NC1192 Station Annual Report

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

Submitted by: Dr. Theresa Ollivett . DVM, PhD, DACVIM.

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Participating Experiment Stations:, Kansas State University, Iowa State University, Louisiana State University, Mississippi State University, South Dakota State University, University California-Davis, University Georgia, University Nebraska-Lincoln, University Tennessee, University Wisconsin-Madison, West Texas A&M.

Participants of Annual Meeting:

Sharif Aly (University of California, Davis), Natalia Cernicchiaro (Kansas State University), Chris Chase (South Dakota State University) Grant Dewell (Iowa State University), Laurel Gershwin (University of California, Davis),Brandi Karisch (Mississippi State University),Robert Larson (Kansas State University), Terry Lehenbauer (University of California, Davis), Florencia Meyer (Mississippi State University), Theresa Ollivett (University of Wisconsin – Madison), Roberto Palomares (University of Georgia), John Richeson (West Texas A&M), Liesel Schneider (University of Tennessee), Amelia Woolums (Mississippi State University), and Shi-Hua Xiang (University of Nebraska-Lincoln). George Smith (Michigan State University, NIMSS representative).

Brief summary of minutes of annual meeting

- Annual meeting was on September 21, 2020 via Zoom due to restrictions associated with COVID-19. Dr. Ollivett welcomed and lead introduction of experiment station members and their station reports.
- We discussed on renewing the NC1192 project for 2021, and also the possibility that the group would submit a proposal for a Coordinating Committee rather than a Multistate Research Project. The way that members of NC1192 have historically interacted has perhaps been more consistent with a Coordinating Committee than a Multistate Research Project. Due to needs of some members to obtain funding and increased multistate collaboration a Multistate Research Project was determined to be the best option.
- Annual report requirements were discussed and Dr. George Smith emphasized 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.

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

Seven stations sent reports for 2019 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.*

Pathogen profiles and loci associated with enhanced resistance to BRD in 1000 pre-weaned calves in Wisconsin: A USDA-NIFA funded proposal **(Collaboration among WSU, Texas A&M University, University of Missouri, University of Wisconsin**; PD Seabury and Co-PD Neibergs) was initiated to identify pathogen profiles and loci associated with enhanced resistance to BRD in 1000 pre-weaned calves in Wisconsin. 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.

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

1. *Development of methods to passively survey feedlot cattle for antimicrobial resistant Mannheimia haemolytica:* A USDA CEAH funded proposal **(Collaboration between WTA&M and MSU)** led by TX, investigators at MS are working to develop methods to survey groups of feedlot cattle for antimicrobial resistant (AMR) *Mannheimia haemolytica* (*M. haemolytica).* While AMR *M. haemolytica* are increasingly reported, identification has traditionally required collection of nasopharyngeal swabs from individual cattle. This collaborative research effort between WTA&M and MSU will determine whether sampling of ropes that cattle chew on, or water bowls in feedlots, can provide information regarding the prevalence of AMR *M. haemolytica* that is comparable to nasopharyngeal swabbing of individual cattle, but with less handling of the cattle.

Participants: WTA&M: Paul Morley, John Richeson; MSU: Amelia Woolums

Development of a respiratory endoscopic score (ES) for evaluation of the upper respiratory tract (URT) of dairy calves vaccinated and infected with BVDV2 and BHV1. Clinical examination and health score for BRD diagnosis may fail to identify cases of subclinical pneumonia. Endoscopy is a tool that permits prompt evaluation of the URT of affected animals, before bronchial and lung lesions appear. **Researchers from GA (Drs. Roberto A. Palomares and Alejandro Hoyos) in collaboration with AU** (Drs. Jessica Rush, Misty Edmondson and Manuel Chamorro) developed a respiratory endoscopic score (ES) for evaluation of the upper respiratory tract in dairy calves vaccinated and infected with BVDV and BHV1. In this study UGA performed and analyzed 60 endoscopic evaluations of the upper respiratory tract of dairy calves vaccinated with MLV

vaccines (IN or SC) and treated with injectable trace minerals (ITM) or saline in a 2x2 factorial. Currently on manuscript preparation.

Participants from UGA: Drs. Roberto A. Palomares and Alejandro Hoyos, AU: Drs. Jessica Rush, Misty Edmondson and Manuel Chamorro

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. Assessment of the effect of on-arrival mass treatment of high risk stocker cattle with long acting macrolide on AMR in *M. haemolytica*: A USDA NIFA funded proposal (award #2019-67017-29111) (**Collaboration between MSU and WTA&M**). In a project we are leading, in collaboration with TX, we are assessing the prevalence of AMR *M. haemolytica* nasopharyngeal shedding by high risk stocker cattle that are treated with a long acting macrolide antimicrobial at arrival ("metaphylaxis"), vs cattle not receiving metaphylaxis. We will assess AMR by measuring minimum inhibitory concentrations (MIC) for antimicrobials by *M. haemolytica* isolated by culture, and we will also assess the nasopharyngeal microbiome by 16S sequencing, and the resistome by shotgun sequencing. We will also develop a novel bait-enriched targeted pull-down method to identify AMR *M. haemolytica* in the DNA isolated from nasopharyngeal swabs for microbiome and resistome assessment.

Participants: MSU: Amelia Woolums, Brandi Karisch, John Blanton, Bill Epperson; WTA&M: Paul Morley, Sarah Capik

2. Assessment of the effects of maternal vaccination or neonatal calf vaccination on systemic and mucosal immune responses and resistance to BRSV challenge in postweaned beef calves: In a project led by Auburn (**Collaboration between Auburn and MSU**), we are collaborating on work to assess the effects of maternal vaccination and vaccination of young calves on resistance to BRSV challenge in calves at weaning. Calves from dams vaccinated in late gestation vs not, or calves vaccinated in the first week of life vs not, are sampled at various time points between birth and weaning for measurement of serum and nasal antibodies directed against BRSV. Calves are experimentally challenged post weaning with BRSV, and serum and nasal secretions are collected at various time points post challenge. We will compare the difference between groups in clinical signs of disease, viral shedding, serum neutralizing antibodies to BRSV, and serum and nasal IgA, IgG1, and total IgG directed against BRSV.

Participants: Auburn: Manuel Chamorro, Thomas Passler, Ricardo Stockler; MSU: Amelia Woolums

3. Quantification of the impacts of pre-weaning vaccination and post-weaning commingling on BRD morbidity and mortality during postweaning backgrounding: A USDA NIFA funded proposal (**Collaboration between TAMU, KSU and MSU)** to quantify 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) will be 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.

Participants: WTA&M: Sarah Capik, John Richeson; KSU: Brad White, Bob Larson, David Amrine; MSU: Brandi Karisch, Jane Parish, Amelia Woolums

4. BRSV efficacy study. A research project (**Collaboration between SDSU, MSU and ISU**) to evaluate BRSV efficacy an ELISA was developed to evaluate the BRSV specific IgA in nasal secretion of the assigned heifers. The study was aimed to examine mucosal immunity following parenteral vaccine and a challenge model against BRSV. Calves were vaccinated at approximately 1 month of age and challenged~90 days later when BRSV systemic antibodies were <1:4. Body temperature was lower at 6 and 7 days post challenge and other clinical signs were also lower in the vaccinates. Nasal viral shed was 3–4 times lower in the vaccinated animals as measured by virus isolation and polymerase chain reaction (PCR) and peaked 5 days post challenge compared to the controls (who peaked at days 6 and 7). On day 8 following challenge, animals were necropsied, and lung lobes were scored and tested for virus by PCR and indirect fluorescent assay (IFA).There was a 25-fold reduction in PCR virus detection in vaccinates and two of the vaccinated calves' lungs were PCR negative. Only 29.4% of vaccinated calves were BRSV positive on IFA testing at necropsy, while 87.5% of control calves were BRSV positive. Vaccinated calves developed a mucosal BRSV IgA response with over 50% of the vaccinated calves having IgA prior to challenge and all vaccinated calves were positive following challenge. Additionally, vaccination stimulated the production of Interferon gamma (IFN-c) in mononuclear cells to prime the immune system.

Participants: SDSU: Chris Chase, MSU: Amelia Woolums, and ISU: Jodi McGill

5. Inflammatory and humoral responses and adverse reactions induced by vaccines. A research project (**Collaboration between SDSU, Brazil and UG**), examined the inflammatory and humoral responses and adverse reactions induced by three adjuvanted commercial vaccines against bovine viral diarrhea virus (BVDV) and bovine herpesvirus 1 (BHV-1). Holstein heifers (n = 35) were divided into four groups by adjuvant compounds: Vaccine A (Alum; n = 9), Vaccine B (Oil-in-water; n = 10), Vaccine C (Amphigen/Quil A cholesterol and dimethyl-dioctadecyl ammonium (DDA) bromide (QAD; n = 10), and Control (n = 6). Heifers were assessed at 0 h, 6, 24, 48, 72 and 168 h post-vaccination; serology was evaluated at first dose (D0), booster (D21) and D42. Heifers vaccinated with Vaccine B ($p = 0.0001$) and C ($p = 0.0001$) had a more intense local reaction, while there was a higher rectal temperature detected in heifers vaccinated with Vaccine C ($p = 0.020$). There was greater systemic reaction observed for heifers vaccinated with Vaccines B and C at 48 h ($p = 0.002$) after a second dose. Clinical pathology parameters [white blood count (WBC) ($p = 0.001$), neutrophils ($p = 0.0001$) and haptoglobin concentrations ($p = 0.0001$)] were higher in animals vaccinated with Vaccine C.

Neutralizing Abs against BVDV type 1 strains, NADL and Singer, were detected in animals vaccinated with Vaccines A or C at D42, while BVDV-2 antibodies were detected only in animals vaccinated with Vaccine C. A BHV-1 antibody was detected in all three vaccine groups (Vaccines A, B or C) at day 42 (21 days post booster vaccination). The findings of this research were based on three different commercial laboratory formulations and also according to the conditions which the study was conducted. In this context, vaccine containing mineral oil or Amphigen/QAD presented greater local reactivity and induced a significant systemic inflammatory response. Vaccinated heifers with Alum and Amphigen/QAD commercial vaccines enhanced humoral immune response against BVDV and BHV-1.

Participants: SDSU: Chris Chase, UG: David Hurley, Brazil

6. Genome sequencing of BHV. A research project (**Collaboration between SDSU and OSU**) to perform complete genome sequence of the first two bovine isolates BHV-1.1 LA strain and Cooper strain from the 1950's and six wild-type BHV-1.1 isolates were compared and this study was recently published. The Cooper strain is the major strain in almost all US BHV-1 vaccines A nucleotide sequence divergence of 0.74% was noted across the two complete genomes, caused by 19 single-nucleotide polymorphisms (SNPs) involving 12 genes and insertions/deletions that primarily affected the number of repeats within reiterated repeat regions of the genome. Phylogenetic analysis revealed that Cooper and LA strains are genetically the most ancient strains from which all of the more-recently isolated field strains of BoHV-1.1 evolved.

Participants: SDSU: Chris Chase, OSU: Jean d'Offay

7. Develop dual challenge model. Research project (**Collaboration between SDUS and OSU),** we developed a dual challenge model using BVDV 1b and *Mannhemia hemolytica*. This model resulted in excellent lung pathology. This model was used in a comparative vaccine efficacy with 4 different vaccine combinations and the results are currently be analyzed.

Participants: SDSU: Chris Chase, OSU: Jared Taylor

8. Comparison of the immune response following subcutaneous versus intranasal modified-live virus booster vaccination against bovine respiratory disease in pre-weaning beef calves. Performed in **collaboration with Amelia Woolums (MSU).** Booster vaccination of young beef calves using either SC or IN route two months after IN MLV primary vaccination resulted in comparable SNA titers, cytokine gene expression profile and virus-specific IgA concentration in nasal secretions. Only a few differences in the systemic and mucosal immune response against BHV1 and BRSV were observed between vaccinated groups. Manuscript submitted for publication. Currently under review.

Participants: MSU: Amelia Woolums, UGA: Roberto Palomares

Objective 4: *To determine how attributes of cattle production systems including epidemiologic, societal, and economic forces contribute to BRD, and to develop ways to catalyze change in*

those systems to reduce the occurrence of BRD and improve cattle health, welfare, and productivity.

1. Effect of handling stress. A research project (**collaboration between KSU, SDSU and PAC Group**) study, we examined the effect of handling stress. The objective of this study was to determine if the effects of cattle handling intensity at processing had an effect on physiological, inflammatory, and immune stress markers in newly received feeder calves. Crossbred heifers (n=80, BW =355+/- 24 kg) from a single cohort were used for this study at a commercial cattle feeding facility in central Nebraska. These heifers were systematically allocated to treatment and used over a 42-day period to evaluate the effects of 2 handling treatments: Low stress handling (LSH): Cattle walked calmly through a crowding tub and snake processing facility up to a hydraulic chute. Electric prods and striking were not permitted. Noise from the handlers was kept to a minimum; and Aggressive handling (AH): Cattle moved through the crowding tub and snake processing facility at a lope. An electric prod was applied twice (1 s per impulse) before entering a hydraulic chute. A radio was playing and yelling and whistling were encouraged. Cattle administered the AH treatment had higher respiratory rates (P=0.017) than the LSH cattle immediately after treatment administration. Low stress handled cattle tended to have lower norepinephrine plasma concentrations (P=0.05) than AH cattle immediately post-treatment. AH cattle had higher D-lactate concentrations compared to LSH cattle at post-treatment (P<0.0001). Aggressively handled cattle had higher serum amyloid A concentrations at post-treatment (P=0.0002). Cattle handling did not have an effect on immunological measures (P>0.30) in cattle. These results indicate aggressive handling causes negative physiological and inflammation responses in newly received beef cattle.

Participants: KSU: Dan Thomson, SDSU: Chris Chase, Johan Osorio, PAC Group

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*.

2019 Bovine Respiratory Disease Symposium: In collaboration with UC-D, UG, ISU, KSU, OSU, and SDSU, MSU worked to organize and deliver the 3rd 2019 Bovine Respiratory Disease Symposium in Denver, Colorado on August 7-8, 2019, in conjunction with the Academy of Veterinary Consultants Summer meeting. Over 200 attendees from the U.S. and Canada participate. The proceedings will be published in a special issue of the journal Animal Health Research Reviews (AHRR) in December 2020. After the papers are published in AHRR they will be available on the BRD Symposium website (www.brdsymposium.org).

Scientific and Professional events:

II. Impact-

Objective 1:

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Objective 2:

- 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.
- Respiratory endoscopic score permitted prompt detection of inflammation and damage of the URT of 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.

Objective 3:

- We will 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.
- We will 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.
- Research will provide new information regarding the relative impacts of maternally-derived passive antibody compared to vaccine-induced active antibody to improve resistance to a virus that commonly contributes to BRD in calves. The results will help veterinarians and cattle producers make more informed decisions when developing vaccine protocols to keep calves healthy.
- Research will lead to a new tool, an ELISA assay to measure total IgG and IgG1 directed against BRSV, which will be useful to researchers who working to determine the relative impact of passive and active antibody responses in resistance to BRD.
- 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.
- Improving the immune response to vaccination in young dairy calves using IN booster vaccination and administration of ITM might have a significant impact on prevention of BRD and future health status of dairy heifers.

Objective 4:

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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.
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III. Publications/deliverables-

Publications:

Bittar JHJ, **Palomares RA**, Hurley DJ, Hoyos-Jaramillo A, Rodriguez A, Stoskute A, Hamrick B, Norton N, Adkins M, Saliki JT, Sanchez S; Lauber K. Immune response and onset of protection from Bovine viral diarrhea virus 2 infection induced by modified-live virus vaccination concurrent with injectable trace minerals administration in newly received beef calves. Veterinary immunology and Immunopathology. 225 (2020).

Chamorro MF and **Palomares RA**. Bovine respiratory disease vaccination against viral pathogens: Modified-live versus inactivated antigen vaccines, intranasal versus parenteral, what is the evidence? Veterinary Clinics of North America Food Animal Practice 2020; 36:461-472

Dewell RD, Millman ST, Parsons RL, Sadler LJ, Noffsinger TH, Busby WD, Wang C, and **Dewell GA**. 2019. Clinical trial to assess the impact of acclimation and low-stress cattle handling on bovine respiratory disease and performance during the feedyard finishing phase. The Bovine Practitioner. 53(1):71-80

Kramer L, Mayes MS, Downey-Slinker E, Tait R, **Woolums AR, Chase CCL**, Reecy J. Genome-wide association study for response to vaccination in Angus calves. BMC Genetics. 2019. 20:6 doi: 10.1186/s12863-018-0709-5.

Presentations and Abstracts

Chamorro MF, Martinez D, **Woolums A,** Stockler R, Passler T, Silvis S. Effect of vaccination of beef cows during gestation on transfer of passive immunity and clinical protection of calves against experimental challenge with BRSV. American Association of Bovine Practitioners, Annual Convention. Louisville, KY. Sept 24 - 26, 2020

Hoyos-Jaramillo A, **Palomares RA**, Bittar J, Divers S, Kirks S, Urdaneta J, Ibrahim M, **Chamorro MF**, Edmonson M, Rush J, Miller J, Rodriguez A, Gonzalez E. Health status and endoscopic evaluation of the upper respiratory tract of dairy bull calves inoculated with BVDV2 and BHV1 after vaccination and trace minerals injection. Bovine Respiratory Disease Symposium, Denver, CO Aug 7-8, 2019.

Bornheim H, **Chamorro MF, Woolums AR, Larson R**, Huser S, **Cernicchiaro N**, Thoresen M, Jones K, Weaber B. Priming antibody responses against BRSV in beef calves through early vaccination. 2019 ACVIM Forum, Phoenix, AZ, June 6 – 9, 2019. Journal of Veterinary Internal Medicine. 2019; 33: 2460-2461.

Akter, A.*, E. Eckelkamp, J. L. Edwards, C. C. Okafor, G. M. Pighetti, J. M. Caldwell, P. Myer, and **L. Schneider**. 2019. Differentiation of the nasopharyngeal microbiomes in stocker calves experiencing BRD-associated activity change. UTIA Graduate Research and Poster Symposium, UTBFC Annual Research and Recommendation Meeting, Knoxville, TN.

Akter, A.*, J. M. Caldwell, G. M. Pighetti, and **L. Schneider**. 2020. Immunological response to naturally occurring bovine respiratory disease in stocker cattle during early management. Conference for Research Workers in Animal Disease Proceedings.

Akter, A. , M. Caldwell1, G. Pighetti1 and **L. Schneider** 2020. Hematological and physiological changes observed in commercial stocker operation during early management. American Society of Animal Science Annual Meeting.

Beyi AF, Hawbecker T, Slagel C, Ruddell B, Hassall A, Dewell R, **Dewell G**, Sahin O, Zhang Q, **Plummer P**. Alteration of gut microbiota following treatment of bovine respiratory disease with Danofloxacin in beef calves. Conference for Research Workers in Animal Disease. Chicago, IL, November 2-5, 2019. #239