NC1192 Station Annual Report (2021)

NC1192, "An integrated approach to the control of bovine respiratory disease"

Submitted by: Dr. Sharif Aly, BVSc, MPVM, PhD

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Participating Experiment Stations (Report submitted):

AL	Auburn University
CA	University of California Davis
CO	Colorado
GA	University of Georgia
KS	Kansas State University
MS	Mississippi State University
TN	University of Tennessee
TX	Texas A&M University
WA	Washington State University

Participants of Annual Meeting:

Sharif Aly, Laurel Gershwin, Terry Lehenbauer (University of California Davis); Catie Cramer (Colorado State University); Natalia Cernicchiaro, Brad White (Kansas State University); Manuel Chamorro(Auburn University); Chris Chase (South Dakota State University); Grant Dewell (Iowa State University); Matthew Scott, Sarah Capik (Texas A&M University); Christine Navarre (Louisiana State University); Holly Neibergs (Washinton State University); Roberto Palomares (University of Georgia); Leisel Schneider (University of Tennessee); Amelia Woolums (Mississippi State University).

Invited talks/presentations: George Smith (Michigan State University, NIMSS representative), Timothy Sullivan (USDA NIFA update)

Brief summary of minutes of annual meeting

- Annual meeting was on August 24, 2021 via Zoom due to restrictions associated with COVID-19. Dr. Aly welcomed and lead introduction of experiment station members and their station reports.
- Updates related to the renewed NC1192 project starting in 2021 by group members and Dr. George Smith, and related to USDA NIFA by Dr. Timothy Sullivan were followed by station reports.
- Discussion around new projects and collaborations between teams across both beef and dairy cattle
- Annual report requirements were discussed with emphasis that members should focus their annual reporting on ongoing integrative and collaborative research/programs on BRD between states/participants in NC-1192, and any kind of interaction between members.
- Membership updates included Aly assigned as Chair and Schneider assigned as Secretary

Accomplishments, impact and deliverables focused on the NC1192 project's objectives

Nine stations sent reports for 2021 activities (list of participating stations are on NIMSS website).

I. Accomplishments –

Objective 1: *To elucidate pathways by which host characteristics, pathogen virulence mechanisms, and environmental impacts interact to produce BRD, and to develop strategies to mitigate detrimental factors and enhance protective mechanisms.*

1. Pathogen profiles and loci associated with enhanced resistance to BRD in 1000 pre-weaned calves in Wisconsin.

   A USDA-NIFA funded proposal was initiated to identify pathogen profiles and loci associated with enhanced resistance to BRD in 1000 pre-weaned calves in Wisconsin. A second site in Wisconsin was investigated but didn't work out due to personnel issues. A third dairy site has been initiated but sampling is yet to begin there. Bacteriology and virology will be used to identify pathogen profiles from mid-nasal and deep pharyngeal swabs and Illumina BovineHD BeadChips will be used for genotyping. Genome-wide association results will be compared with previous results in pre-weaned dairy calves in California and New Mexico. Analysis was also completed on previous samples taken on beef and dairy cattle affected with bovine corona virus in conjunction with and without BRD to further define its role in the pathogenesis of BRD. Disseminated research results on the role of corona virus in BRD.
   Participants: WSU, Texas A&M University, University of Missouri, University of Wisconsin (PD Seabury, Co-PD: Neibergs)

2. Digital gene expression profiling for bovine respiratory disease prediction model development in high-risk beef cattle populations.

   Selectively analyzed 56 mRNA molecules from randomly selected at-arrival whole blood samples of beef cattle across seven independent high-risk populations. This work employed the use of NanoString digital gene expression profiling, aimed at validating previously identified DEGs and developing a novel classification model for at-arrival BRD prediction. Additionally, this study further associates mRNA expression related to host inflammatory and leukocyte-associated mechanisms, clinical BRD treatment frequency, and production records. The increased expression of genes associated with anti-inflammatory processes, immune function, and antimicrobial peptide production were increased in cattle never requiring treatment for BRD. Cattle requiring clinical therapy BRD possessed increased expression of pro-inflammatory, and type I interferon-associated mRNA. An increase in treatment frequency, associated as a more severe course of BRD, resulted in significant decreases in weight gain. An at-arrival decision tree model developed from gene expression cutoffs of six mRNA molecules resulted in the ability to classify cattle which would become severely diseased (treated for clinical BRD twice or more and/or die) with 90% classificational accuracy.
   Participants: MS (Amelia Woolums, Brandi Karisch), TX (Matthew Scott)

Objective 2: *To develop and validate methodologies for accurate BRD diagnosis, objective risk assessment, and surveillance to detect new trends in BRD occurrence.*

1. *Developing mechanistic models for BRD.*
   Stochastic models can be an effective way to explore the best strategies to implement on-farm changes, particularly to find a balance between reducing infection duration at pen scale and the amount of antimicrobials required to do so during fattening. A first stochastic mechanistic model was designed to represent fattening pens in French farms, accounting for the variability of host response to infection and made it possible to compare two strategies (collective treatment and early detection based on temperature sensors) with a reference scenario reflecting classical French veterinary recommendations (individual treatment of diseased animals based on the visual appraisal of clinical signs, followed 12 hours later by manual temperature measurement). Yet, this model targeted typical European farms with extremely small pen size (10 animals). To increase the robustness of the underlying assumptions and the confidence in the outcomes, the model was adapted to also account for typical US farms which involve larger pens (100 animals). Initial conditions of the new model were calibrated based on the lethality and morbidity distributions found in US farms. The US low-risk scenario is close to the reference EU scenario in terms of disease duration and number of antimicrobial doses at pen scale, but with a much smaller variability in simulation outcomes and with much higher pen size, which denotes a better efficacy per animal and questions the supposed parsimony of European fattening systems. On the contrary, the US high-risk scenario leads to long cumulate disease durations and a very high total number of doses (including initial treatment), suggesting to further investigate the benefits of implementing contrasted detection strategies (such as early BRD detection) according to the specific risk levels induced by batch composition (Picault et al., 2020).
   Participants: White B, Amrine D: Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, Kansas, 66506, USA.
   Picault S, Ezanno P, Assié S: BIOEPAR, INRA, Oniris, CS 40706, 44307, Nantes, France.

2. Clinical status and endoscopy of the upper respiratory tract of dairy calves infected with Bovine viral diarrhea virus 2 and Bovine herpes virus 1 after vaccination and trace minerals injection.

   Researchers developed a respiratory endoscopic score (ES) for evaluation of the upper respiratory tract in dairy calves vaccinated and infected with BVDV and BHV1. Endoscopic evaluation of the calves' URT showed: 1. differences in the appearance of the respiratory mucosa before and after BVDV2 + BHV1 challenge; 2. contrast between vaccinated and unvaccinated calves, and 3. demonstrated positive effects of trace minerals supplementation concurrent with IN vaccination on the URT mucosa health. This was the first study using endoscopy as an ancillary tool to evaluate the effects of BVDV2 + BHV1 co-infection on the characteristics of the respiratory tract mucosa and to assess clinical protection elicited by vaccination concurrent with trace mineral injection. Manuscript submitted for publication.
   Participants: GA (R. Palomares and A. Hoyos, AL (M. Chamorro and Rush)

3. Development of methods to passively survey feedlot cattle for antimicrobial resistant *Mannheimia haemolytica*

   In a project led by Paul Morley at TAMU CVMBS in partnership with West Texas A&M and

Mississippi State A&M, we will work on evaluating passive sampling methods for the estimation of AMR M. haemolytica prevalence and evaluate whether they are comparable to nasopharyngeal swabbing of individual cattle (the most commonly accepted sampling method).
Participants: TX (Paul Morley, John Richeson, Sarah Capik), MS (Amelia Woolums)

4. Investigation of the Respiratory Microbiome and Metatranscriptome of Beef Cattle and Their Influences on Bovine Respiratory Disease.

   We hypothesize that the nasal microbiome is associated with the incidence of clinical bovine respiratory disease (BRD) and that specific changes in the nasal microbiome can be used as biomarkers for accurate diagnosis, prognosis, and treatment of BRD as well as improve understanding of BRD pathogenesis. A deeper understanding of the correlations between the nasal microbiome and BRD is a critical step towards developing more refined and efficient management of BRD.
   Participants: TX (TAMU: J. Zhao, E. Kegley, P. Beck, J. Powell, J. Lee, J. Koltes, S.F. Capik; WTAMU: J. Richeson)

5. Supervised machine learning applications for interpreting gene expression patterns related to experimentally induced bovine respiratory disease.

   Employed supervised machine learning (ML) framework on previously published RNA-Seq datasets to discover gene signatures which could be utilized for BRD classification modeling and novel genomic mechanisms identification. This approach was capable of identifying genes in cattle experimentally challenged with bovine herpesvirus-1 (IBR) and bovine respiratory syncytial virus (BRSV) which classified them with 100% balanced accuracy, when compared to sham controls; genes identified in these two groups were largely involved in antiviral defense, type-I interferon production pathways. The novel identification of gene expression related to reduced mitochondrial oxygenation and ATP synthesis was detected in consolidated lung tissue from cattle experimentally challenged with *Mycoplasma bovis*, *Mannheimia haemolytica*, and IBR.
   Participants: TX (Matthew Scott), MS (Amelia Woolums)

6. Etiology and risk factors to bovine respiratory disease in pre-weaned calves on California dairies and calf ranches.

   The study is based on data from the BRD CAP grant and sheds light on the strength of the associations between each of the different pathogens isolated from calves and respiratory disease. Two different approaches are contrasted, the first is based on a single calf ranch and relies on scoring calves, the second is based on multiple calf ranches and dairies and utilizes thoracic ultrasound and/or auscultation, and the CA scoring system. In order of the strength of the association with clinical disease, *Histophilus somni, M. haemolytica, P. multocida,* bovine respiratory syncytial virus, *and Mycoplasma* spp. were significantly associated with respiratory disease using the scoring system. In contrast, using thoracic ultrasound, *Mycoplasma* spp. and *P. multocida* were associated with abnormal thoracic ultrasound findings and/or auscultation. Bovine coronavirus was significantly associated with score positive calves when calves.
   Participants: CA (Sharif Aly, Terry Lehenbauer, Alison Van Eenennaam, P. Blanchard, B. Crossley) and NC (William Love).

7. Development of a bovine respiratory disease risk assessment tool for preweaned dairy calves.

   The multiple etiologies of BRD and its complex web of risk factors necessitate a herd-specific intervention plan for its prevention and control on dairies. Hence, a risk assessment is an important tool that producers and veterinarians can utilize for a comprehensive assessment of the management and host factors that predispose calves to BRD. Practices of known or suspected effect on BRD in preweaned calves have been explored in 2 large studies correlating management factors to BRD prevalence (BRD 100 study) and incidence (BRD 10K study) and forming the scores presented here. Scores for 100 dairies across California were used to benchmark a dairy's risk on a spectrum. With the help of the risk assessment tool, dairy producers, calf managers, and veterinarians may be able to adjust management factors that affect BRD risk on a farm and objectively monitor BRD prevalence before and after management interventions. As a result, the BRD risk assessment tool described here is the first comprehensive and quantitative assessment with scores based on the magnitude of the associations between risk factors and BRD and that can be used for herd-specific BRD control and prevention.
   Participants: CA (UC Davis: Sharif Aly, Terry Lehenbauer; UC Agriculture & Natural Resources: Betsy Karle), NC (William Love)

Objective 3: *To develop and validate management practices and responsibly applied therapeutic and preventative interventions, such as vaccines, antimicrobials, and immunomodulators, to minimize the impact of BRD on cattle, producers, and society.*

1. *Quantification of the impacts of pre-weaning vaccination and post-weaning commingling on BRD morbidity and mortality during postweaning backgrounding.*

   In work including MS and KS, and collaborators at Texas A&M, we are determining the impacts of preweaning vaccination and postweaning commingling through an auction market on BRD morbidity and mortality in weaned beef calves during the postweaning backgrounding period. Calves born in one of the cow-calf herds in the Mississippi Ag and Forestry Experiment Station (MAFES) are randomly allocated to groups to be vaccinated against respiratory viruses or not preweaning; calves in each of vaccinated or not-vaccinated treatment groups will be randomly allocated to travel through an auction market and order buyer facility, or not, after weaning. Cattle will then all be transferred to TX for backgrounding. While vaccination and commingling are widely recognized risk factors for BRD, little properly-controlled research has been published to allow objective quantification of the degree of effects of these factors. This work is funded by a USDA NIFA proposal, lead institution TAMU, with KS and MS receiving subcontracts. Initiation of the research was delayed for 1 year due to the COVID-19 pandemic, but the first of 3 annual planned trials is underway.
   Participants: TX (Sarah Capik), KS (Brad White, Bob Larson, David Amrine), MS (Brandi Karisch, Kelsey Harvey, Jane Parish, Amelia Woolums)

2. *Antibody responses against BRSV induced in beef calves through early vaccination.*

   Vaccination of calves before complete absorption of immunoglobulins from colostrum may result in better priming of humoral and cell mediated immune responses. In collaboration with Auburn University (Manuel F. Chamorro) Mississippi State University (Amelia Woolums), and

Kansas State University (Robert Larson, Natalia Cernicchiaro) assessed the efficacy of different 3 MLV vaccination protocols in beef calves on the induction of serum and nasal secretion specific BRSV antibody titers at 2 months and 6 months of age. This manuscript resulting from this study has been accepted for publication at the American Journal of Veterinary Research and it will be published in the September 2021 issue of this journal.
Participants: AL (Manuel Chamorro), MSU (Amelia Woolums), KSU (Robert Larson and Natalia Cernicchiaro)

3. *Effect of vaccination of beef cows during gestation on transfer of passive immunity and clinical protection of calves against challenge with BRSV.*

   Current vaccination protocols of calves against BRSV have not resulted in significant reduction of BRD-associated morbidity and mortality. Prolonged duration of maternally derived immunity through vaccination of dams during gestation may be an alternative to provide clinical protection against BRSV in young calves. Researchers from Auburn University (Manuel F. Chamorro, David Martinez, Thomas Passler, and Paul H. Walz) in collaboration with Mississippi State University (Amelia Woolums) assessed the effect of vaccination of beef cows during the last trimester of gestation with an inactivated-BRSV vaccine on the transfer of passive immunity and clinical protection of beef calves against experimental challenge with BRSV. Serum neutralizing antibodies against BRSV at 48 hours of age were higher in Calves that nursed colostrum from vaccinated dams. Calves that nursed colostrum from vaccinated dams had lower clinical scores and shed less BRSV in nasal secretions after experimental challenge compared with calves that nursed colostrum from unvaccinated dams. Nasal secretion BRSV IgA titers were negligible before experimental challenge with BRSV in all study calves and increased similarly in both groups after challenge. Vaccination of dams during gestation with two doses of an inactivated-BRSV vaccine 21 days apart is a practical strategy to increase passive immunity and provide clinical protection of calves against BRSV infection during the first 4 months of life. The results of this study were presented at the 53rd American Association of Bovine Practitioners (AABP) Annual Conference in Louisville, KY, Sept 22-26, 2020 and at the 2021 CRWAD Conference in Chicago, IL, Dec. 5-7, 2020. Manuscript in preparation.
   Participants: AL (Manuel F. Chamorro, David Martinez, Thomas Passler, and Paul H. Walz), MS (A Woolums)

4. *Effect of vaccination of young beef calves with an intranasal modified-live virus (MLV) BRSV vaccine within 6 hours of birth on clinical protection against experimental challenge with BRSV at 3.5 months of age.*

   Current vaccination protocols of calves against BRSV have not resulted in significant reduction of BRD-associated morbidity and mortality. Vaccination of young calves with a MLV BRSV vaccine shortly after birth could avoid interference by maternally-derived immunity and result in adequate priming of cell mediated immune responses before complete absorption of passive antibodies from colostrum. Researchers from Auburn University (Manuel F. Chamorro, David Martinez, Thomas Passler, and Paul H. Walz) in collaboration with Mississippi State University (Amelia Woolums) assessed the effect of vaccination of beef calves under 6 hours of age with an IN MLV BRSV on clinical protection against experimental BRSV challenge at 3.5 months of age.

The mean serum and nasal secretion BRSV antibody titers before challenge were similar among vaccinated and unvaccinated calves. The mean rectal temperatures and respiratory scores were similar among vaccinated and unvaccinated calves. After experimental challenge with BRSV, the mean nasal secretion BRSV-IgA titers increased similarly among vaccinated and unvaccinated calves. A greater proportion of unvaccinated calves shed BRSV after challenge compared with that of vaccinated calves. Vaccination of beef calves shortly after birth with an IN MLV BRSV vaccine might reduce viral shedding but do not reduce clinical signs associated with experimental challenge with BRSV at 3.5 months of age. Results from this study are preliminary and have not been presented as a scientific abstract presentation or proceedings.
Participants: AL (Manuel F. Chamorro, David Martinez, Thomas Passler, and Paul H. Walz), MS (A Woolums)

5. *The costs and benefits associated with the use of metaphylaxis (or no metaphylaxis) to determine how metaphylaxis affects net return distributions for fed cattle were compared.*

   Net returns were measured across cattle placement weight (600 or 800 pounds), placement season (October to March referred to as "Winter" or April to September referred to as "Summer"), and the antimicrobial tier administered. ("Upper Tier" antimicrobial, "Lower Tier" antimicrobial, or no metaphylaxis). These findings have important implications for producers deciding how, when, and what type of antimicrobial to use for metaphylaxis. Results indicated higher mortality caused increased feed conversion, increased health costs, and lower daily gains. Both the "Upper Tier" and "Lower Tier" antimicrobials reduced expected mortality when used for metaphylaxis on high-risk cattle. High-risk cattle not treated using metaphylaxis had the largest mortality as well as higher mortality variation across all seasons and weight placements. When compared to "Lower Tier" antimicrobials used for metaphylaxis, "Upper Tier" antimicrobials had lower mortality while no metaphylaxis use had higher mortality. For summer placements, the difference in expected net returns per head between administering an "Upper Tier" ("Lower Tier") to "no metaphylaxis" was $96.08 ($50.39) for 600 pounds and $90.36 ($51.14) for 800 pounds. The difference in expected net returns per head for winter placement between administering an "Upper Tier" ("Lower Tier") to "no metaphylaxis" was $122.55 ($65.72) for 600 pounds and $148.65 ($49.65) for 800 pounds (Elliot et al., 2021).
   Participants: NE (Dennis E), KS (Schroeder T, Renter DG)

6. *The serum and nasal secretion antibody responses to BRSV in beef calves following vaccination with three different protocols was evaluated.*

   Sixty purebred beef calves were assigned to one of three different treatment groups. Group IN-SC VAC received an intranasal (IN) modified-live (MLV) BRSV vaccine at birth and a subcutaneous (SC) MLV BRSV vaccine at 2-months. Group SC-IN VAC received a SC MLV BRSV vaccine at birth and an IN MLV BRSV vaccine at 2-months whereas group NO-IN VAC was not vaccinated at birth and received an IN MLV BRSV vaccine at 2-months-of-age. Nasal secretion and serum samples were collected for assessment of BRSV antibodies prior to vaccination at <24 hours, 2-months, and 6-months-of-age. The titers of BRSV antibodies in nasal secretions and serum were similar among treatment groups at each sampling point. At birth, the mean log-transformed BRSV nasal IgA titers were negligible in all groups. At 2-months-of-age, the mean log-transformed BRSV nasal IgA titers in IN-SC VAC, SC-IN VAC, and NO-IN VAC calves were 192.84, 224.49, and 114.71,

respectively. At 6-months-of-age, the mean log-transformed BRSV nasal IgA titers in IN-SC, SC-IN, and NO-IN calves were 178.84, 159.33, and 266.62, respectively. Serum and mucosal immune responses to vaccination with MLV BRSV vaccines in a combination protocol at birth and at 2-months-of-age were not different from those following single IN MLV vaccination at 2-months-of-age in beef calves under the conditions of this study (Bornheim et al., 2021).
Participants: AL (Chamorro MF), KS (Cernicchiaro N), MS (A Woolums)

7. Effect of administration of trace minerals (Se, Zn, Cu, Mn) on the systemic and mucosal immune response elicited by IN MLV vaccine in young dairy calves**.**

   T cell populations in dairy calves infected with *BVDV2* and *BHV1* after MLV vaccination and trace mineral injection. In this study, there were remarkable differences in proportion of circulating $CD4^+$ $CD8^+$ T-cells (determined by flow cytometry) in vaccinated dairy calves after BVDV2+BHV1 infection depending on the vaccination route and injection of trace minerals or not. Calves receiving subcutaneous MLV vaccination showed greater number of $CD4^+$ T cells on day 3 following BVDV infection. In addition, the proportion of $CD8^+$ T cells was significantly greater in calves receiving injectable trace minerals at the time of booster vaccination (by either IN or SC route), compared to calves treated with saline. **Manuscript under preparation.**
   Participants: GA (Drs. Roberto A. Palomares and Alejandro Hoyos), FL (Dr. Joao Bittar)

8. *Abundance and distribution of T cell populations ($CD4^+$, $CD8^+$, $WC1^+$, $CD25^+$) as well as T cells expressing memory ($CD45^+RA^+$) and homing markers ($CD62L^+$) on lymphoid organs and respiratory mucosa (by immunohistochemistry) during acute infection with BVDV-2 and BHV-1 in dairy calves.*

   This is an ongoing study at the stage of laboratory analysis. We hypothesize that the vaccination route and supplementation with Cu, Se, Zn & Mn affect the proportion of T cells in lymphoid tissues after BVDV2 +BHV1 infection. Calves vaccinated through different routes and treated with injectable trace minerals or not may have different number of T cell populations ($CD4^+$, $CD8^+$, $WC1^+$) and activated T cells ($CD4^+CD25^+$, $CD8^+CD25^+$, & $WC1^+CD25^+$) in lymphoid tissues and respiratory mucosa/submucosa. In addition, we also hypothesize that the number of lymphocytes expressing memory ($CD45^+RA^+$) and homing markers ($CD62L^+$) on lymphoid and upper respiratory tract tissues is affected by the vaccination route and trace mineral injection.
   Project on stage of laboratory analysis.
   Participants: GA (Drs. Roberto A. Palomares, Kaori Sakamoto, Uriel Blas-Machado) and CA (Post doc: Alejadro Hoyos-Jaramillo)

9. *Assessment of the effect of on-arrival mass treatment of high risk stocker cattle with long acting macrolide on AMR in M. haemolytica.*

   This project is led by Mississippi State University with collaboration from Texas A&M University faculty (Sarah Capik and Paul Morley) and is working to determine the effect on on-arrival mass medication of high risk stocker cattle on AMR as measured by culture and antimicrobial susceptibility testing, characterization of the 16S metagenome, the resistome, and identification of *M. haemolytica* genomes using a novel bait-enriched pulldown assay.
   Participants: MS (Amelia Woolums, Brandi Karisch, Bill Epperson) TX: (Paul Morley, Sarah Capik)

10. *Systematic Review of vaccine efficacy against Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in North American cattle.*

    One of the most frequent questions we receive from both beef and dairy producers centers around vaccine efficacy and choice. The most recent systematic review of vaccine efficacy regarding the 3 main BRD bacteria was performed over 10 years ago and thus does not contain the most recent information regarding new vaccines that have become commercially available during that time.
    Participants: TX (Sarah Capik), KS (Robert Larson), Heather Moberly

Objective 4: *To determine how attributes of cattle production systems including epidemiologic, societal, and economic forces contribute to BRD, and to develop ways to promote changes in those systems to reduce the occurrence of BRD and improve cattle health, welfare, productivity and antimicrobial stewardship.*

1. *Associations between weather conditions and management factors with the incidence of death attributable to bovine respiratory disease complex (BRDC) were evaluated in high-risk auction-sourced beef calves.*

    Cohorts (n = 3,339) of male beef calves (545,866) purchased by 1 large cattle feeding operation from 216 locations and transported to 1 of 89 feeding locations (backgrounding location or feedlot) with similar management protocols. Associations between weather conditions and management factors on the day of purchase (day P) and during the first week at the feeding location and cumulative BRDC mortality incidence within the first 60 days on feed were estimated in a mixed-effects negative binomial regression model. Significant factors in the final model were weaning status; degree of commingling; body weight; transport distance; season; precipitation, mean wind speed, and maximum environmental temperature on day P; environmental temperature range in the first week after arrival at the feeding location; and interactions between distance and wind speed and between body weight and maximum environmental temperature. Precipitation and wind speed on day P were associated with lower cumulative BRDC mortality incidence, but wind speed was associated only among calves transported long distances (≥ 1,082.4 km). Higher mean maximum temperature on day P increased the incidence of cumulative mortality among calves with low body weights (< 275.5 kg) (Wisnieski et al., 2021).
    Participants: TN (Wisnieski L) and KSU (Amrine DE, Cernicchiaro N, Sanderson MW, Renter DG)

2. From September 2020 to 2021, we have been able to plan collaborative projects between TN and MS. The first planned project plans to better predict calfhood vaccination history of stocker calves at the point of arrival to stocker facilities. We will begin data collection on this project in Fall 2021. In addition, we have developed a survey that will be used to better understand purchasing decisions of stocker producers in the southeastern US. This is in collaboration with MS and TN stations. The survey has received IRB approval from TN and will begin circulation this fall.
    Participants: TN (Schneider), MS (Karisch, Harvey)

Objective 5: *To promote dialogue and exchange among scientists, veterinarians, allied industry professionals and cattle producers to advance BRD research initiatives, to implement outreach, to disseminate research results, and to facilitate the translation of research findings to practical field applications*.

1. 2019 Bovine Respiratory Disease Symposium. Papers from 2019 BRD Symposium were published in *Animal Health Research Reviews* (AHRR) in December 2020. MS collaborated with other stations to organize and deliver the 2019 BRD Symposium, and worked with SD and others to assist speakers who submitted their papers to AHRR.
   Participants: SD (Chris Chase); MS (Amelia Woolums); CA (Sharif Aly, Terry Lehenbauer)

2. The results of collaborative research have and will be presented in regional and international conferences, including the American Association of Bovine Practitioners, and the Conference on modeling in animal health.
Participants: KS (Brad White, Natalia Cernicchiaro, Robert Larson, David Renter)

3. We hosted the visit of Dr. Florencia Meyer from MSU to explore collaborative research opportunities about the effects of trace minerals to prevent infections with BRD pathogens.
Participants: GA (Palomares)

4. Provided three lectures on genomic selection and BRD to undergraduate students.
   Participants: WA

5. The Gershwin lab has presented research results on the two projects (both USDA funded) each year at the CRWAD. There are four publications thus far and several in progress for this USDA funded “Dual purpose-dual benefit” grant.

Objective 6: *To assess the economic impact of BRD across different sectors of cattle industry.*

II. Impact

Objective 1:

- Further the understanding of the etiology of BRD and the role that corona virus plays in BRD
- Provide additional genomic tools for selection of animals resistant/resilient to BRD
- These projects identify genes and immune functions which help us understand why some cattle develop BRD and others do not, regardless of stressors and infectious organisms. Our focus with this collective work was to look at healthy cattle in a similar way as we do with diseased cattle, instead of as a control group. Here, we discover at-arrival host gene expression patterns involved in the inflammatory and immune systems which may be used to develop novel therapies against BRD.

Objective 2:

- Endoscopy of the respiratory tract permitted prompt detection of mucosal inflammation and damage caused by BVDV2 and BHV1, before bronchial and lung lesions appear. This tool allowed to demonstrate the positive effects of vaccination (and injectable trace minerals) protecting calves from URT damage caused by BVDV2 + BHV1 infection. Endoscopic evaluation of the calves' URT showed: 1. differences in the appearance of the respiratory mucosa before and after BVDV2 + BHV1 challenge; 2. contrast between vaccinated and unvaccinated calves, and 3. demonstrated positive effects of trace minerals supplementation concurrent with IN vaccination on the URT mucosa health.
- Development of passive methods of sampling cattle for AMR respiratory bacteria will allow better tracking of AMR and its impact in feedlot cattle.
- Measurement of AMR in feedlot cattle will support the development of improved management practices that decrease the dissemination of AMR.
- Develop a systems biology approach for a comprehensive analysis of the ecological, microbiologic, and pathophysiologic events that culminate in BRD; to delineate the interactions within and between the nasal microbiome and the host and to ultimately develop novel strategies (e.g., probiotics) that decrease or replace antimicrobials to prevent or mitigate the effect of BRD in the beef industry.
- With advancements in computational, sequencing, and statistical methods, we are capable of developing new models that may predict BRD risk and severity at facility arrival from a blood sample. Together, these projects have given us new concepts of why certain cattle develop BRD and some do not, and allowed us to use that information to classify cattle at the highest risk of BRD before they demonstrate clinical signs.
- Multiple bacterial and viral etiologies vary in their association with bovine respiratory disease in the preweaned calves which emphasizes the complexity of this disease.
- Development of a BRD risk assessment tool for preweaned dairy calves that can be used to determine herd-specific management changes on a dairy to control and prevent BRD.

Objective 3:

- This research will provide objective data regarding the relative impacts of preweaning vaccination and postweaning auction market exposure on BRD incidence. Such data are surprisingly rare. This information will support the development of models that identify the most cost effective management strategies to prevent BRD.
- Development of vaccination strategies for cow-calf operations to reduce disease caused by BRSV infection in young calves.
- Elucidating the role of the vaccination route and trace minerals injection on protective immunity elicited by vaccination in young dairy calves might help enhancing the efficacy of vaccination protocols and have a significant impact on BRD prevention in dairy calves.
- We increased our knowledge on risk factors for BRD; specifically, weather factors on the day of purchase and first week at the feedlot, or arrival quarter were associated with the timing of BRD morbidity. Similarly, we learned that the probability of large losses can be reduced through the use of metaphylaxis in high risk cattle, and that when developing BRD treatment protocols, the sequence and type of antimicrobial treatment (cidal or static) should be considered as they are related to the probability of BRD retreatment. Moreover, shorter intertreatment interval was associated with higher BRD case fatality rate. Antibody response to BRD pathogens such as BRSV during early vaccination (birth and at 2 months of age), via intranasal or subcutaneous administration, did not differ compared to vaccinating cattle at 2 months. These findings have implications for BRD surveillance and risk assessment, targeted BRD treatment protocols and improved antimicrobial stewardship.
- Determine whether mass medication at arrival to prevent BRD induces more AMR than medication of cattle for BRD as it occurs. This information will help veterinarians and farmers make decisions to support cattle health with the least possible pressure to expand antimicrobial resistance.
- Develop a new tool, bait-enriched targeted pulldown of M. haemolytica genomes, which will allow characterization of genomes without isolation. This will expand the ability of scientists to study the ecology of antimicrobial resistance in bacteria that induce BRD.
- Our over-arching goal is to identify management interventions that reduce BRD incidence. By decreasing the number of animals that get BRD, the sustainability and efficiency of beef production will improve and less antimicrobials will be needed for treatment.
- Updating and expanding this systematic review will help provide the best guidance to producers regarding how to use these vaccines.
- Substantiate specific genes and mechanisms at-arrival in multiple populations of high-risk beef cattle, distinguishing promising molecular targets for BRD prediction model and novel therapeutic development. Such a development could reduce BRD morbidity and mortality rates in high-risk beef cattle populations by identifying BRD prior to the onset of clinical signs and lead to a more targeted therapeutic approach.
- Classify novel mechanisms and gene expression modules which may be utilized in future BRD molecular detection methods. Furthermore, this study illustrates the approach and capacity in which ML techniques may be utilized with publicly-available mRNA sequencing data.
- Development of an at-arrival prediction model for BRD using mRNA expression data. Indication that genes involved in leukocyte development, inflammatory resolution, and

type I interferon production are significantly associated with BRD development and clinical severity. This at-arrival, multi-marker gene expression approach provides a promising foundation for predicting BRD in high-risk populations of beef cattle.

- BRD may be as much of an inflammatory disease as it is an infectious one. Some cattle, which demonstrate an increase in gene expression related to anti-inflammatory and antimicrobial peptide (also known as host defense peptides) mechanisms may be less likely to incur chronic or severe BRD. First, if this information can be used in a real-time manner, it would allow us to specifically target the cattle at highest risk of developing severe BRD, and potentially reduce both antimicrobial usage and overall morbidity. And second, this work could drive the development of new alternative therapies which target the mechanisms and pathways involved in BRD resistance or acquisition.

Objective 4:

- These findings help illustrate how host-driven responses at facility arrival impact eventual BRD development and production loss. The ability to accurately predict BRD prior to clinical signs would potentially enable beef production systems to reduce antimicrobial usage, allow for a more targeted approach to BRD, and reduce disease in high-risk populations of beef cattle.

Objective 5:

- The BRD Symposium provides scientists, veterinarians, members of industry, and policy makers in North American and worldwide an opportunity to learn the most current information regarding BRD, based on research and the practices of progressive veterinarians and producers.
- *Because Animal Health Research Reviews s indexed on PubMed, publication of the 2019 BRD Symposium papers in AHRR makes them available internationally, greatly expanding the impact of the information presented at the 2019 BRD Symposium.*
- *Dr. Meyer's visit was a great opportunities to discuss future research projects on the use of trace minerals to contribute to prevention and control of pathogens involved in BRD.*
- Educate students on the importance of BRD in beef and dairy production
- Educate students on the role of genetics on predisposition to disease
- Educate students on the use of genomic selection to reduce infectious disease
- To better disseminate these data, three primary measures are taken: 1) all data and information related to these projects are distributed freely to online repositories, such as the NCBI Gene Expression Omnibus, 2) research results are made as preprints and published in open-access scientific journals, and 3) findings and relevant discussions are delivered at local, national, and international meetings and conferences.

III. Publications/deliverables-

Peer-reviewed scientific publications:

1. Bornheim HN, Chamorro MF, Cernicchiaro N, Reppert EJ, Larson RL, Huser S, Thoresen M, Jones K, Weaber RL, Woolums AR. Antibody responses against BRSV induced in beef calves through early vaccination. Am J Vet Res 2021. Accepted.

2. Palomares RA, Bittar JHJ, Woolums AR, Hoyos-Jaramillo A, Hurley DJ, Saliki JT, Ferrer MS, Burlington AC, Rodriguez A, Murray T, Thoresen M, Jones K, Stoskute A. Comparison of the immune response following subcutaneous versus intranasal modified-live virus booster vaccination against bovine respiratory disease in pre-weaning beef calves that had received primary vaccination by the intranasal route. Vet Immunol Immunopathol. Jul;237:110254. doi:10.1016/j.vetimm.2021.110254.
3. Bornheim HN, Chamorro MF, Cernicchiaro N, Reppert EJ, Larson RL, Huser S, Thoresen M, Jones K, Weaber RL, Woolums AR. Evaluation of specific immunoglobulin A in nasal secretions and neutralizing antibodies in serum collected at multiple time points from young beef calves following intranasal or subcutaneous administration of a modified-live bovine respiratory syncytial virus vaccine. Am J Vet Res 2021; accepted.
4. Wisnieski L, Amrine DE, Cernicchiaro N, Sanderson MW, Renter DG. Weather conditions associated with bovine respiratory disease mortality in high-risk male auction market-sourced beef calves. Am J Vet Res. 2021; 82(8): 644-652.
5. Wisnieski L, Sanderson MW, Bello NM. Predictive modeling of bovine respiratory disease in feedlot cattle. Livest Sci. 2021 (in press).
6. Bornheim HN, Chamorro MF, Cernicchiaro N, Reppert, EJ, Larson RL, Hauser S, Thoresen M, Jones K, Weaber RL, Woolums AR. Antibody responses against BRSV induced in beef calves through early vaccination. Am J Vet Res. 2021 (accepted).
7. Coetzee JF, Cernicchiaro N, Sidhu PK, Kleinhenz M. Short Communication: Association between antimicrobial drug class selection for treatment and retreatment of bovine respiratory disease (BRD) and health, performance and carcass quality outcomes in feedlot cattle. J Anim Sci. 2020; 98(4): skaa109.
8. White BJ, Larson RL. Impact of bovine respiratory disease in beef cattle. Anim Health Res Rev.2020: 21(2): 132-134.
9. Aly SS, Karle BM, Williams, DR, Maier GU, Dubrovsky S. Components of a risk assessment tool for prevention and control of bovine respiratory disease in preweaned dairy calves. Animal Health Research Reviews 1–7, 2020; https://doi.org/10.1017/S1466252320000201
10. GU Maier, WJ Love, BM Karle, SA Dubrovsky, DR Williams, JD Champagne, RJ Anderson, JD Rowe, TW Lehenbauer, AL Van Eenennaam, SS Aly. A novel risk assessment tool for bovine respiratory disease in preweaned dairy calves. J. Dairy Sci. 2020; 103:9301–9317 doi.org/10.3168/jds.2019-17650
11. Deepak, AlySS, Love WJ, Blanchard PC, Crossley B, Van Eenennaam AL, Lehenbauer TW. 2021 Etiology and risk factors to bovine respiratory disease inpre-weaned calves on California dairies and calf ranches. Prev Vet Med, 2021; doi:10.1016/j.prevetmed.2021.105506 (in press)

Scientific Abstracts/presentations:

1. Martinez DA, Chamorro MF, Passler T, Stockler R, Silvis S, Raithel G, Thoresen M, Walz PH, Woolums AR. Vaccination of beef cows during gestation provides passive immunity and clinical protection to young calves against experimental challenge with BRSV. In proceedings: 2021 Conference of Research Workers in Animal Disease (CRWAD). Chicago, IL Dec 5-7, 2020. Pp:1
2. Chamorro MF, Martinez D, Woolums AR, Stockler R, Passler T, Silvis S, Raithel G, Walz PH. Effect of vaccination of beef cows during gestation on transfer of passive immunity and clinical protection of calves against experimental challenge with BRSV. In proceedings: 53rd American Association of Bovine Practitioners (AABP) convention. Louisville, KY Sept 24 – 27, 2020. Pp:370
3. Picault S, Ezanno P, White B, Amrine D, Assié S. Modelling contrasted fattening systems in Europe and the USA and their impact on Bovine Respiratory Disease burden. Modeling in Animal Health, August 26-28, 2021, Nantes, France.

4. Akter, A., M. Caldwell, G. Pighetti, and L. G. Schneider. Effects of naturally occurring bovine respiratory disease on immune parameters in stocker beef cattle. UT beef and forage center annual research and recommendation meeting, December 15, 2020.
5. Akter, A., M. Caldwell, G. Pighetti, and L. G. Schneider. Immunological response to naturally occurring bovine respiratory disease in stocker cattle during early management. Annual Conference of Research Workers in Animal Diseases (CRWAD), December 5-8, 2020.
6. Palomares RA, et al., 2021. Comparison of the immune response following subcutaneous versus intranasal modified-live virus booster vaccination against bovine respiratory disease in pre-weaning beef calves that had received primary vaccination by the intranasal route. Veterinary Immunology and Immunopathology 237, 110254.
7. Scott MA, Woolums AR, Swiderski CE, Perkins AD, Nanduri, B. Genes and mechanisms associated with experimentally induced bovine respiratory disease identified with supervised machine learning methodology on integrated transcriptomic datasets. Scientific Reports (In review). Preprint available at Research Square. doi: 10.21203/rs.3.rs-789747/v1
8. Scott MA, Woolums AR, Swiderski CE, Perkins AD, Nanduri, B, Smith DR, Karisch BB, Epperson WB, Blanton JR. Multipopulational transcriptome analysis of post-weaned beef cattle at arrival further validates candidate biomarkers for predicting clinical bovine respiratory disease. Scientific Reports (In review). Preprint available at Research Square. doi: 10.21203/rs.3.rs-600364/v1.
9. Associations of pen management characteristics and bovine respiratory disease morbidity in the first 45 days post-arrival in feedlot cattle. H.A. Rojas, D.E. Amrine, R.L. Larson, S.F. Capik, and B.J. White. Submitted to *Translational Animal Science* in 2021.
10. H.A. Rojas, D.A. Amrine, R.L. Larson, S.F. Capik, B.J. White; Associations of cattle pen management characteristics and cattle morbidity in the first 45 days post-arrival in the feedlot. Presented at the Conference of Research Workers in Animal Disease (CRWAD) 2020. December 5-8th, 2020; Virtual Conference. Abstract #245.
11. W.B. Crosby, B.B. Karisch, J.D. Loy, L. Hiott, W. Epperson, J. Blanton Jr., P.S. Morley, S.F. Capik, C. Jackson, J. Frye, A.R. Woolums; The effect of tulathromycin on morbidity and prevalence of *Mannheimia haemolytica* Genotype 2 in 84 stocker heifers. Presented at the Conference of Research Workers in Animal Disease (CRWAD) 2020. December 5-8th, 2020; Virtual Conference. Abstract #153
12. W.B. Crosby, J.T. Richeson, J.D. Loy, S.P. Gow, S.F. Capik, N. Padilla, A.R. Woolums, P.S. Morley; Comparison of 3 sampling methods for recovery of *Mannheimia haemolytica* from feedlot cattle. Presented at the Conference of Research Workers in Animal Disease (CRWAD) 2020. December 5-8th, 2020; Virtual Conference. Abstract #246.

Other activities:

WA station

1. Three lectures on BRD host genomics to undergraduate students in:

ANIM SCI 474	Beef Production
ANIM SCI 472	Dairy Production
VET CLIN 361	Agricultural Animal Health