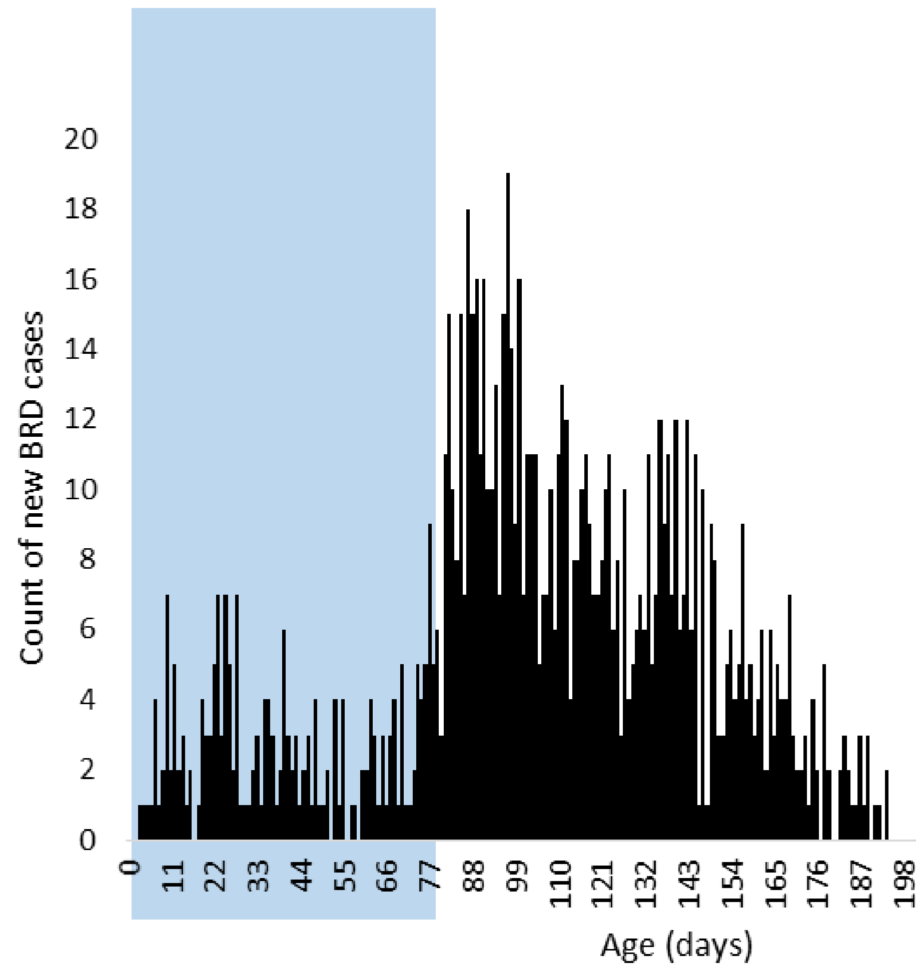
21 of 384 calves (5%) with IgG data were treated for BRD

Calves with inadequate passive transfer were 3.4 times more likely to be treated for BRD than calves with adequate transfer ($p=0.03$)

Passive transfer of maternal antibodies

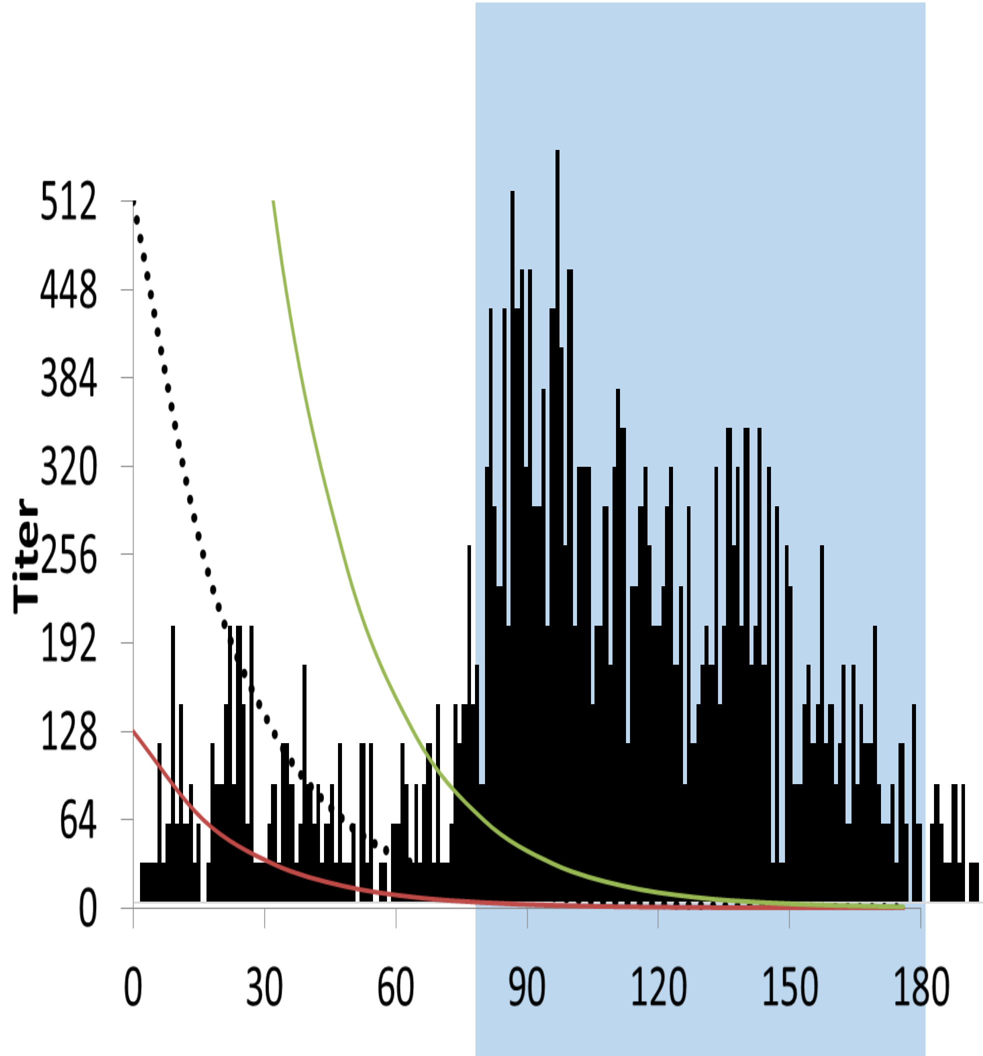
21 calves treated for BRD had IgG data

- Calves with inadequate passive transfer were 3 times more likely to be treated for BRD in the first 80 days of age
- Fisher's exact p-value =0.08



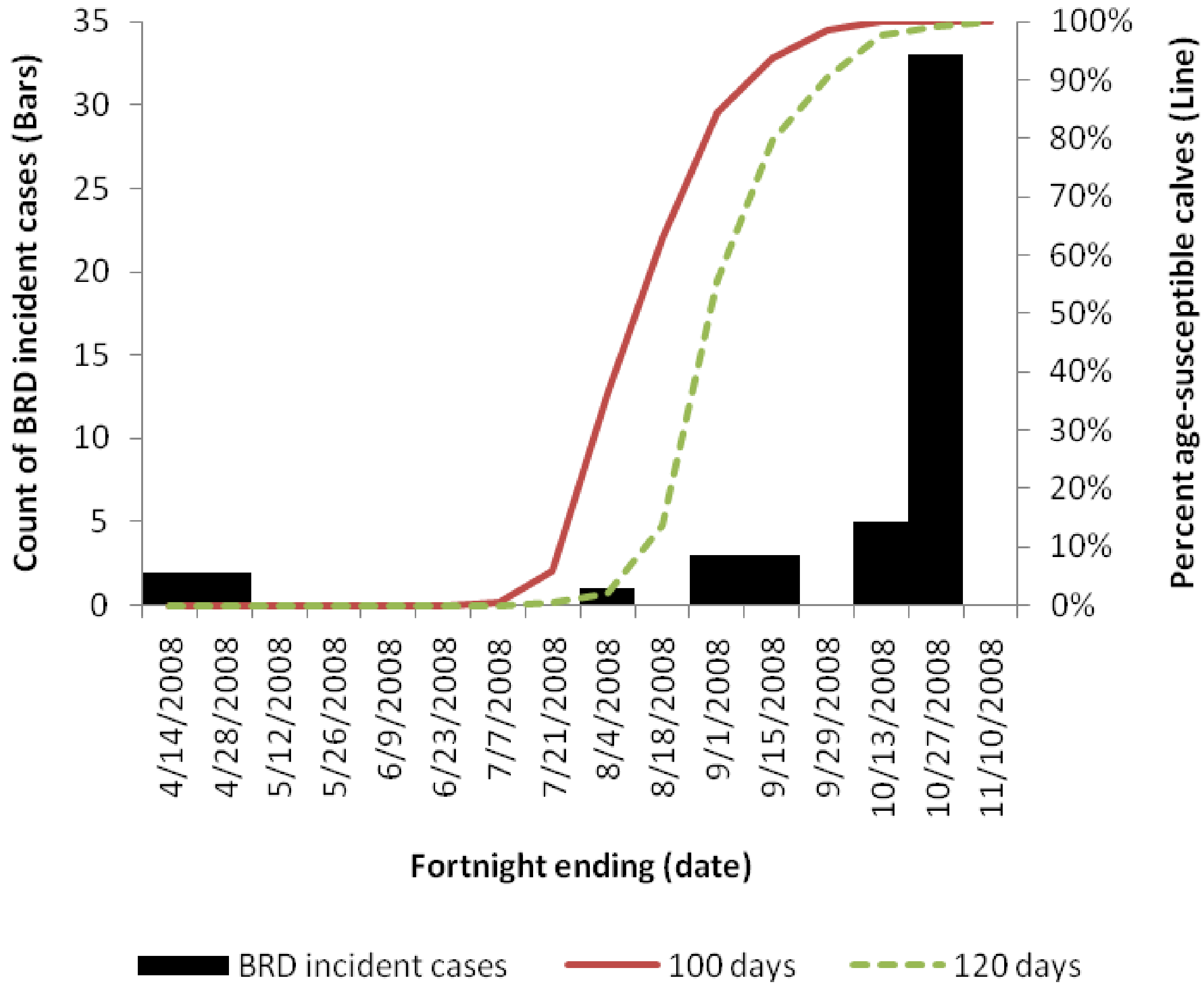
Discussion

- Failure to receive colostrum puts those calves at risk for pneumonia prior to 80 days of age
- **What explains the larger number of cases after 80 days of age?**



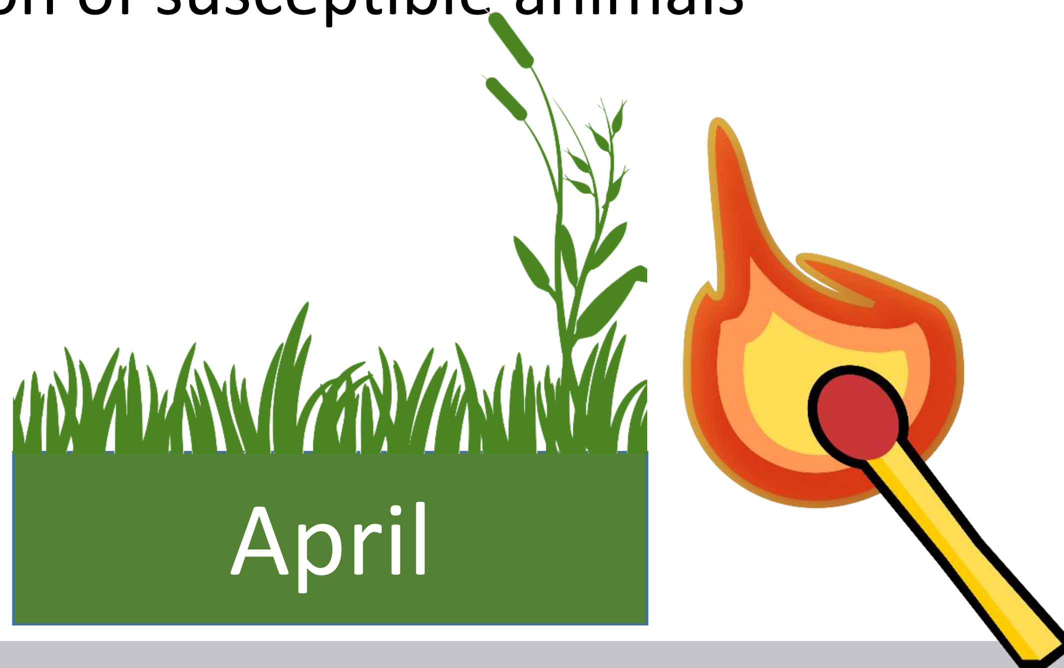
Loss of herd immunity

When a large portion of the calves have lost immunity from colostrum the group loses herd immunity and outbreaks of disease may occur



Herd immunity

- Transmission is hindered because a majority of animals are immune –inefficient transmission means the pathogen may "die out" (R_0 <1) before everyone is exposed
- Results in protection of susceptible animals within the group
- Grass-fire analogy



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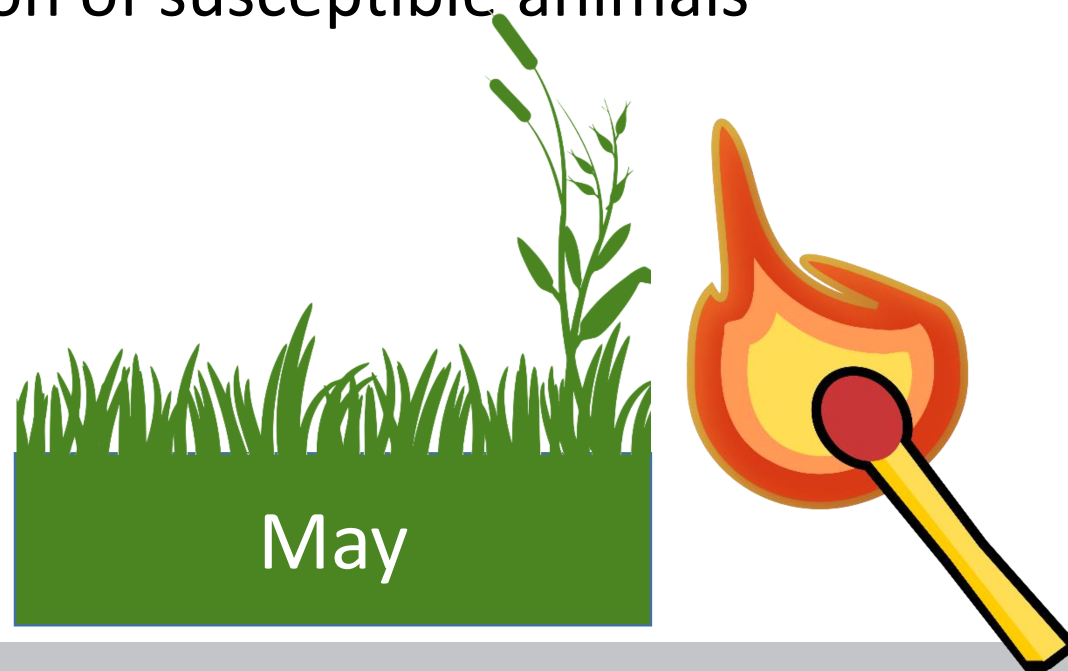

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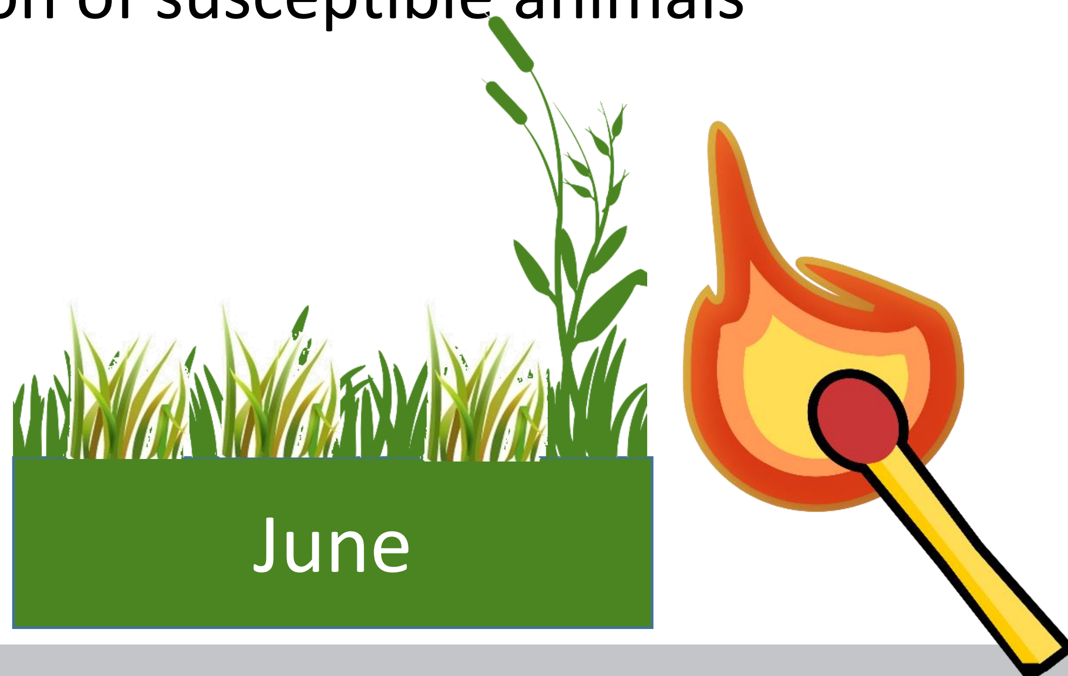

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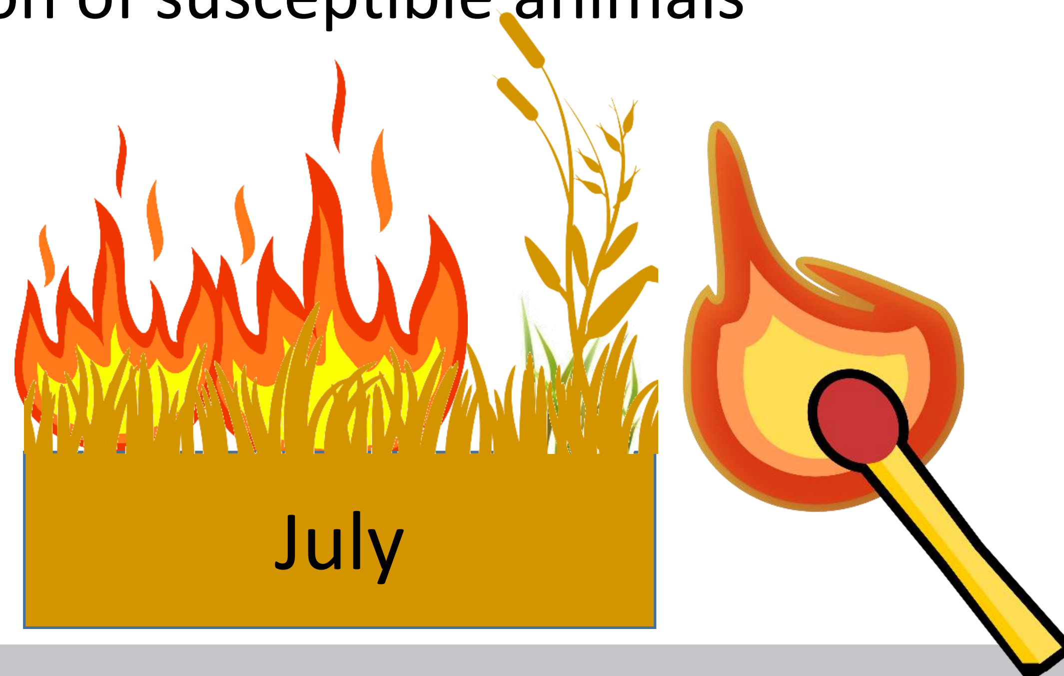


Conclusions from ranch BRD outbreak investigations

- The two epidemic patterns may be related to factors of immunity:
  - **failure of passive transfer** resulting in **sporadic cases** of pneumonia in very young calves (<75 days)
  - **Loss of herd immunity** resulting in **outbreaks** of pneumonia in older calves (75-150 days of age) that are more rapid in onset and of higher incidence.

Environmental factors

JAVMA, Vol 243, No. 4, August 15, 2013 538-547

Producer survey of herd-level risk factors for nursing beef calf respiratory disease

Amelia R. Woolums, DVM, PhD, DACVIM; Roy D. Berghaus, DVM, PhD, DACVPM; David R. Smith, DVM, PhD, DACVPM; Brad J. White, DVM, MS; Terry J. Engelken, DVM, MS; Max B. Irsik, DVM, MAB; Darin K. Matlick, DVM; A. Lee Jones, MS, DVM; Roger W. Ellis, DVM, MS; Isaiah J. Smith, DVM, MFAM; Gary L. Mason, DVM, PhD, DACVP; Emily R. Waggoner, DVM

Objective—To identify herd-level risk factors for bovine respiratory disease (BRD) in nursing beef calves.
Design—Population-based cross-sectional survey.
Sample—2,600 US cow-calf producers in 3 Eastern and 3 Plains states.

Results –Bovine respiratory disease had been detected in at least 1 calf in 21% of operations

JAVMA, Vol 243, No. 4, August 15, 2013 538-547

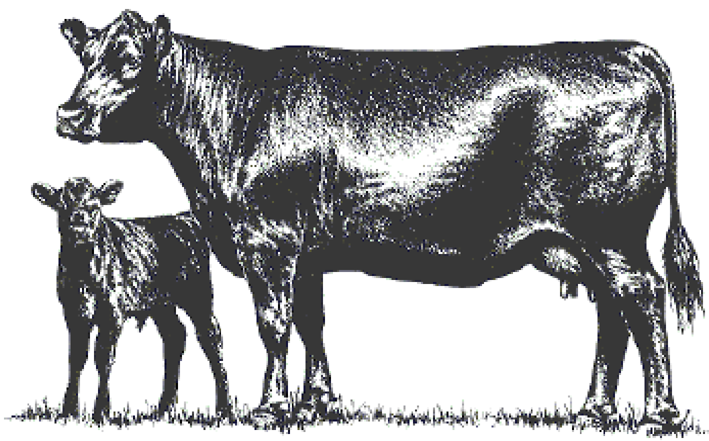
"Detection of BRD in calves was

- Positively associated with **large herd size**, detection of BRD in cows, and diarrhea in calves. Calving season length was associated with BRD in calves in Plains states but not Eastern states.

Cumulative incidence of BRD treatment was

- Negatively associated with **large herd size** and examination of cows to detect pregnancy
- Positively associated with calving during the winter, introduction of calves from an outside source, offering supplemental feed to calves, and **use of an estrous cycle synchronization program for cows**."

Understanding Herd Level Risk Factors for Pneumonia in Calves Prior to Weaning



- **Case-control study** of herd level risk factors for nursing calf BRD
- Phone interviews of producers
  - case herds: treated ≥ 5% of nursing calves for BRD
  - control herds: treated ≤ 0.5% of nursing calves for BRD
  - 2 control herds enrolled for each case herd
- Herds in SD, ND, and NE (30 case herds, 54 control herds)

Management practices:

- Cow numbers
- Were cows and calves managed in more than one group?
- Was intensive grazing used?
- Did cattle have fence-line contact with other herds?
- Were cows or calves given supplemental feed?
- Were any cattle brought onto the farm from outside sources?
- Were cows synchronized after calving?
- Were cows checked for pregnancy?
- Were cattle tested for bovine viral diarrhea (BVD) virus?
- Were cows and calves ever moved more than one mile on foot?
- Length of calving season?
- Did any calves develop diarrhea?
- Were respiratory vaccines given to cows and/or calves?
- Were any cows/heifers treated for respiratory disease?

Management practices:

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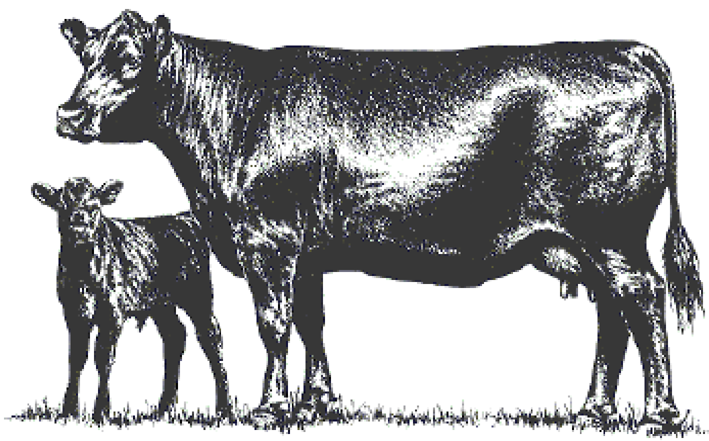
Herd Level Risk Factors, Case-Control Study



Significant risk factors:

- **Number cows/heifers calving**
  - **Versus herds with < 150 cows**
  - If 150 – 499 cows: OR = 7.9 (2.0 – 31) *P* = 0.03
  - If ≥ 500 cows: OR = 12 (2.0 – 70) P = 0.02
- **Intensive grazing**
  - **Versus not:** OR = 3.3 (1.2 – 9.2) *P* = 0.05
- **Cows or heifers synchronized**
  - **Versus not:** OR = 4.5 (1.5 – 14) *P* = 0.02

Attributable fraction

The **impact** of the exposure on the exposed. (e.g. What proportion of an individual's disease is explained by the exposure?)

- Herd size
  - AF (150-499) = 71%
  - AF (≥ 500) = 74%
- Intensive grazing
  - AF = 60%
- Estrus synchronization
  - AF = 64%

Each of these factors contributes meaningfully to disease risk for the herds that have them

Population attributable fraction

The **impact** of the exposure on the population (e.g. what proportion of the disease in the population is attributed to the factor?)

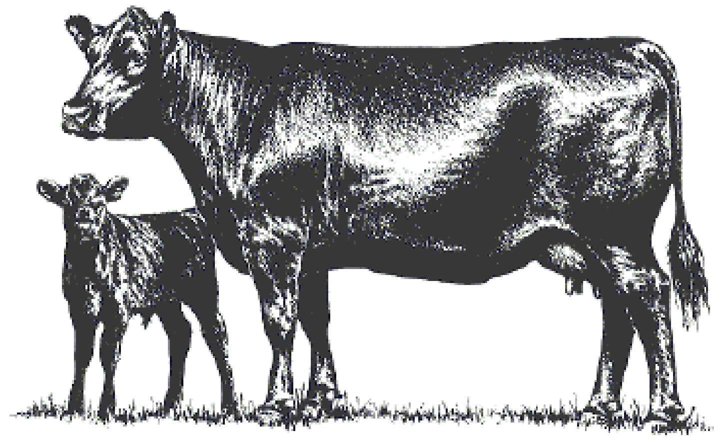
- Herd size (4% of herds 150 -499 cows; 1% of herds 500 cows or greater)
  - pop AF (150-499) = 9%
  - popAF (($\geq$ 500) = 3%
- Intensive grazing (30% of herds)
  - popAF = 31%
- Estrus synchronization (8% of herds)
  - popAF = 13%

These 3 factors may explain more than half of the occurrence of calfhood BRD

Larger herds, intensive grazing, and estrus synchronization increase the rate of effective contacts

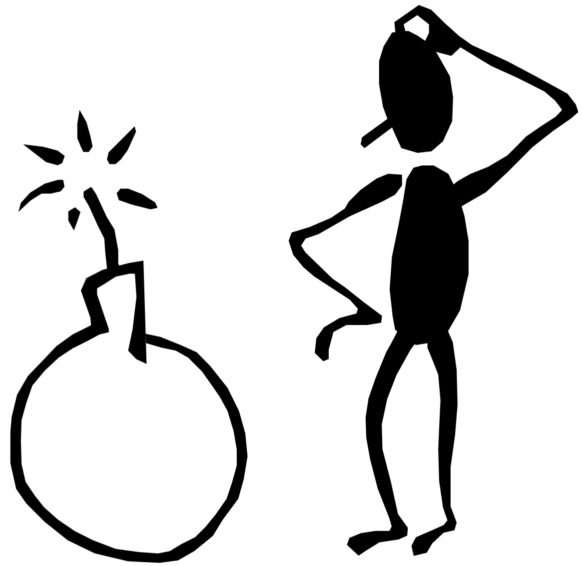
An **effective contact** is defined as any kind of **contact** between two individuals such that, if one individual is infectious and the other susceptible, then the first individual infects the second

Pneumonia in calves prior to weaning



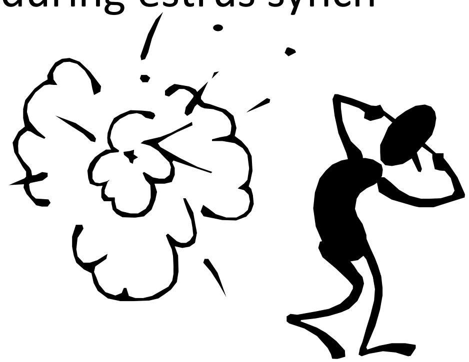
- A "childhood disease" of cattle due to age-related susceptibility and loss of herd immunity
- Parodoxically associated with practices of highly managed herds!
- A "systems" problem requiring a systems solution

Risk Management



Manage pre-weaning BRD risk by:

- Age of vaccination
  - Twice before 90 days of age
  - Some evidence of success!
  - Bovine coronavirus?
- Age of exposure
  - Commingling early or late
  - Merging groups during estrus synch is probably not good
  - Minimize crowding (effective contacts) and stress during estrus synch
- Age of stressors
  - Wean early or late
  - Trailing or transportation
- Monitor calves during high risk ages



BRD in calves after weaning

The first several days from farm of origin to the stocker operation or feedlot can result in the accumulation of stress events that are detrimental to calf health.

- By the time calves have moved through marketing channels and arrive at the destination feedlot or stocker facility, they may be exhausted, dehydrated, challenged by a variety of social and physical stressors, and incubating a respiratory or enteric infection.
- Unfortunately, the marketing system may not reward the small cow-calf farmer for adopting practices that improve immunity and decrease stress

BRD in calves after weaning

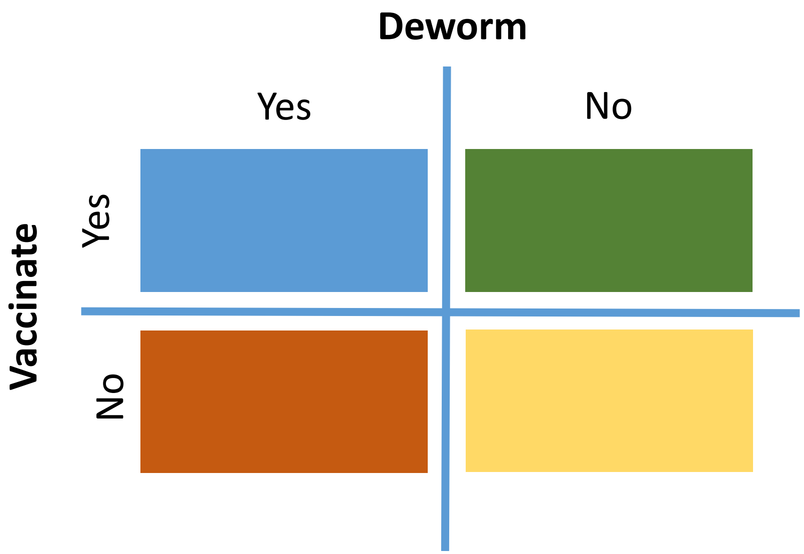
- By far, the most common illness post-weaning is BRD
- Most BRD morbidity occurs in the first 21 days after arrival in the stocker operation.
- Evidence supports the efficacy of mass medication with antibiotics -metaphylaxis

Two questions:

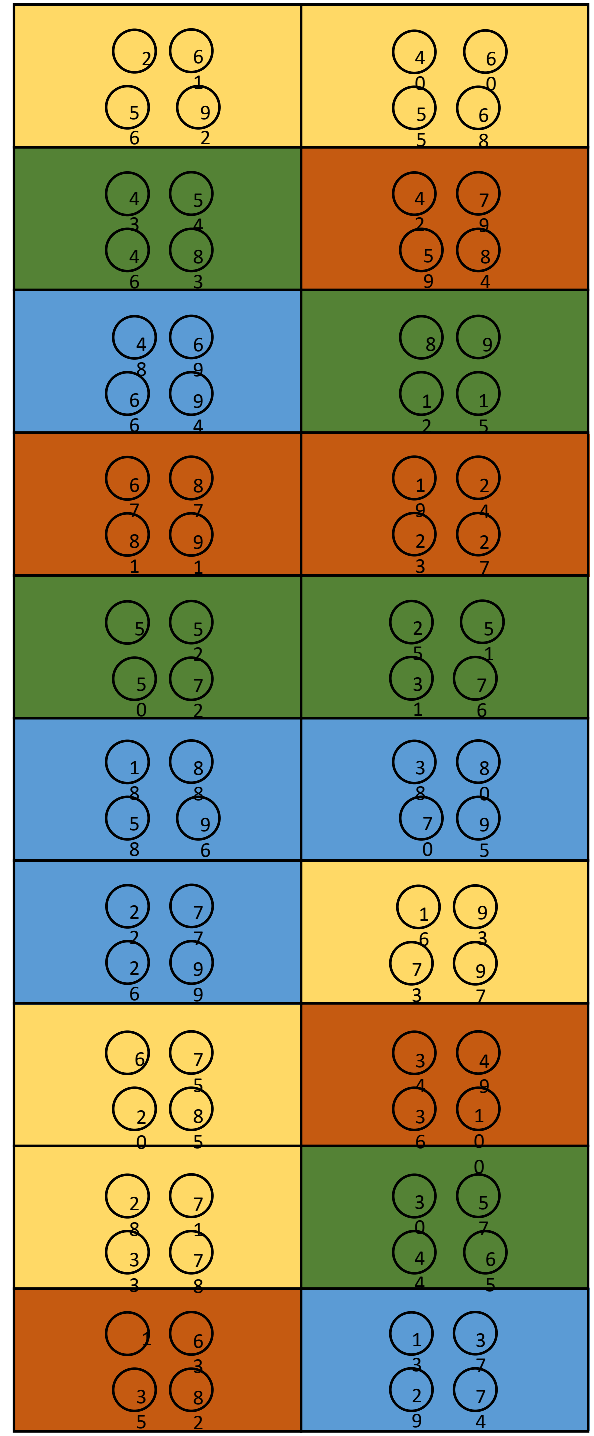
Is metaphylaxis good antimicrobial stewardship?

How effective are other receiving strategies?

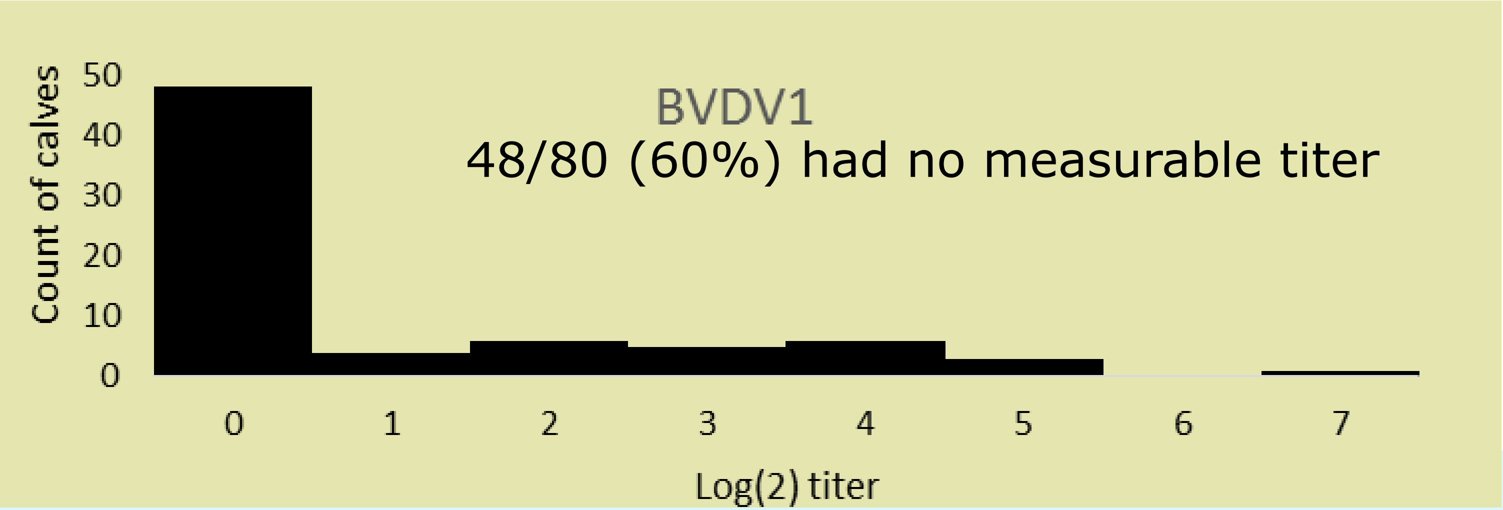
Evaluation of on-arrival vaccination and deworming on stocker cattle health and growth performance

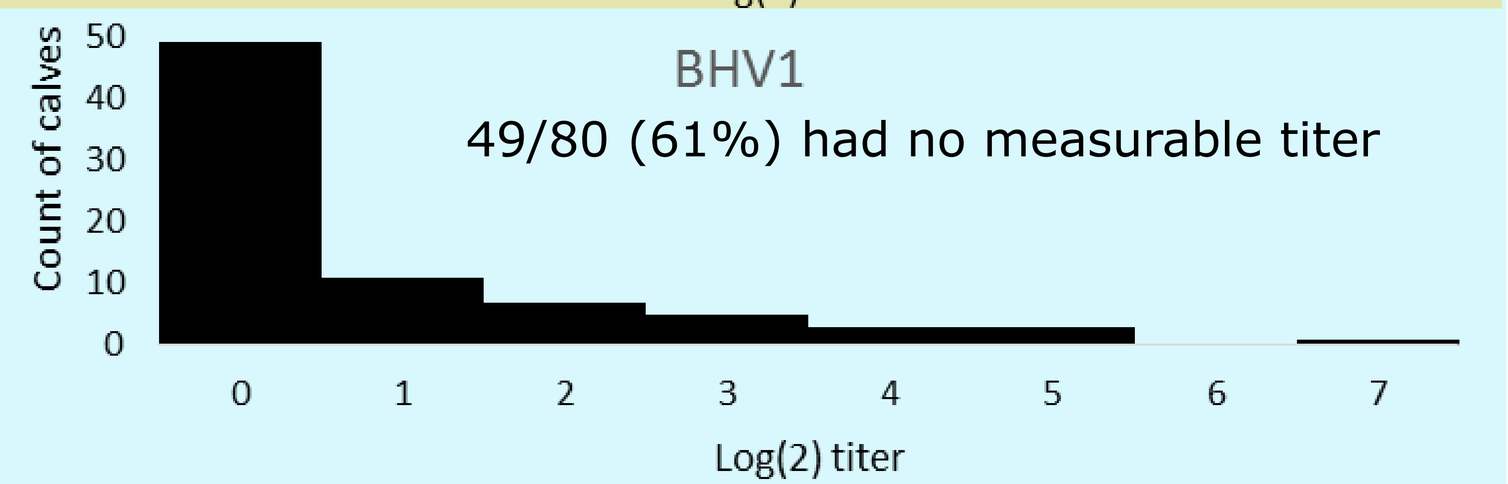


- Vaccinated calves received 5-way modified live BRD and Clostridial vaccines
- Dewormed calves received oral fenbendazole and levamisole



Serology at arrival



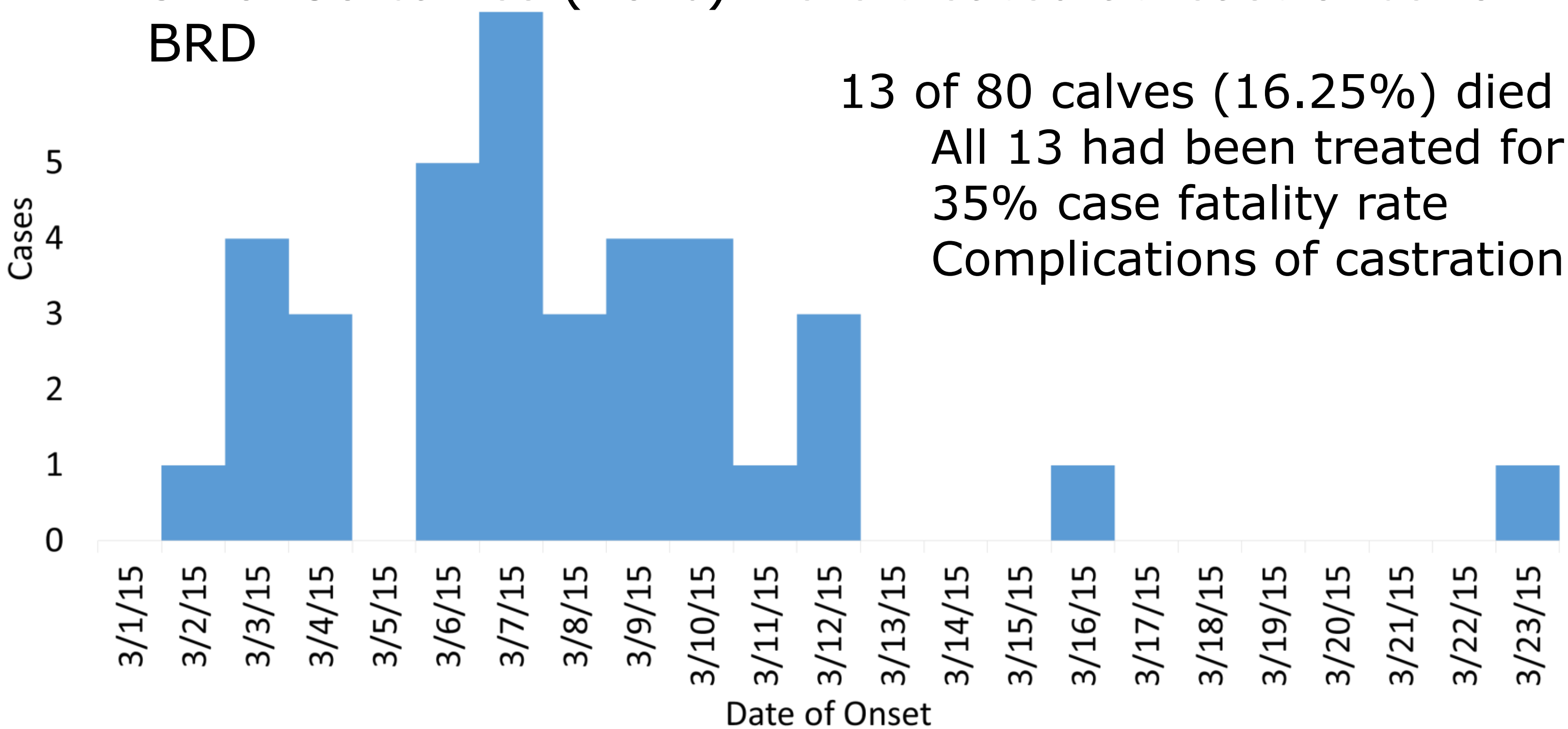


BRD morbidity and mortality

- 85 day trial
- 37 of 80 calves (46%) were treated at least once for BRD

13 of 80 calves (16.25%) died

- All 13 had been treated for BRD
- 35% case fatality rate
- Complications of castration

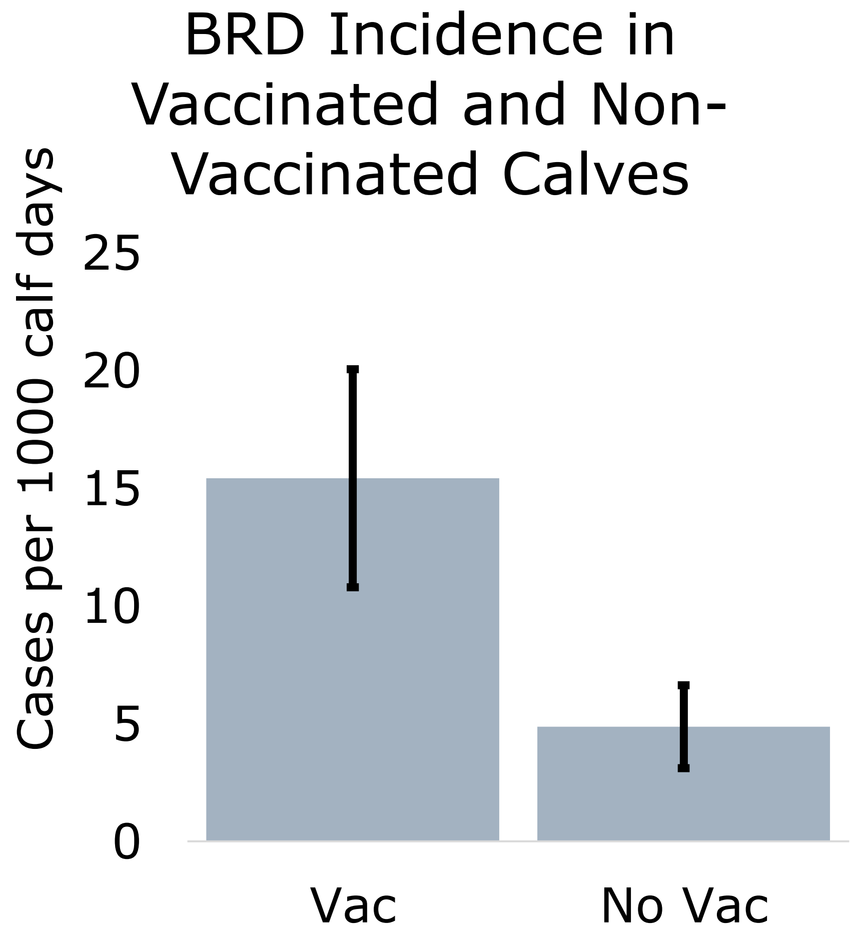


BRD Morbidity

Adjusting for other variables in the model:

Vaccinated calves were 3.2 times more likely to be treated for BRD

- RR=3.2 (CI=1.2-8)

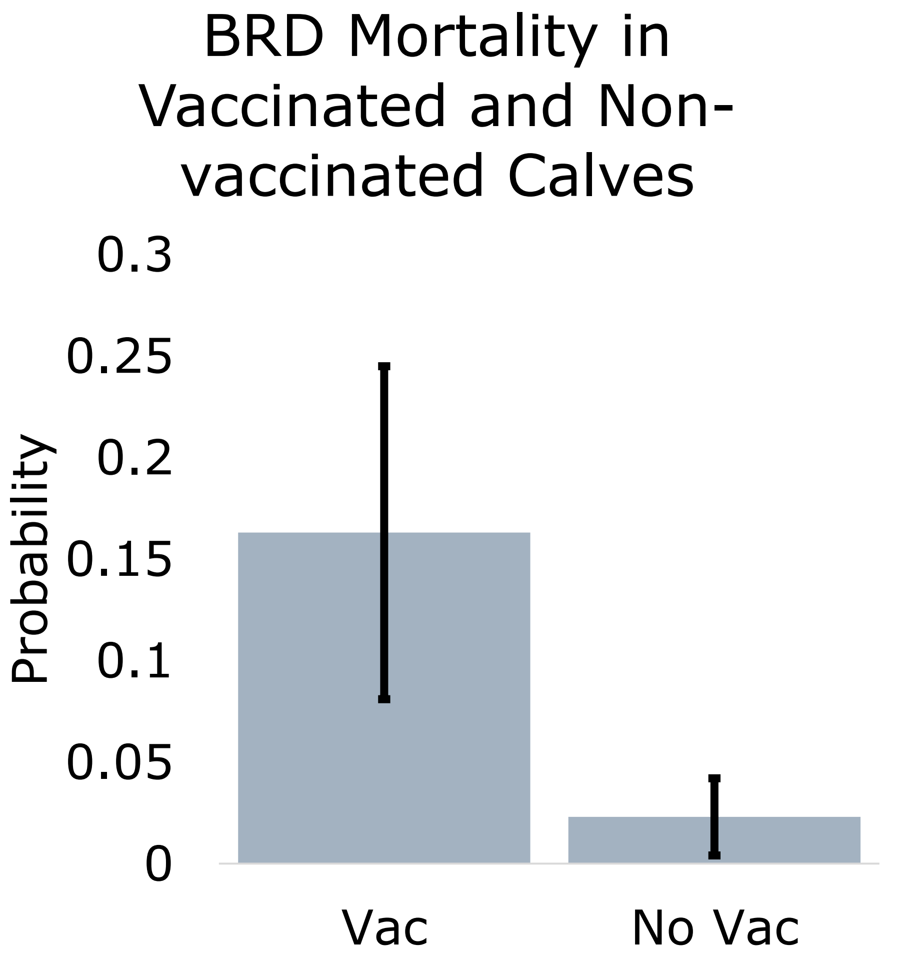


BRD Mortality

Adjusting for other variables in the model:

Calves vaccinated at d0 were at 8.3 times greater odds of death

- OR=8.3 (CI=1.4-51.5)



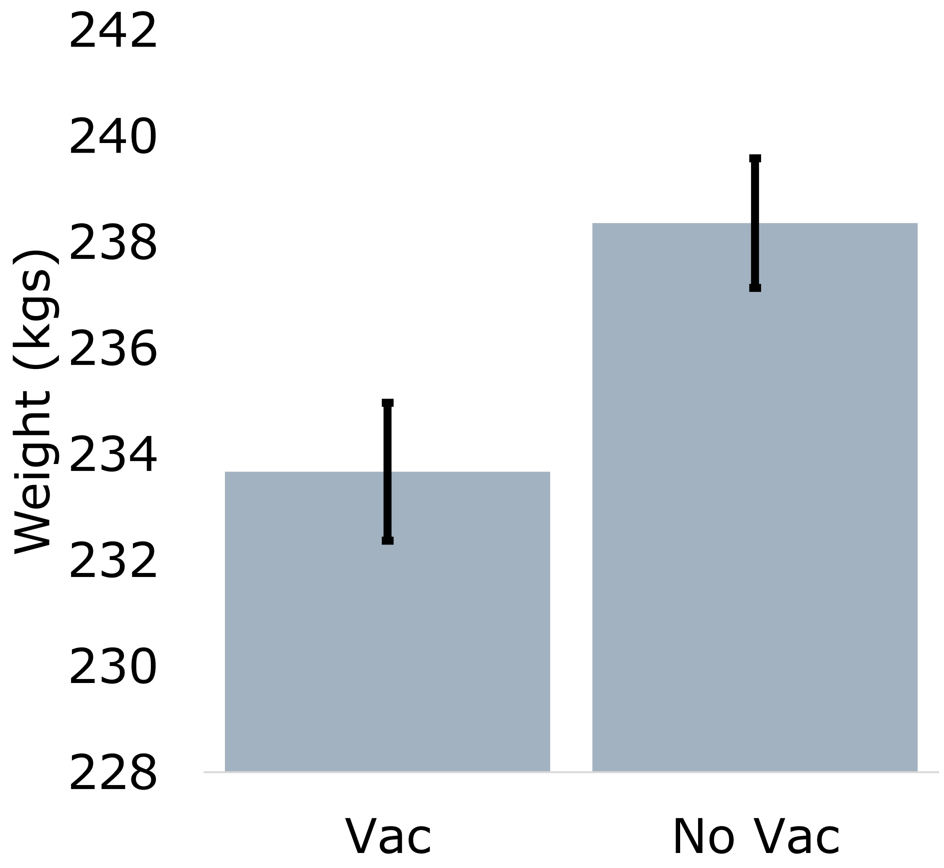
Performance

Adjusting for other variables in the model:

Vaccinated calves weighed 4.7 kgs less than non-vaccinated calves

- -4.7 kgs (SE=1.9)

Model-Adjusted Weights in Vaccinated and Non-vaccinated Calves



Conclusions

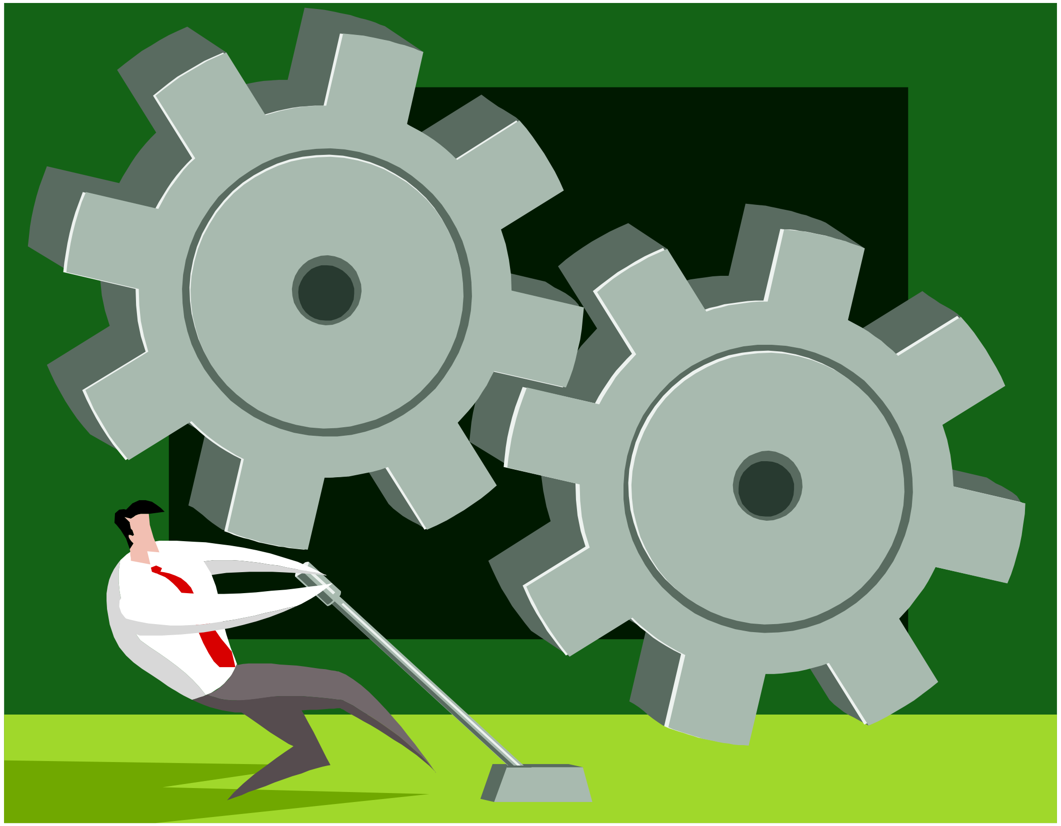
- Calves arrived with problems (parasitism, fever, low immunity) that could not be solved with the receiving program
- Vaccinating some groups of calves at arrival may adversely affect their health and growth performance
- In spite of the importance of FEC on health and performance, deworming calves at arrival did not mitigate losses in health or performance
- **Perhaps we should occasionally question our assumptions about what we know about keeping cattle healthy!**

What do we do about antimicrobial resistance?

Systems thinking as an approach to problem solving

Our challenge is to recognize how the system is influencing antimicrobial resistance

AND to find the leverage point for <u>changing the system</u>

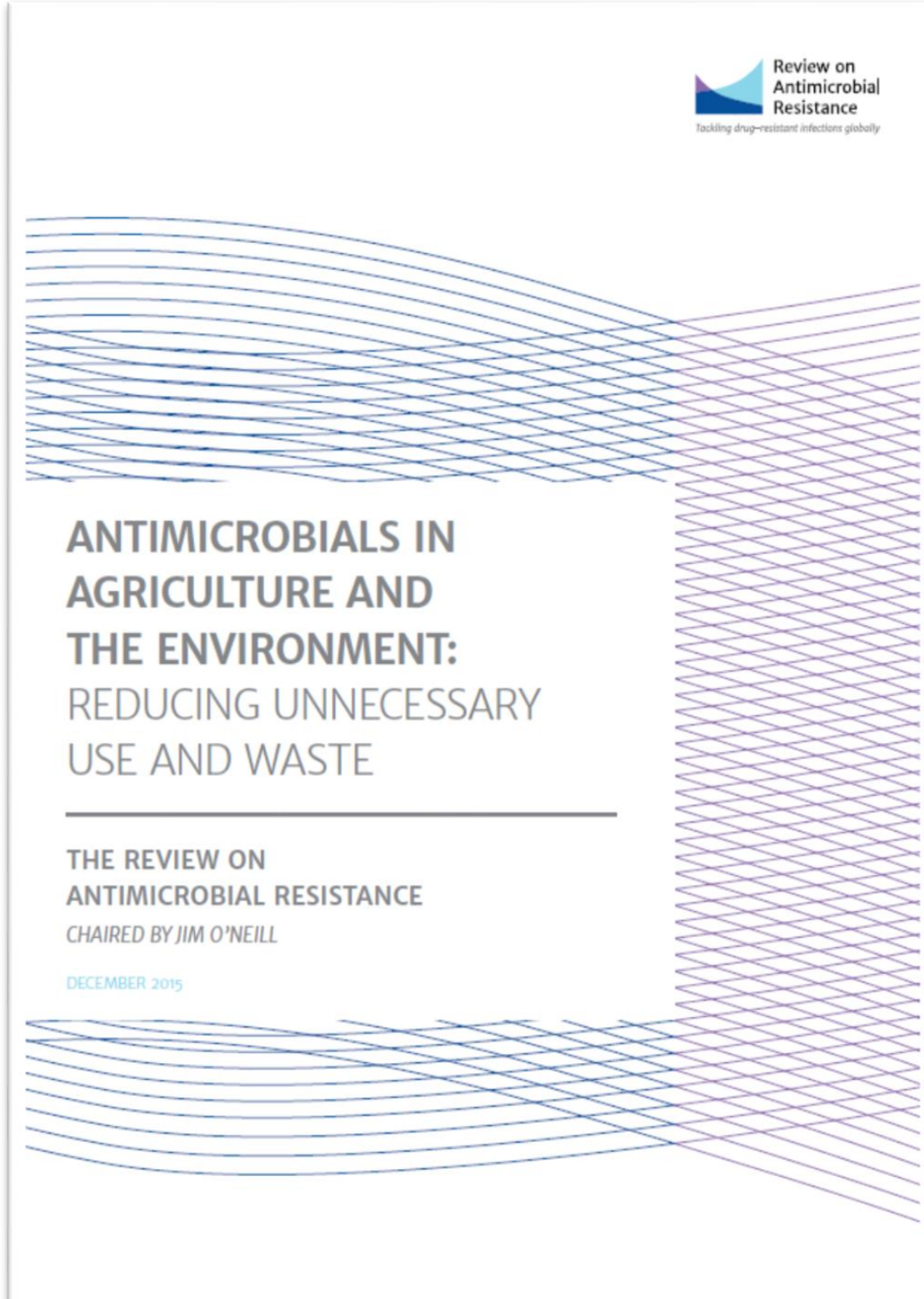


Tomorrow…

"…Interventions will no doubt include improvements in **infection control**, better animal **husbandry** practices, greater use of **vaccines** and the adoption of **diagnostic** devices to ensure better-targeted and more appropriate veterinary prescribing."

Executive summary

The Review on AMR was commissioned by the British Prime Minister, and is hosted by the Wellcome Trust. It is tasked with recommending, by the summer of 2016, a comprehensive package of actions to tackle AMR globally. [This report is one of] a series of papers looking at individual aspects of the wider AMR problem.



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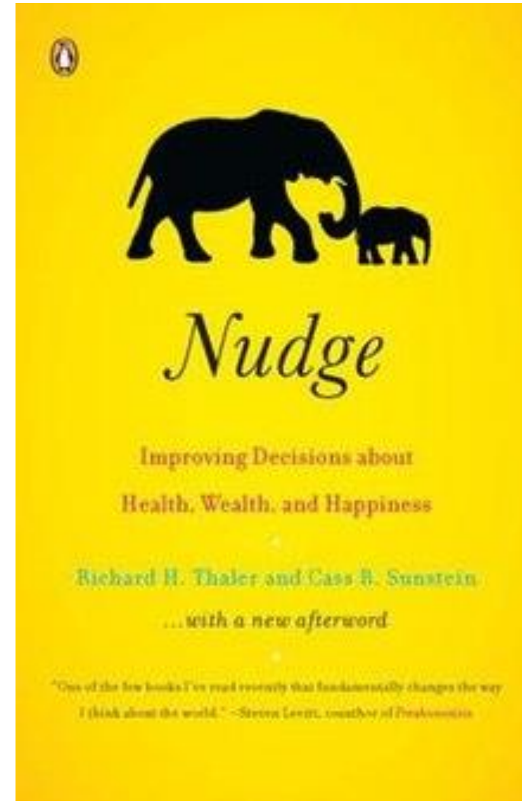
Can you get paid for that?

Today, we can nudge…

- The principles of antibiotic stewardship require that veterinarians commit to actions that preserve antibiotic effectiveness.
- As antibiotic stewards, veterinarians should help cattle producers in all stages of production implement systems of husbandry that reduce the risk for pneumonia.
- When pneumonia does occur, or is likely to occur, then antibiotics should be used judiciously and records should be used to evaluate therapeutic success.



Summary

- Antibiotic resistance is a **One Health** concern
  - Increasing resistance seen in pathogens of man and animals
  - It is not clear that antibiotic use in animals is increasing risk of human exposure to antibiotic resistant microorganisms
- Being responsible stewards of antimicrobials is in everyone's best interest

Summary

Veterinarians can help cattle producers discover and adopt production and marketing systems that favor animal health and reduce reliance on antibiotics

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Supported in part by grants from Zoetis

The Risk Project

Applying risk-based strategies to solve everyday problems in animal populations

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