# A 2 × 2 factorial randomized controlled trial of a commercial *M. bovis* (CMB) vaccine and a conditionally licensed *M. bovoculi* vaccine (CLMB) to prevent IBK

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## Introduction

Infectious bovine keratoconjunctivitis (IBK) is an economically important disease of beef cattle. Currently, there is little public evidence from randomized controlled trials that the different vaccines and vaccination regimes available to prevent IBK in cattle are effective, including autogenous and commercial vaccines directed at *Moraxella bovis* or *Moraxella bovoculi.* The combined use of a commercial *M. bovis* (CMB) vaccine and a conditionally licensed *M. bovoculi* vaccine (CLMB) has yet to be publicly evaluated.

## Materials and methods

The conduct of the study was approved by the Iowa State University IACUC committee. A protocol for the trial was finalized in April 2021 using the SPIRIT guideline. We conducted a 4-arm parallel controlled trial: no vaccine (NV), commercial *M. bovis* (CMB) vaccine, a conditionally licensed *M. bovoculi* vaccine (CLMB) and CMB + CLMB. Two doses of vaccines were administered subcutaneously. The allocation unit was the calf, and calves with ocular lesions at enrollment were not eligible to be included in the study. The primary outcome, IBK, was diagnosed by farm staff or a previously undiagnosed centrally located corneal scar detected at weaning. The randomization schedule was generated prior to eligible assessment in Excel using the RAND() function. To work with the farm workflow, all calves were assigned based on the allocation schedule, and notes were taken on animals with lesions. The animals with lesions were subsequently excluded. Separate notes were taken by staff on ocular lesions, and animals enrolled with noted lesions were excluded from the data analysis. To maximize the power of the study, it was pre-planned that the results would be incorporated into a network meta-analysis using previously proposed methods, so even allocation to arms was not used. No identifying features/tags were used to identify animals that received treatment, so the ability to deviate from the assigned protocol was considered minimal (i.e., blinding). A logistic regression model was used to evaluate the statistical significance of the main effects and interaction terms. The risk ratios were calculated from raw data without adjustment for other variables.

## Results

The study ran from June to October 2021 at an Iowa farm. A total of 241 spring-born Angus calves were eligible for assessment, and 189 calves completed the study. At enrollment, the average weight of the enrolled calves in each group did not differ meaningfully by weight: NV = 241 lb, CMB = 224 lb, CLMB = 223 lb, CMB+CLMB = 232 lb. The IBK incidence was as follows: NV = 11/31 (35%), CMB = 13/29 (45%), CLMB = 11/28 (36%), CMB + CLMB = 49/101 (49%). The overall model *P*-value from an unadjusted logistic regression model for the comparison to the null model was 0.748. The unadjusted risk ratio of the pairwise comparison of the no-vaccine group to both groups was 1.37 (95% confidence interval (CI) : 0.812-2.29). The unadjusted risk ratio of the pairwise comparison of the no-vaccine group to the commercial *M. bovis* groups was 1.263 (95% CI: 0.678, 2.36). The unadjusted risk ratio of the pairwise comparison of the no-vaccine group to the conditionally licensed *M. bovoculi* vaccine groups was 1.18 (95% CI: 0.57 to 2.145). No adverse events were noted during the trial.

## Significance

The trial was not able to document evidence of the benefit of individual or combined vaccination with a commercial *M. bovis* vaccine and a conditionally licensed *M. bovoculi* vaccine (CLMB) in the prevention of IBK. The major limitation of the trial is that it only presents a single herd, and the uneven allocation reduces power for some pairwise comparisons. However, none of the observed effect sizes were protective (i.e. < one) . Combination with data from other trials in a network meta-analysis is pending.

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