Beef Session

Bovine respiratory disease modeling: Advantages, limitations, and considerations

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Abstract

The bovine respiratory disease (BRD) complex involves the classic components of the disease triad: host factors, pathogen factors, and environmental factors. The multiple components included in each of these categories have the potential to overwhelm the immune system of cattle and become recognized as "the cause" of the disease. However, it is the net effect of multiple factors that comprise a final result that we recognize as "disease" (BRD). This presentation discusses how these interrelated factors can be managed in the development of disease models to assess the efficacy of product. Mitigating or managing the sources of animal-to-animal variation creates more robust and dependable models, but also creates populations that may be different than the population for which we are evaluating an intervention.

Key words: BRD, respiratory disease, pneumonia, modeling

Résumé

Le complexe respiratoire bovin (CRB) implique les composantes classiques de la triade de la maladie : les facteurs reliés à l'hôte, les facteurs reliés au pathogène et les facteurs reliés à l'environnement. Les composantes multiples qui sont incluses dans chacune de ces catégories ont le potentiel de l'emporter sur le système immunitaire des bovins et de devenir reconnues comme étant 'la cause' de la maladie. Toutefois, c'est l'effet net des multiples facteurs qui englobent le résultat final que l'on reconnait comme la 'maladie' (le CRB). Cette présentation abordera comment ces facteurs inter-reliés peuvent être gérés dans le développement de modèles de maladie pour évaluer l'efficacité du produit. Minimiser ou gérer les sources de variation d'un animal à l'autre génère des modèles plus robustes et plus fiables mais peut aussi créer des populations qui peuvent être différentes de la population que nous sommes en train d'évaluer pour une intervention.

BRD Disease Modeling

Disease models have been instrumental in bringing new products to assist cattlemen for years. Recently, many of the same models have been used to help leverage the technology to increase the efficiency of cattle health management. To name just a few, work is being conducted to validate systems that:

1. Help animal care staff identify sick cattle by the use of temperature sensors, mobility tracers, body position trackers, and infra-thermography.
2. Help increase the accuracy of diagnostic efforts by augmenting clinical assessment with computer-aided thoracic stethoscopes, real-time CBC data, chute-side PCR and pulse oximetry.
3. Help increase the efficiency and accuracy of drug and animal tracking by having an animal's medical data follow them for life.

Despite the efforts, BRD remains our most important and expensive disease challenge that we recognize in the beef cattle industry. The ongoing struggle against BRD and other infectious disease complexes will be supported by disease models that are designed to provide for the most humane care possible that allows us to study an infectious disease in the host animal. Such designs should use the least number of animals possible by providing definitive outcomes in populations of animals relevant to intended use of the products being developed.

BRD complex, by definition is a multi-factorial disease. Large numbers of variable factors create obstacles in the determination of best practices or best products. In order to minimize variability and conduct scientific evaluations that are manageable, we strive to control as many variables as possible.

Product efficacy statements on the labels of vaccines and antimicrobials are generally specific to the organisms for which a product has proven efficacy. The study designs and expectations differ between products approved by the USDA and the FDA-CVM; however, the guiding principles are the same. For companies to promote a product for use against a specific pathogen they must present data from randomized, blinded, controlled studies to the regulatory services for assessment. Such products must also be shown to be safe to the animals and to the people that consume food produced from these animals.

Challenge studies play an important part in the pathway for development of many of these products. Reliable and repeatable challenge models are important for early proof of concept work, dose ranging studies, pK in sick animal studies, and may even serve as the definitive efficacy data

package for certain diseases that occur too sporadically to effectively model in a field study that relies on naturally occurring disease.

Advantages

The advantages of experimental modeling are numerous. The most significant include:

1. The ability to manage seasonality. BRD is generally considered to be most significant in the fall and winter of northern hemisphere countries. Modeling allows us to work year around with repeatability.
2. Modeling allows scheduling convenience for staff and cooperating third party laboratories. A project protocol that requires post-challenge sample collection can be initiated on a Monday and allow seamless workflow.
3. Environmental effects can be controlled. If a model requires elevated environmental temperature or specific humidity levels to be controlled, that is possible.
4. Confounding (potentially) factors can be mitigated by using similar age, weight, genetics, and gender animals that have been acclimated together and housed in identical conditions.
5. The scheduling of time between arrival and vaccination, vaccination and challenge, challenge and final assessment can all be optimized to give a product the best opportunity to demonstrate efficacy.

Limitations

Experimental models certainly have limitations.

1. Models are often conducted in facilities, in cattle, or in the absence of other disease pressures that don't align very well with intended field use conditions.
2. Models often yield data that demonstrate a greater magnitude of response than field experience ultimately observes. This can be due to differences in case definition, the removal of confounding factors or cattle type, as well as several other causes.
3. Models often provide data in a class of animal that may not be relevant to your client's operations. For example, data generated in colostrum-deprived Holstein steer calves raised in a BSL-2 environment, may or may not be meaningful to your group of high-risk 400 lb (180 kg) feedlot calves.

Considerations

The advantages and limitations are reason for your complete understanding of the work, its careful consideration and interpretation. Ask yourself the following questions.

1. Understand precisely how with data was generated. It matters!

2. How is this model similar or different from my client's situation?
3. How applicable is the data provided?
4. What additional data do I need (if any) to make a decision to initiate a new product use or replace an existing use?

I show a few slides of cattle in Bio-Safety Level 2 containment and dairy cows in a clean conventional milk parlor. The cows pictured in containment are not Holstein cows, although we conduct mastitis/lactation studies in containment. Depending upon the parameter of interest, the cows in BSL-2 may provide data that is very applicable if the parameters are directly related to a mastitis challenge (somatic cell count or California Mastitis Test), but not at all applicable to other production measurements due to loss of milk yield.

Housing Considerations

The discussion is primarily focused on the pathogen factors; however, in managing confounding effects, it is important to be aware of possible effectors, so that they may equalized across treatment groups. If cold weather is expected during a study, protection from the wind and bedding should be equally available to all animals to help avoid bias. Shades and sprinklers should be equally available to all cattle in cases of excessive heat index. Likewise, nutritional and physiologic status across treatment groups should be managed to be as similar as possible. Factors such as animal age, colostral consumption, previous disease exposure, and maternal antibody levels in your calves may be important factors to consider when randomizing animals to treatment group. In many study designs, pre-study screening is conducted to assure that all animals are not persistently infected with bovine viral diarrhea virus.

Housing plans require careful consideration to balance the biologic needs of the study design with the statistical comparisons plan. For example, "pen" is the most appropriate experimental unit for a live vaccine study in which the vaccine may shed between animals, whereas "the calf" is the logical experimental unit for an implant comparison where implanted and non-implanted animals are allowed to graze the same pasture at that same time. It is also common to adjust the housing plan for cattle at predetermined times. In the case of the viral vaccine example above, it would be appropriate to commingle all cattle into a single pen immediately prior to challenge to avoid the bias resulting when some of the non-vaccinated cattle start to become ill following challenge.

Appropriate housing decisions can be made only after the protocol, the test articles and primary parameters are clearly understood so that the biology of the product, and the random assignment of cattle to treatment to improve blinding of data collection procedures can all be optimized.

I have included several slides of cattle in research facility environments. These include:

1. A bed-pack barn in which 200 to 250 head cattle reside together in close quarters. This penning design

would work well for non-shedding vaccine work or any individual animal treatment, like an implant for which the assessment can be made independently for each animal (ex. body weight).

2. A free-stall dairy barn in which naturally occurring disease monitoring or individual animal monitoring can be conducted (ex. somatic cell count).

3. Small (10-head) pens can be used for disease or performance work where the pen must be the experimental unit. Projects that assess feed intake and conversion are good examples of utility of these pens.

4. The group of calves in BSL-2 containment can be group-housed during the challenge phase of a vaccine efficacy study.

5. Individual calf pens are useful if animal-to-animal contact or cross-contamination needs to be controlled. Salmonella and other enteric pathogen challenge studies use these housing designs.

Two Tenets of Data Assessment

It is important to keep these 2 tenets of good science in mind before you start to look at data. If you can't answer "yes" to these 2 questions, be skeptical about the results.

1. Was the population of animals in the study randomized properly?

2. Was the study blind (masked)?

Randomization methodology depends on the questions that you are trying to answer, so there is no single formula for all work. Think about what matters most in the generation of the data you care about, as that will guide your thought process of which factors to give the highest priority in randomization. A few examples for which you might like to control are:

1. Age
2. Body weight
3. Colostral intake status
4. Somatic Cell Count

5. Serologic titer
6. Genetics (breed/sire/dam)
7. Parity

Decide what parameters you will assess. For BRD, case definition is critical and often explains the difference between research trial data and field experience. I have included an example of a clinical illness assessment system that we use for BRD (Table 1).

Here is an example of how one might use clinical definitions to arrive at treatment decisions.

Calves that show signs of clinical BRD may be pulled and examined to determine if treatment is necessary. Calves with a CIS of 1 accompanied by rectal temperature > 104.0°F (40°C) will be treated. Calves with a CIS ≥ 2, regardless of rectal temperature, will be eligible to receive treatment. There will be an approximate 7-day moratorium after the first treatment with tulathromycin, and an approximate 3-day moratorium after the second treatment.

This example demonstrates how and when treatment regimens are activated. As you might envision, a product being evaluated under a slightly different set of rules, could provide different results.

Infectious Bovine Rhinotracheitis (BHV-1)

I have included several slides of the pathology that we commonly see following a BHV-1 challenge. Briefly:

1. Cattle are febrile and develop rectal temperatures between 105.0°F and 108.0°F (40.5°C and 42.2°C) beginning 3 to 4 days following intranasal challenge.

2. Depression is milder than you might expect with the fever and is mild to moderate.

3. Serous nasal discharge is common by day 3 and progresses to mucoid and purulent with secondary bacterial infection later in the disease process.

4. Elevated respiratory rate is common, often over 30/minute.

5. Serous ocular discharge is common.

Table 1. Clinical illness score categories.

CIS	Severity	Observed behavior
0	Normal	Bright, alert, responsive. No abnormal clinical signs.
1	Mildly depressed	May stand isolated with head down, ears drooping, but responsive to stimulation. May have mild dyspnea with gauntness and nasal/ocular discharges.
2	Moderately depressed	May remain recumbent or stand isolated with head down, depression obvious when stimulated. May stumble if forced to trot. Noticeable dyspnea with gauntness and nasal/ocular discharges.
3	Severely depressed	May be recumbent and reluctant to rise or, if standing, is isolated and reluctant to move. When moving, ataxia, knuckling or swaying evident. Unable to stand, approaching death. Head carried low with ears drooping. Eyes dull, possible excess salivation/lacrimation. Pronounced dyspnea and gauntness. Mouth breathing. Nasal and ocular discharges.
4	Moribund	Euthanize

Influenza Type D

1. Cattle are febrile and develop rectal temperatures between 103.0°F and 105.0°F (39.4°C and 40.5°C) beginning 3 to 4 days following intranasal challenge and continuing through days 6-8.
2. Depression is present, but minimal.
3. Infection looks like influenza of pigs and dogs inasmuch as you will see
4. Serous nasal discharge is common by day 3 that is self-limiting.
5. Elevated respiratory rate is common, but not as severe as IBR.
6. Serous ocular discharge, but uncommonly.
7. Necropsy findings include:
   a. Mildly inflamed nares
   b. Swollen/edematous vocal folds
   c. Viscous exudate in the trachea (yellow/brown)
   d. Diffuse "flu-like" pattern of lung consolidation (diaphragmatic lobe)
   e. Swollen tracheal bronchial lymph nodes

Mannheimia haemolytica

1. Rectal temperature ranges between 103.0°F and 106.0°F (39.4°C and 41.1°C) beginning 1 to 2 days following challenge.
2. Depression can be severe initially, related to endotoxemia, then moderates until day 4-5, and then can become pronounced.
3. Labored respiration
4. Cough (wet/deep)
5. Necropsy findings include:
   a. Fibrinous pleuropneumonia – anterior ventral
   b. Acute phase often has excessive pleural effusion
   c. Excessive fibrinous reaction
   d. Fibrin plug associated with pneumonia
   e. Fibrinous tags begin by day 4
   f. Abscessation by day 5
   g. Swollen tracheobronchial lymph nodes
   h. Trachea and upper tract may be normal

Pasteurella multocida

1. Rectal temperatures ranges between 103.0°F and 104.0°F (39.4°C and 40°C) beginning 1 to 2 days following challenge.
2. Depression can be severe initially, related to endotoxemia, then moderates until day 4-5, and then can become pronounced.
3. Labored respiration
4. Cough (wet/deep)
5. Necropsy findings include:
   a. Consolidative pneumonia that is progressive from ventral to dorsal

b. Fibrin plug associated with pneumonia
c. Yellow abscesses present by day 7
d. Swollen tracheobronchial lymph nodes
e. Trachea and upper tract may be normal

Histophilus somni

1. Fever with temperatures ranging between 105.0°F and 108.0°F (40.5°C and 42.2°C) beginning 1 to 2 days following challenge.
2. Depression can be severe initially, related to endotoxemia, then moderates until day 4-5, and then can become pronounced.
3. Labored respiration
4. Cough (wet/deep)
5. Necropsy findings include:
   a. Fibrinous pleuropneumonia – anterior ventral – often very dark.
   b. Acute phase often associated with excessive pleural effusion
   c. Excessive fibrinous reaction
   d. Fibrin plug associated with pneumonia
   e. Dark abscesses present by day 5
   f. Swollen tracheobronchial lymph nodes
   g. Upper tract may be normal
   h. Check heart muscle and joint for lesions and isolation

Mycoplasma bovis

1. Mild fever of less than 104.0°F (40°C) beginning 5-10 days following challenge
2. Mild depression unless complicated by confounding infection.
3. Increased respiratory rate
4. Necropsy findings include:
   a. Fibrogranuloma lesions (BBs)
   b. Dark red consolidation
   c. Swollen joint and tendon sheath if lame

Summary

BRD disease modeling is an important part of further understanding the interaction between the numerous factors that result in BRD. As we continue to seek understanding of the BRD complex, reproducible test systems will remain an important part of that quest.

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