Take-home Messages

1. Regardless of vaccination or future BRD diagnosis, gene expression pathways related to the innate and adaptive immune system increased over time.
2. Antigen presentation cell activity, cellular chaperoning, and Th17 cell immunity remains elevated 60 days post-initial vaccination.
3. Antimicrobial peptide production, IL3/5 cytokine signaling, and neutrophil degranulation may predict later BRD occurrence at backgrounding.

The impact of preweaning vaccination on gene expression in cattle that remain healthy or develop BRD during the backgrounding phase

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Objective:

Bovine respiratory disease (BRD) remains a priority within livestock research. Vaccination of pre-weaned calves against BRD-related pathogens is one of the leading management tactics to manage BRD. However, the influence pre-weaned vaccination strategies have on long-term health outcomes and immunomodulation is poorly understood.

Comparison of gene expression pathways in vaccinated and unvaccinated calves that later develop or resist BRD would improve concepts that may result in improved health and performance following vaccination.

Materials and Methods:

1. Bull calves (n=84) were enrolled in a split-plot randomized controlled trial, equally assigned to receive vaccination or not (**VAX or NOVAX**) then later assigned to direct transportation to a backgrounding facility post-weaning or sent to an auction market/order buyer facility prior to transportation (**Direct or Auction**).
2. Calves for this study were evaluated at four timepoints (Figure 1):
   - **a)** **T1**; vaccination (median age=107 days)
     - i. Tested via ear notch ELISA for Bovine Viral Diarrhea Virus persistent infection and received a multivalent respiratory vaccine (Pyramid 5) subcutaneously (**VAX**) or given 0.9% saline subcutaneously (**NOVAX**)
   - **b)** **T2**; seven days post-vaccination (median age=114 days)
   - **c)** **T3**; revaccination and surgical castration (median age=183 days)
     - i. Revaccinated according to treatment
     - ii. All calves received a multivalent clostridial bacterin-toxoid subcutaneously (Covexin 8) and surgically castrated
   - **d)** **T4**; weaning (median age=230 days)
3. Jugular blood samples were taken at each timepoint into Tempus Blood RNA Tubes.
4. 45-day backgrounding phase following T4:
   - a) Cattle were examined daily by trained caretakers for clinical signs of BRD and treated based on a standard protocol.
   - b) Cattle were defined as BRD (treated for BRD during backgrounding) or NO BRD (not treated for BRD during backgrounding).
5. Bioinformatic pipeline and analysis performed identical to Scott et al. 2022 (https://doi.org/10.3389/fvets.2022.1010039).

Figure 1. Overview of Sampling Timepoints (T1-T4):

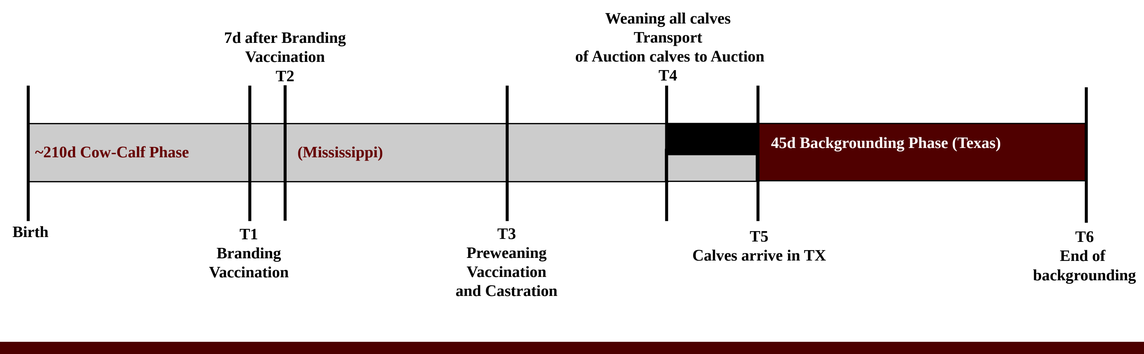


Figure 2. Principal Component Analysis (PCA) biplots of significantly correlated PCs with BRD and/or vaccination groups for A) T1, B) T2, C) T3, and D) T4.

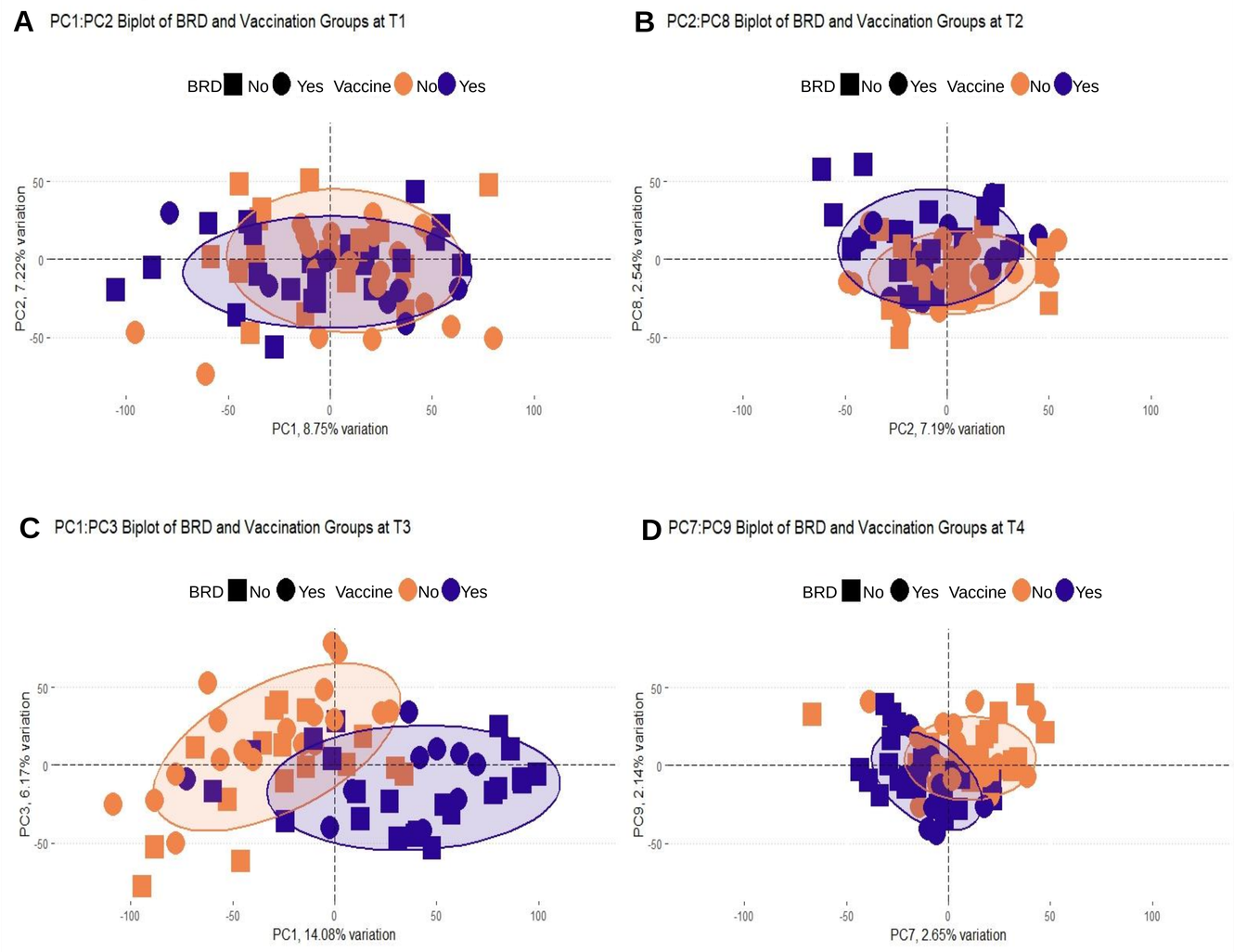
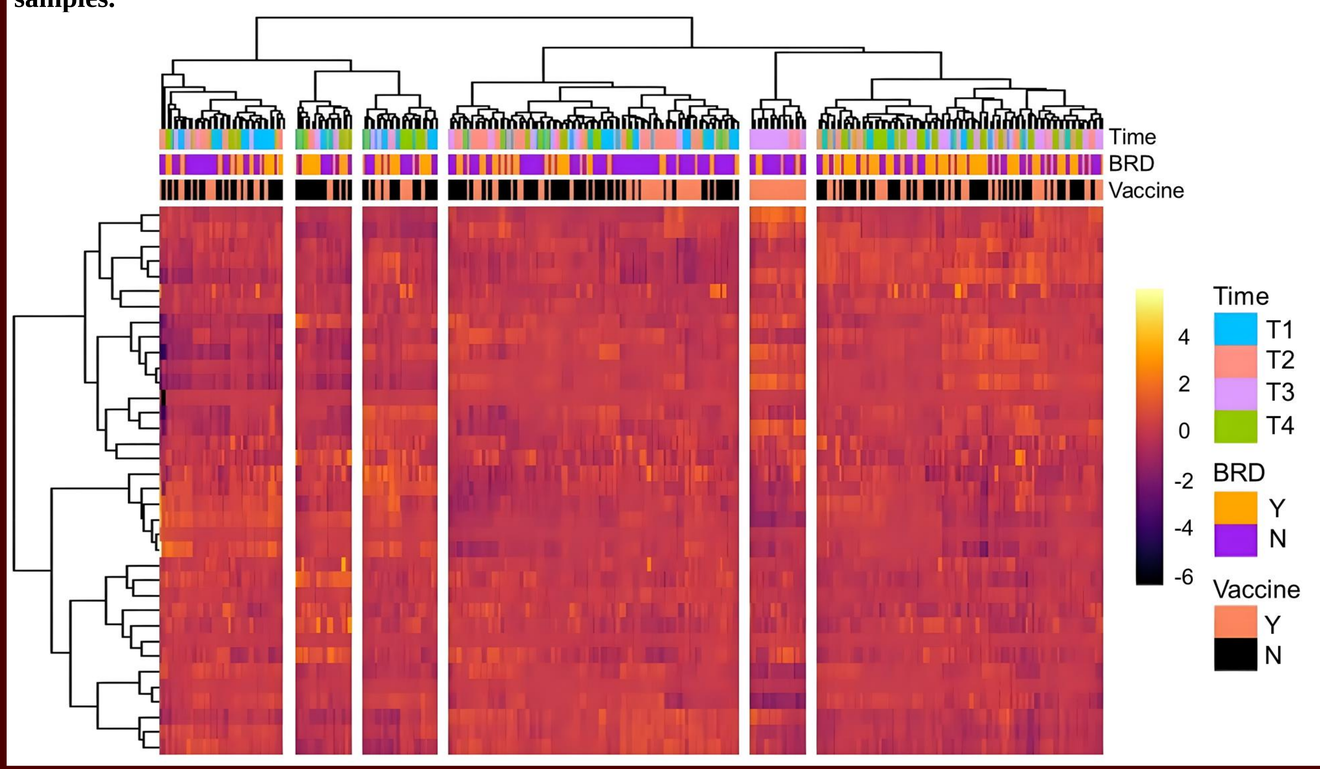


Figure 3. Heatmap and unsupervised hierarchical clustering analysis of global gene expression patterns of all samples.



Results:

Time:

Time was evaluated by comparing timepoints and blocking for the effects of VAX and BRD, resulting in 10,397 differentially expressed genes (DEGs) across all timepoints. These DEGs enriched pathways related to the innate and adaptive immune system, interleukin signaling, and protein transcription and translation. Gene expression related to these pathways was upregulated from T1 to T3 and then downregulated to T4. Figure 3 demonstrates the correlations between variables of interest, time is a driver of variation within the data.

Vaccination:

A total of 112 DEGs across all timepoints were enriched related to vaccination. At T3 VAX cattle had increased gene expression pathways related to cellular response to stress, neutrophil degranulation, and antigen processing and presentation compared to NOVAX cattle. Global gene expression patterns demonstrated that cattle that received a vaccine (VAX), at T3, were clustered uniquely together compared to all other samples (Figure 3). Across all timepoints, there were a lack of interferon pathways, natural killer cell responses, and neutrophil activity, however antigen presentation pathways were found to be enriched.

BRD:

A total of 243 DEGs were enriched for across all time points for BRD. Gene expression pathways for BRD cattle were related to oxygenation, cellular metabolism, and cytokine signaling at T4, when compared to cattle which resisted BRD.

Conclusions:

Regardless of vaccination or future BRD diagnosis, immunological development is indicated by adaptive immunity, lymphocyte development, and inflammatory resolution. The identification of immune and metabolic genomic mechanisms that may influence health and performance outcomes of cattle could provide information used for predicting vaccination history and/or immunomodulation post-viral exposure. These findings provide a foundation for future research in developing disease-predictive assays and targeted management approaches in commercial beef cattle operations.

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