The use of a dual-challenge Bovine Viral Diarrhea Virus-*Mannheimia haemolytica* model to compare vaccine efficacy in calves in the face of maternal immunity

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Introduction

Bovine respiratory disease continues to be the greatest threat to calf health. One of the common recommendations is to vaccinate young beef and dairy calves at 30-60 days of age to provide protection at weaning or when commingled. A study was designed to determine if vaccination in the face of maternal antibody would provide protection against a dual challenge with bovine viral diarrhea virus (BVDV) and *Mannheimia haemolytica* ~5 months after vaccination.

Materials and methods

In this study, colostrum-fed dairy x beef calves were vaccinated at ~30 days of age with either a placebo (CON), an adjuvanted parenteral vaccine containing modified live BVDV type 1 and type 2, bovine herpesvirus 1 (BHV-1), bovine parainfluenza virus (PI3) and bovine respiratory syncytial virus (BRSV) and *M. haemolytica* toxoid (Pyramid® 5 + Presponse® SQ)(P5P) or intranasal temperature-sensitive (TS) BHV-1- BRSV-PI3 (Inforce® 3) along with a parenteral vaccine containing modified live BVDV type 1 and type 2 and *M. haemolytica* toxoid (One Shot® BVD) (IOB). The calves were challenged ~150 days post vaccination with BVDV 1b and then 7 days later with *M. haemolytica*. The calves were than euthanized 6 days after the *M. haemolytica* challenge. Pre- and post-clinical observations were performed daily starting -1 days post challenge (DPC) until necropsy. Daily observations included rectal temperatures and clinical signs, including scoring for depression, dyspnea, cough, ocular discharge, nasal discharge, nasal mucosal lesions and oral mucosal lesions. Blood for BVDV 1 and BVDV 2 serum neutralization (SN) and *M. haemolytica* antibody ELISA was collected from each calf on the post-challenge days 0, 3, 7 and 12. Nasal secretion (NSec) samples were tested for BVD virus isolation and PCR, secretory IgA specific for BVDV and *M. haemolytica*, on post-challenge days 0, 3, 7 and 12. Whole blood was collected from all groups for complete blood count (CBC), BVDV viremia from buffy coats by virus isolation and PCR, and BVDV cell proliferation assay for IFN γ levels on days 0, 3, 5, 7, 9 and 12. At necropsy, lungs were scored, and lung tissue samples were collected from the lobe of each calf after lung scoring was complete. One sample was frozen for use in BVDV PCR testing and another sample was processed for histology and BVDV immunohistochemistry.

Results

The dual-challenge model was successful, as indicated by the BVDV PCR results, lung lesion development and microscopic attributes of lung lesions. Clinical signs following BVDV infection were similar in all groups. There was increased rectal temperatures in the IOB on day 7 post BVDV infection. Following *M. haemolytica* infection, temperatures in the CON and IOB groups were significantly elevated. The P5P vaccinated animals had no leukopenia following BVDV infection while the CON and the IOB groups had similar levels of leukopenia. BVDV type 1 and 2 serum titers increased following the vaccination with P5P while the BVDV type 1 and 2 serum titers waned in the CON and the IOB groups. The BVDV PCR results for buffy coats and nasal swabs indicated higher levels of virus present in CON and IOB versus P5P. Gamma interferon response was higher in animals vaccinated with P5P than CON and IOB groups signifying greater immune memory. P5P had the lowest percent pneumonic tissue (1.6%) among the treatment groups owing to a preponderance of fibrocollagenous matrix expanding interlobular septa and impeding lesion advancement. Lesion development was higher in the IOB vaccinates (3.7%) and not surprisingly was greatest in the CON group (5.3%). Coagulative parenchymal necrosis and necrotic inflammatory cells, the so-called "oat cells" were visualized in microscopic pulmonary lesions across vaccinate groups, inferring *M. haemolytica* underlies parenchymal lung disease although the degree of necrosis and presence of oat cells differed between the vaccinates and was far less in the P5P vaccinates owing to lesion reparation and healing.

Significance

Vaccination in the face of maternal antibody with a parenteral Metastim®-adjuvanted vaccine resulted in better protection as compared to a regimen of an intranasal vaccine plus a parenteral adjuvanted BVDV and *M. haemolytica* combination vaccine in a BVDV- *M. haemolytica* dual-challenged model.

