The background features abstract, overlapping blue geometric shapes, primarily triangles and polygons, in various shades of blue, creating a modern and professional look.

K-State Olathe Animal Health Regulatory Affairs Data Quality (CRO perspective) March 6, 2018

Kelly F. Lechtenberg, DVM, PhD

Midwest Veterinary Services, Inc. - Oakland Nebraska

Veterinary and Biomedical Research Center - Manhattan, Kansas

Our Business

- ▶ Helping our customers evaluate
 - ▶ Safety and Efficacy of products for FDA/USDA/EPA approval
 - ▶ Determine appropriate models to provide clinically relevant data
 - ▶ Test model concepts in clinical (field) trials including multi-site studies

Critical Components for Research

- ▶ Knowledge and Commitment to meeting the needs of the animals and staff
- ▶ Knowledge of Commitment to understanding the advantages and limitation of models
- ▶ Knowledge and Commitment to Quality
- ▶ Knowledge and Commitment to Compliance
- ▶ Follow Through

Examples of Project Diversity

- ▶ Pharmacokinetic Studies
- ▶ Reproductive Safety Studies
- ▶ Target Animal Safety Studies
- ▶ Milk and Meat Residue Studies
- ▶ Tissue Toleration (injection site reaction)
- ▶ Pain Management – Model development for clinical applications

Cattle Disease Models

▶ Viral Diseases

- ✓ IBR
- ✓ BVD (type 1 and 2)
- ✓ BRSV
- ✓ PI3
- ✓ Rota virus
- ✓ Corona virus

Protozoal Diseases

Cryptosporidiosis

Coccidiosis

▶ Bacterial Diseases

- ✓ *M. hemolytica*
- ✓ *P. multocida*
- ✓ *H. somni*
- ✓ *M. bovis*
- ✓ *E. coli* O157:H7
- ✓ *F. necrophorum*

✓ *Foot Rot*

✓ *Liver Abscesses*

- ✓ *S. typhimurium*
- ✓ *Leptospira*

▶ *Mastitis Challenge*

- ✓ *Strep, Staph, Mycoplasma*

Swine Disease Models

► Viral Diseases

- ✓ Circovirus (PCV)
- ✓ PRRSV
- ✓ Swine Influenza (SIV)
- ✓ TGE
- ✓ PEDV

► Protozoal Diseases

Coccidiosis

► Bacterial Diseases

- ✓ *A. pleuropneumoniae*
- ✓ *M. hyopneumoniae*
- ✓ *H. parasuis*
- ✓ *S. suis*
- ✓ *B. bronchiseptica* (AR)
- ✓ *P. multocida* (AR)
- ✓ *E. coli* (4 + toxin)
- ✓ *L. intracellularis*
- ✓ *S. cholerasuis*

Poultry (Chicken) Models

▶ Viral Diseases

- ▶ IBDV
- ▶ Vector Viral Vaccines

Performance

Floor Pen studies for Food Safety Produces including competitive exclusion

▶ Bacterial Diseases

- ✓ *E. coli* O78
- ✓ *Salmonella*
- ✓ *Necrotic Enteritis*
- ✓ *Campylobacter*

Protozoal Disease

Coccidiosis - multiple strain challenge studies

Translational Models for Human Disease and Conditions

▶ Viral Diseases

- ▶ Influenza
- ▶ Vector Viral Vaccines

▶ Bacterial Diseases

- ✓ *STEC Enteritis*
- ✓ *Salmonella*
- ✓ *Campylobacter*
- ✓ *MRSA dermal model*
- ✓ *MSRA septicemia*

We deal with a high degree of diversity in our project mix - however - projects all have these needs in common

- ▶ Study Design to match regulatory need and applicable to use
- ▶ Data Capture to fulfill the intentions of the protocol
- ▶ Conduct the work in a fashion compliant to regulations
- ▶ Conduct the work in a fashion applicable to field use
- ▶ Conduct the work in a fashion that is repeatable

Fulfilling the Regulatory Needs

- ▶ Know and understand the requirements of work and the data necessary to support the work
- ▶ Raw/Source Data : Proper DCF Design is critical
 - ▶ Legible
 - ▶ Indelible (permanent)
 - ▶ Contemporaneous
 - ▶ Attributable

Fulfilling the Regulatory Needs

Part 11 Compliance

(Use of electronic equipment versus electron equipment for DC)

- ▶ Electronic Data Capture and Records
 - ▶ Increasingly common for companion animal projects and human medicine - however - for large animals.....
 - ▶ Legible (yes - if we can record in the climatic conditions)
 - ▶ Indelible (permanent)(yes)
 - ▶ Contemporaneous (yes - if all data “stores” as advertised)
 - ▶ Attributable (maybe - still work to do here)
 - ▶ User Safety (more risky?) = Liability of employee injury?
 - ▶ Special concerns (pK, sequential DCFs, cross check)

Encourage CRO to use certain standard “CRO Facility DCFs”

- ▶ Error Codes Listing
- ▶ Chain of Custody Documents
- ▶ Scale Check Logs
- ▶ Facility Diagram Formats
- ▶ Others as appropriate

ERROR CODE	DESCRIPTION
AR	Animal Removed or No longer part of data set
CE	Calculation Error
CF	Clarification
IE	Incorrect Error Code
LE	Late Entry
MD	Missing Data
NR	Not recorded at time of observation
RE (or EE)	Recorded in Error (or Entry Error)
RV	Re-evaluation (to change subjective data after further valuation)
SP	Misspelling
TE	Transcription Error
WO (OW)	Write-Over (or Over-Write)
WP	Wrong Place

SOP 7010 attachment

Midwest Veterinary Services, Inc.
1290 County Road M, Suite A
Oakland, NE 68045
Phone: (402) 685-6502 Fax: (402) 685-6008

Chain of Custody Form

Shipped From: Midwest Veterinary Services, Inc. 1290 County Road M, Suite A Oakland, NE 68045 Phone: 402-685-6502 Fax: 402-685-6008	Shipped To:
---	--------------------

Part 1: Sample Description

Sponsor:	Protocol Number:
Type of Samples:	
Number of Samples:	Date(s) of Collection:
Note: Samples are listed on the reverse. Please verify upon receipt.	

Part 2: Method of Shipment

Shipped by (Circle One): Fed Ex UPS USPS Other* Date: _____

* If "Other" list company or person Delivered by: _____

Condition of Shipment (Circle One): Ice Packs Dry Ice Ambient Other*

* If "Other" please describe: _____

Packaged by: _____; _____
(Print Name) (Signature)

Date: _____

Part 3: Recipient

Received by: _____
(Print Name) (Signature)

Representative of: _____ (Company/Lab) Date: _____

Condition received: Good Poor*

Comments (*If material arrives in poor condition, describe condition and actions taken)

Instructions to Recipient:

1. Upon receipt, please complete Part 3: Recipient & Part 4: Sample Accountability (See back side)
2. Please make copies of this form for your records and mail original to the "Shipped from" address within 24 hours of receipt.

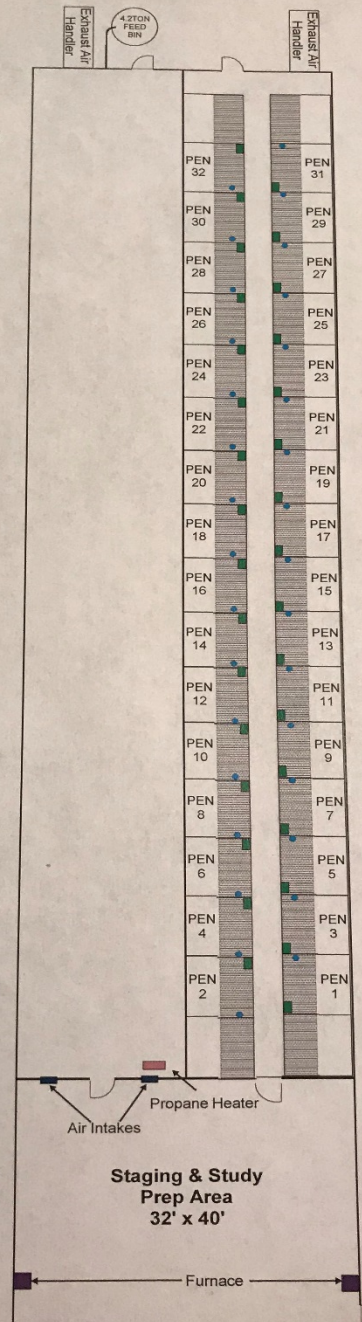
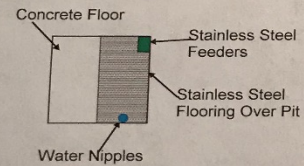
This facility is 180' x 40', consisting of 2 rooms, 148' x 20' each. It has 6" thick concrete exterior and center walls to the ceiling. The pens are 94" x 94", with 6'6" high x 2" thick PVC divider panels. Pen fronts are gate panels.



Facility Diagram Color Code Designates:

- Propane Heater
- Air Inlets
- 4' Wide Expanded Metal Over Pit
- Furnace
- Overhead Door
- Water Nipples
- Stainless Steel Feeders

Example Pen:



Data Capture Forms should be designed for “DATA CAPTURE”

- ▶ Designed for the “user”, not - for the convenience of “data entry”. Data entry personnel are seldom kicked, trampled or risk lightning strike doing their job.
- ▶ Investigator is responsible for appropriate data capture
- ▶ DCF design should be completed after the protocol
- ▶ Protocols should explicitly permit DCF improvements
- ▶ “Example” DCFs may be part of the protocol
- ▶ KISS philosophy: Limit types of data on any particular DCF

Data Capture Forms should be designed for efficient “DATA CAPTURE”

- ▶ Facility Practices and Study Design Varies
- ▶ Environmental Conditions (weather) varies
- ▶ Safety of working environment varies
- ▶ Biosecurity needs are variable
- ▶ Sequential data capture with multiple users may or may not be appropriate
- ▶ Should provide for the ability to cross check in real time to avoid missing data (contemporaneous) (blinding)

Quantity ≠ Quality

- ▶ Do not collect data that you do not intend to utilize/analyze
- ▶ Conducting “animal by animal” physical examinations to include respiratory rate, heart rate, mucus membrane characteristics, etc. may be biologically relevant for some work - but.....
- ▶ But if we need to know that animals are “clinically normal”, how can we justify the stress on the animal collecting data that is not critical
 - ▶ Increased the likelihood of injury
 - ▶ Increases stress
 - ▶ Fills files with information that will not be analyzed
 - ▶ Focus on “what matters”

A photograph of a large herd of black and white cattle in a dry, brown field. In the foreground, the back of a brown horse's head and its ears are visible, looking towards the cattle. The text is overlaid on the image.

Clinical Signs of BRD:

“What Matters Clinically??”

Depression, Dyspnea, Weakness ?
RR, HR, PCV, CRT, Mucus membrane color ?

Errors Happen

- ▶ Develop and use error codes
- ▶ Error Code list should be adequately concise, yet “memorable”
- ▶ Insist on using your own error codes
- ▶ If using EDC, request to insert your own codes
- ▶ Train your QC units to use a common assessment technique

Study Design Should Allow Good Animal Care Practices to Prevail

- ▶ Allow and document therapeutic intervention as required/recommended by attending veterinarian
- ▶ Provide for the reality that the unforeseen “things” can happen
- ▶ Inversely proportional to planning/preparedness (If we plan for the worst, it seems unlikely to happen)

Allow all indicators of health and well being to participate in drug evaluation

- ▶ As we strive for objective measurements of health, it is continually obvious that few indicators of health and well being are more sensitive than:
 - ▶ Positive body weight gain in young animals
 - ▶ Maintaining body weight in mature animals
- ▶ Body weight is a continuous variable that can be biased by eating and voiding patterns in ruminants. Recognize and plan for this reality. The average of two consecutive weights is better than one.

Allow study designs that are optimized by the use of proven and efficacious animal health products

- ▶ Blanket statements that categorically prohibit the use of animal health products with the belief that any concurrent use might bias study data:
- ▶ May be true and often is true, however;
 - ▶ Bias is not necessarily a “bad thing”
 - ▶ It is possible to introduce an “effect” that
 - ▶ Will enhance the quality of the data provided to regulatory services
 - ▶ Be more applicable to end users of the data
 - ▶ Allow benefits to animal care and health
 - ▶ Be consistent with eventual use in the field

Allow study designs that are optimized by the use of proven and efficacious animal health products – Examples for consideration

- ▶ Use of approved products to limit confounding/concurrent clinical disease or gross/histologic pathology
- ▶ Ionophores in ruminants to limit and stabilize the effects of coccidia
- ▶ Beta lactam antimicrobials in the face of Mycoplasma challenge or natural diseases in cattle, swine and poultry

Mycoplasma bovis

(One example)

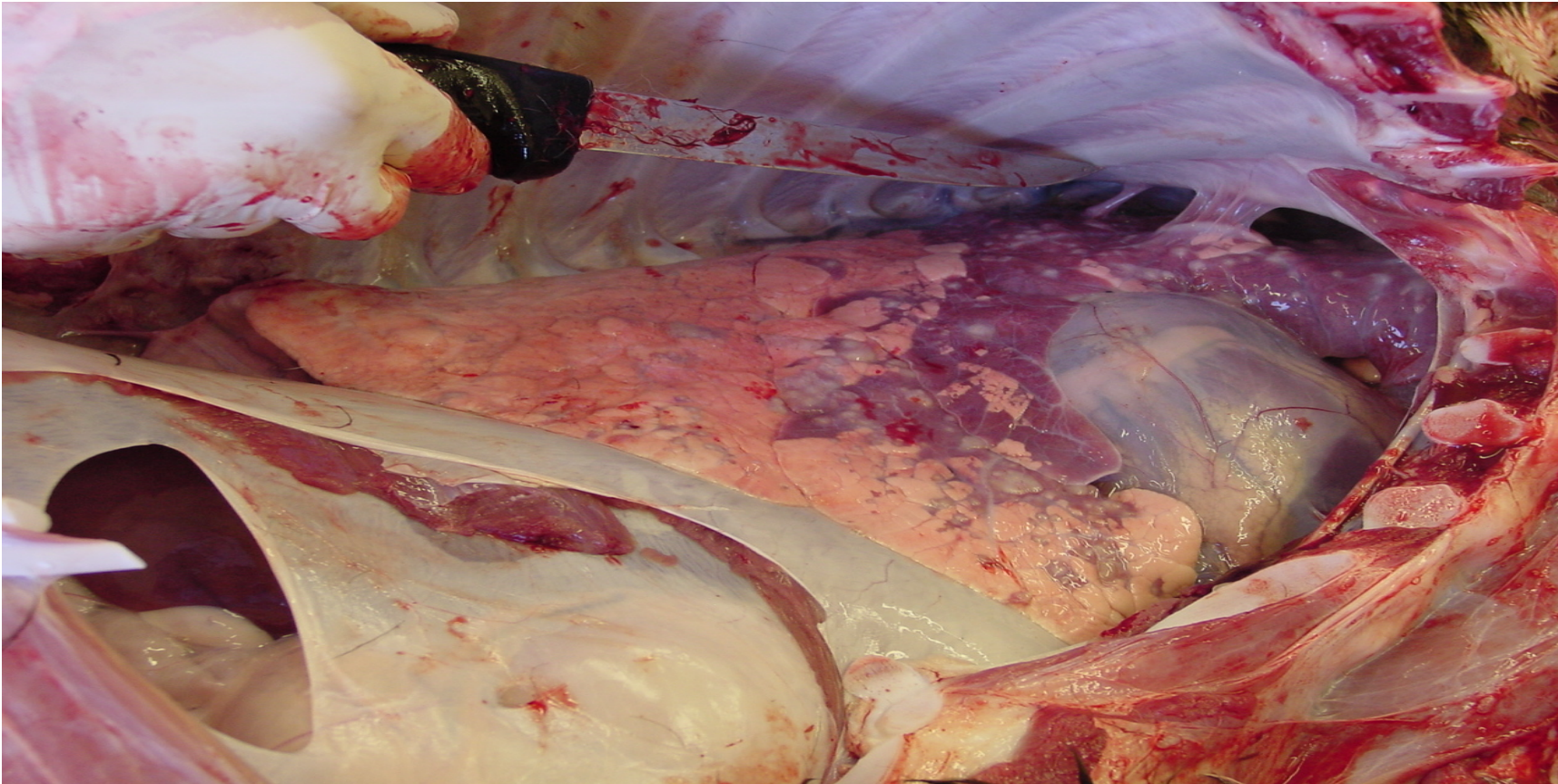
Regulatory Pathway

- ▶ Must show significant difference in lung pathology between vaccinated and non-vaccinated
- ▶ Must begin with susceptible calves
- ▶ Challenge models involved

Intended (Applied) Use

- ▶ Beta lactam use on arrival does affect this bacterial infection
- ▶ Progressive and aggressive
- ▶ Afebrile infection- consider this when developing a program that involves “respirator observe management”

Mycoplasma bovis pneumonic lesions



Mycoplasma bovis (BBs)
pneumonic fibro-granulomatous lesions

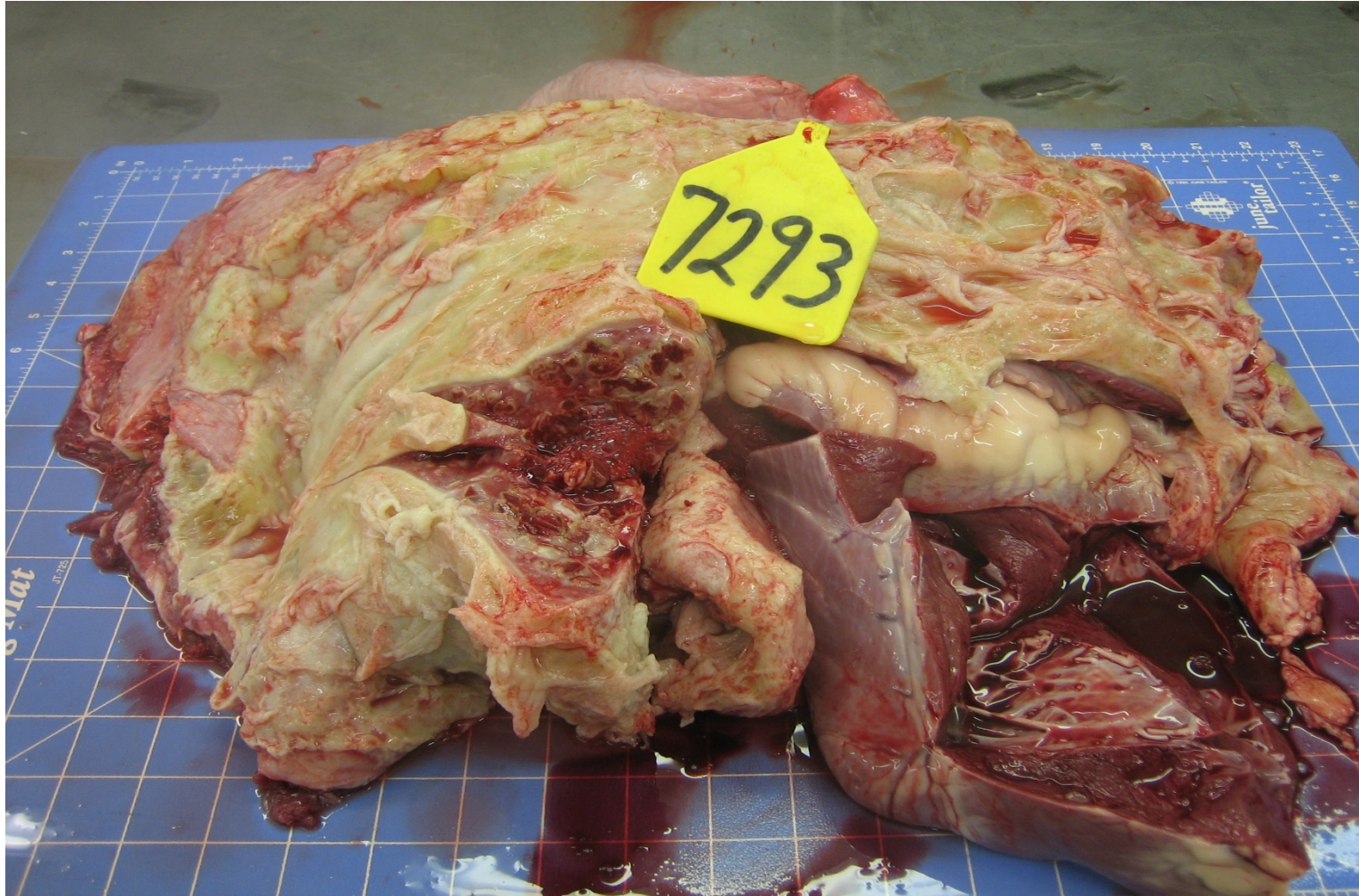


Mycoplasma bovis arthritis

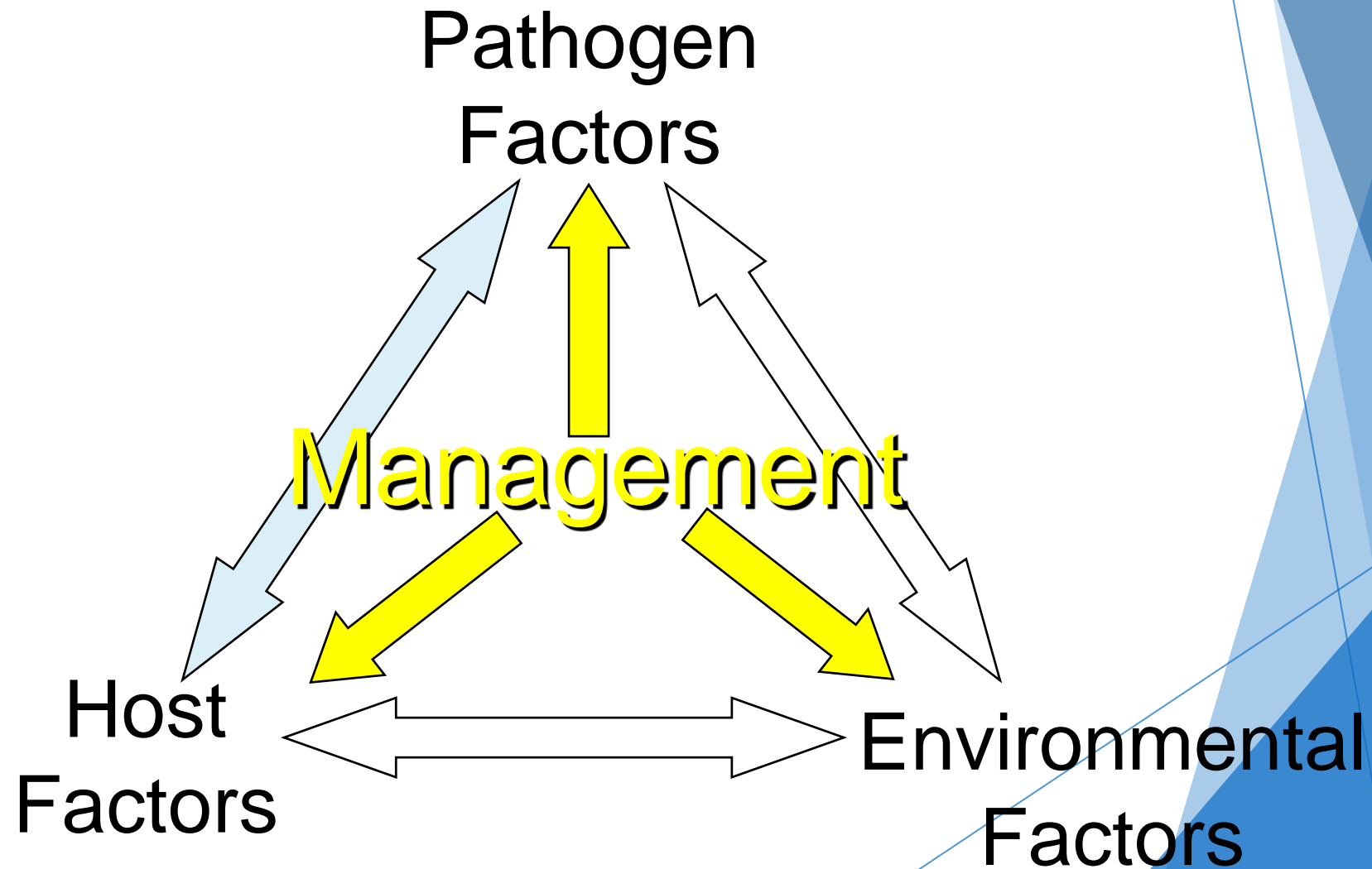


Histophilus somni Challenge

This organism can also be a naturally occurring cofounder that is preventable.



The Disease Triad



Approval Process versus Field Use

Regulatory Pathway

- ▶ United States Department of Agriculture
- ▶ Food and Drug Administration (Center for Veterinary Medicine)
- ▶ Environmental Protection Agency

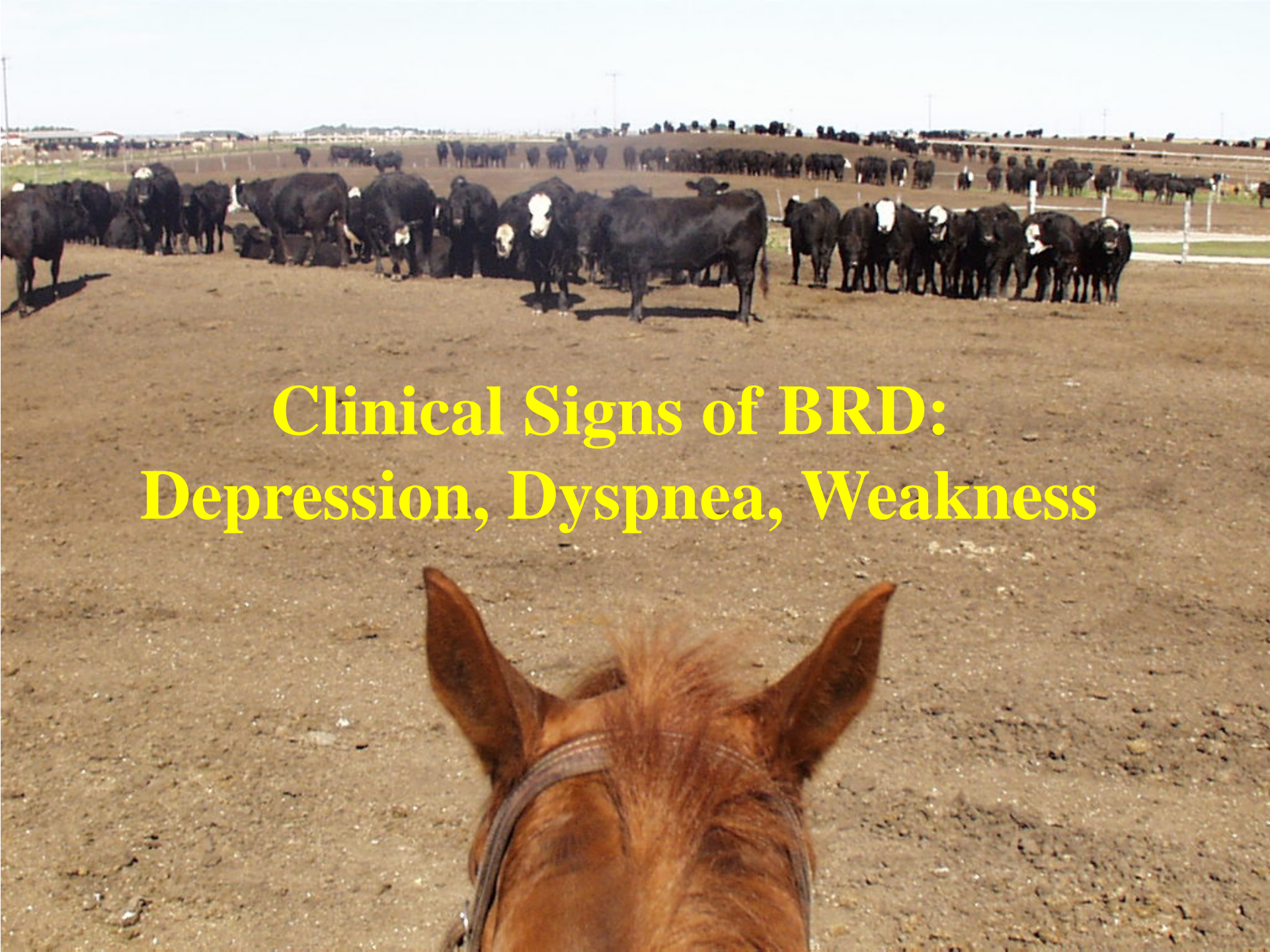


Intended (Applied) Use

- ▶ Individual animal level in backyard or very small production units.
- ▶ Single family farms (conventional or organic)
- ▶ Large commercial livestock operations
- ▶ Corporate owned livestock operations



How do we bridge the gap between approval work and the application of the evaluation and implementation of the interventions in the field?



Clinical Signs of BRD: Depression, Dyspnea, Weakness

Infectious Bovine Rhinotracheitis (IBR)

- ▶ Acute, contagious respiratory disease
- ▶ Caused by Bovine Herpesvirus Type 1 (BHV-1)
- ▶ Can quickly spread
- ▶ Signs:
 - ▶ Fever, Salivation, Rhinitis, Conjunctivitis, Nasal discharge/inflammation/lesions
 - ▶ Primary or secondary pneumonia



Infectious Bovine Rhinotracheitis (IBR)

Regulatory Pathway

- ▶ 25 IBR-susceptible animals
 - ▶ 20 Vaccinates and 5 Controls
- ▶ Serum collected at least once between 14-28 days post-vaccination
- ▶ Challenge and follow for 14 consecutive days
- ▶ If 4/5 of controls do not show signs of IBR, test is inconclusive
- ▶ If more than 1 vaccinate has temp >103.5 for more than 2 days, or if >1 vaccinates shows signs of IBR, virus is unsatisfactory

Intended (Applied) Use

- ▶ If we had vaccines perform this well in the field = 😊
- ▶ We don't vaccinate sero-stable groups
- ▶ We don't acclimate and optimize environment, nutrition, exposure
- ▶ We don't have a common exposure dose or date
- ▶ Other factors of the disease triad

Infectious Bovine Rhinotracheitis (IBR) Following Cooper Strain Challenge

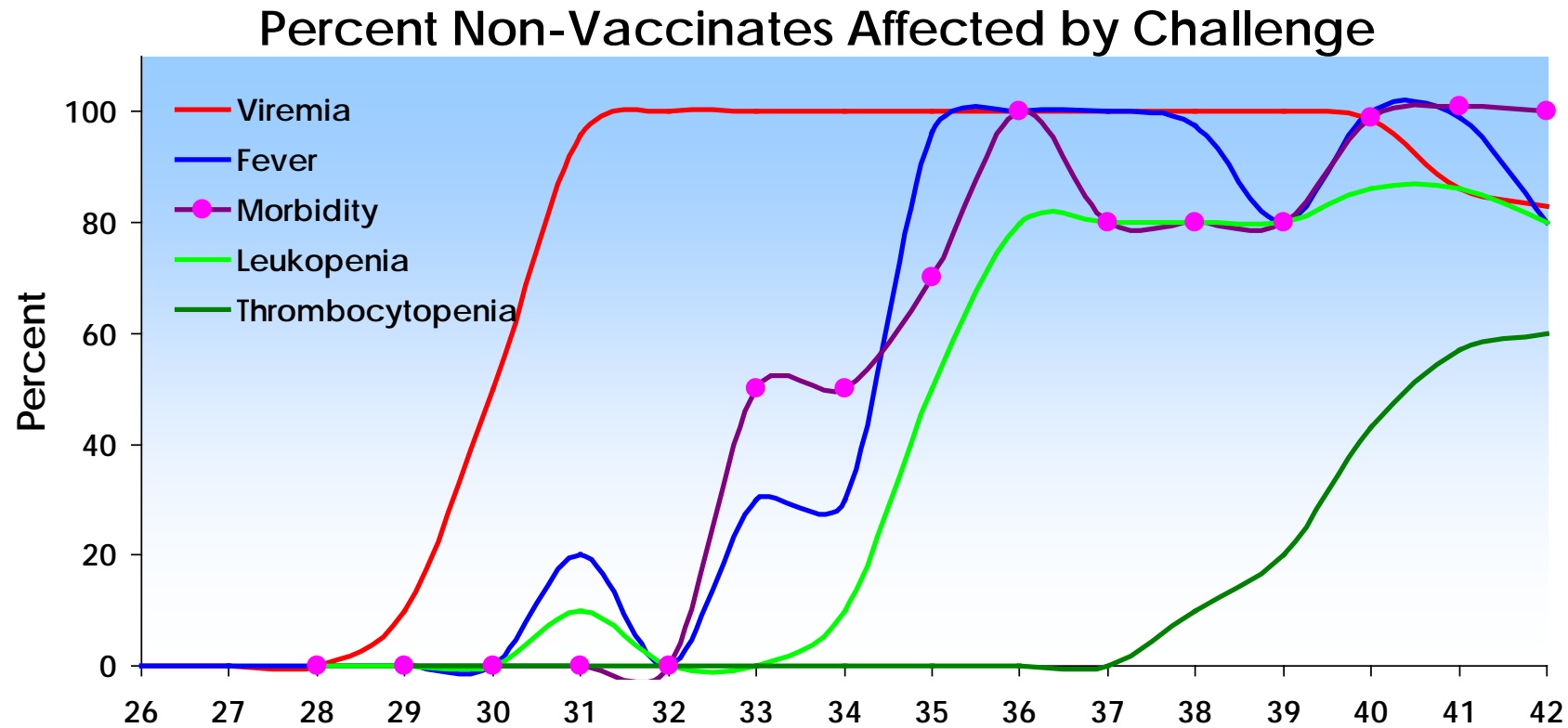
- ▶ Fever
 - ▶ Rectal temperatures hit 105° F to 108° F
 - ▶ Beginning 3 or 4 days and continuing through 8 to 10 days post challenge
 - ▶ Not associated with excessive depression
- ▶ Clinical Signs
 - ▶ Serous Nasal Discharge progressing to yellow mucoid with secondary bacteria
 - ▶ Elevated Respiratory Rate
 - ▶ Mild Depression unless complicated with bacterial pneumonia
 - ▶ Serous Ocular Discharge
 - ▶ “Pulls”, but not terribly sick, unless secondary bacterial involvement

Outcome variables are much different,
depending upon the pathogen(s) involved
DCF Design must recognize this reality

- ▶ BVD: Lab data is critical
- ▶ IBR: Rectal temperature and clinical assessment
- ▶ BRSV and PI-3: viral shedding
- ▶ Mycoplasma: Its all about lung lesion
- ▶ Streptococcus suis: Bacterial isolation and mortality
- ▶ Many other examples

BVDV-2 Efficacy Study

MCL 0308 (challenged on D 28)



Q: How do we bridge the gap between approval work and the application of the evaluation and implementation of the interventions in the field?

A: Appropriately Designed, Accurately Completed and Quality Verified Data Capture Systems are a large part of the bridge.

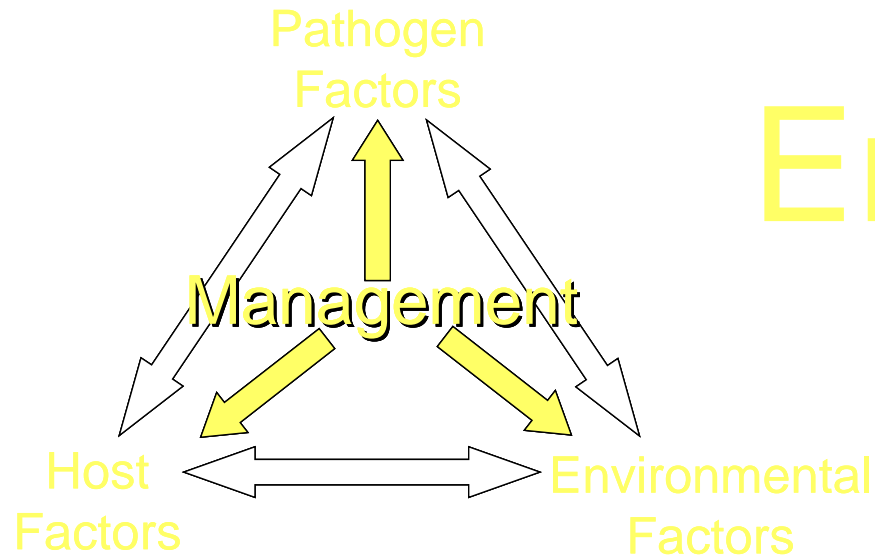
Summary

We are all in this together!

- ▶ Corporate Sponsors (with responsibility to shareholders)
- ▶ CROs (with responsibility to animals and staff in our care)
- ▶ Regulators (with responsibility to consumers)
- ▶ Academicians/educators (with responsibility to educate and mentor – to provide professionals for all of the above sectors)
- ▶ Quality/Compliance Professionals (with responsibility to components of all of the above)
- ▶ We all need to strive to help each other understand the needs and responsibilities

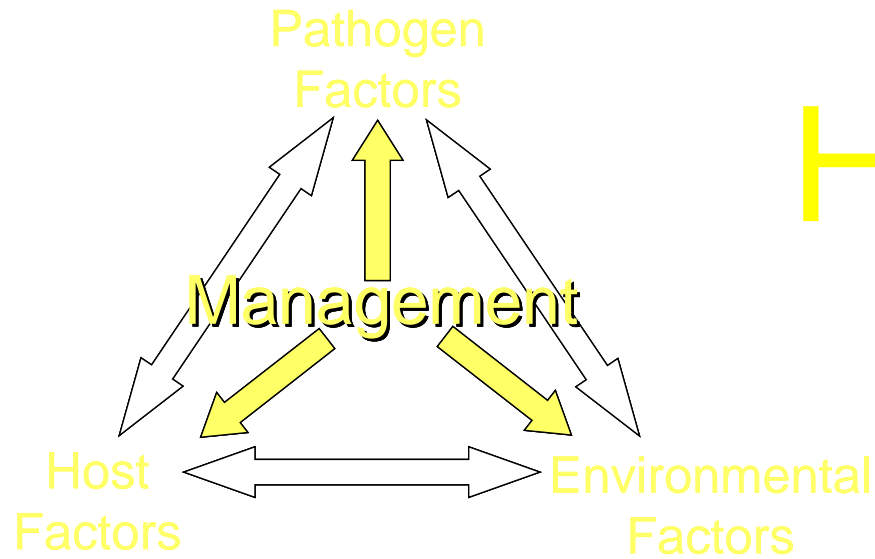
Thank you K-State Olathe for making this interaction possible

- ▶ Dr. Ralph Richardson
- ▶ Dr. Paul Cassidy
- ▶ Angelica Buzard
- ▶ All Meeting Participants



Environmental Factors

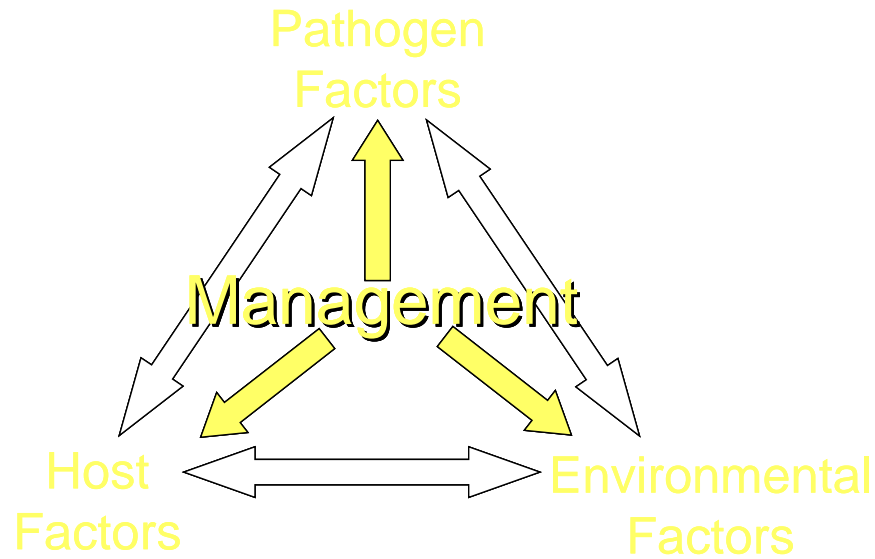
- Sanitation – mud, dust
- Contact pattern – continuous vs. AI/AO
- Animal density
- Animal movement between groups
- Group size
- Social stress



Host / Animal Factors

- Age
 - Innate resistance
 - Immune status
 - Nutritional status
 - Genetics / Heterosis
- Herd Immunity
 - Likelihood of effective contact

Pathogen Factors



- Dose
- Reservoir
- Environmental hardiness
- Contagiousness
- Infectivity
- Virulence

+/- Influence

No Influence