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Prevention of abortion in cattle following vaccination against bovine herpesvirus 1: A meta-analysis

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ABSTRACT

Bovine herpesvirus 1 is ubiquitous in cattle populations and is the cause of several clinical syndromes including respiratory disease, genital disease, and late-term abortions. Control of the virus in many parts of the world is achieved primarily through vaccination with either inactivated or modified-live viral vaccines. The purpose of this meta-analysis was to determine the cumulative efficacy of BoHV-1 vaccination to prevent abortion in pregnant cattle. Germane articles for inclusion in the analysis were identified through four online scientific databases and the examination of three review and ten primary study article reference lists. A total of 15 studies in 10 manuscripts involving over 7500 animals were included in the meta-analysis. Risk ratio effect sizes were used in random effects, weighted meta-analyses to assess the impact of vaccination. Subgroup analyses were performed based on type of vaccine, MLV or inactivated, and the type of disease challenge, experimentally induced compared to field studies. A 60% decrease in abortion risk in vaccinated cattle was demonstrated. The greatest decrease in abortion risk was seen in studies with intentional viral challenge although vaccination also decreased abortion risk in field studies. Both inactivated and modified-live viral vaccines decreased abortion risk. This meta-analysis provides quantitative support for the benefit of bovine herpesvirus 1 vaccination in the prevention of abortion.

1. Introduction

Bovine herpesvirus 1 (BoHV-1) is a member of the *Alphaherpesvirinae* subfamily of the family *Herpesviridae*. The virus is the cause of several clinical syndromes in cattle populations worldwide, resulting in its classification as an OIE-listed disease (OIE, 2016) due to its socio-economic and/or public health importance and significance to international trade of animals and animal products. Clinical syndromes, including respiratory disease, vaginitis, balanophosthitis, abortion, and conjunctivitis may be observed after acute infection or subsequent to viral recrudescence following periods of stress. Fetal infections may also result in stillborn or weak calves with increased mortality during the first few weeks of life. The virus is a key pathogen in the bovine respiratory disease complex, but the reproductive consequences of the virus may be more important to cow-calf and dairy producers (Raaperi et al., 2012).

The abortifacient properties of virulent BoHV-1 have long been recognized, following either natural exposure (Crane et al., 1964; Sattar et al., 1965) or administration of early modified-live viral (MLV) vaccines (Kelling et al., 1973; Mitchell, 1974). Classically, the virus is viewed as a late-term abortifacient with the majority of abortions occurring after seven months of gestation. Abortion generally occurs within a few weeks of viral exposure but may be delayed for as long as three to four months post-exposure if viral latency occurs in the placenta (Radostits et al., 2007). In herd outbreaks, abortions are often observed after signs of respiratory disease with expulsion of the fetus possibly delayed for weeks to months. Abortion is often associated with retention of the fetal membranes but rarely impacts future fertility of the dam (Radostits et al., 2007).

In the half-century that has elapsed since the original clinical reports of BoHV-1 induced abortion, cattle producers, veterinarians, and industry stakeholders alike have sought to decrease the risk of BoHV-1 abortion through the use of biosecurity protocols, diagnostic testing, and effective vaccination programs (reviewed by Newcomer and Givens, 2016). Effective protection through vaccination not only provides immunity to the dam but will also protect the fetus from the abortifacient properties of the virus. Both inactivated and MLV BoHV-1 vaccines are widely marketed and vaccine selection will depend on the goals of the producer in

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light of the herd history and current management scheme. In general, MLV vaccines have a more rapid onset of immunity, generate higher neutralizing antibody titers, and provide a longer duration of immunity than inactivated vaccines. In addition to stimulating high levels of neutralizing antibodies, MLV vaccines also stimulate cell-mediated immunity (Woolums et al., 2013). Inactivated vaccines are generally safe for use in pregnant cattle although certain MLV vaccines have received label claims for administration to pregnant cattle provided certain conditions have been met (reviewed by Newcomer and Givens, 2016).

Despite its long history, BoHV-1 remains the most commonly diagnosed cause of bovine viral abortion in North America (Anderson et al., 1990; Yamini et al., 2004). Furthermore, reports of abortion in vaccinated dams have led some to question the ability of vaccination to prevent abortions caused by BoHV-1 infection. Therefore, the primary purpose of this study was to analyze published reports to determine the efficacy of BoHV-1 vaccination to prevent abortion in pregnant cattle. Subgroup analyses were performed based on type of vaccine, MLV or inactivated, and the type of disease challenge, experimentally induced compared to field studies.

2. Materials and methods

A search for pertinent articles using four relevant scientific databases (PubMed, Web of Science, CAB Abstracts, and AGRICOLA) was performed in February 2016. To ensure the identification of the broadest range of manuscripts, numerous searches were performed using one of several terms for BoHV-1 (BHV 1, BHV-1, BoHV, BoHV 1, BoHV-1, IBR) in conjunction with the search terms "abortion" or "vaccine". The reference lists of pertinent review articles (Plowright, 1978; Nandi et al., 2009; Graham, 2013) and from studies included in the final meta-analysis were examined to identify additional relevant manuscripts. Three criteria established a-priori were used as conditions for inclusion of identified studies in the final meta-analysis: 1) the study was a controlled, primary study; 2) the study was pertinent to the objective of this meta-analysis; and, 3) data from the study could be extracted for further analysis. No limitations based on language or year of publication were imposed on the search. Articles in languages other than English were translated to English by the authors or with the help of an online translation service (Google Translate, Mountain View, CA). Search results were initially screened using the title and abstract. All published studies that examined the use of BoHV-1 vaccination in pregnant cattle were selected for further scrutiny. Studies were not excluded based on breed or purpose of cattle in the study or due to study location. Vaccine formulation was not a limiting factor in selecting studies for this meta-analysis. Thus, MLV and inactivated viral vaccines, as well as both monovalent and multivalent vaccines were included in the study; however, studies with experimental challenge with pathogens other than BoHV-1 (e.g. bovine viral diarrhea virus) were excluded from further analysis.

Data relating to the abortion risk following vaccination for BoHV-1 were extracted from all studies meeting the study inclusion criteria. Two of the authors were involved in data extraction (BWN, LGC). Data extracted from the primary studies included animal type and use, vaccination formulation and brand name (if applicable), route of viral challenge, stage of gestation at challenge, and the viral challenge method in addition to the number of abortions and total group size for both the vaccinates and unvaccinated controls in each study. To analyze the risk of abortion, the total number of recorded abortions and total number of pregnancies for both the vaccinated and the unvaccinated control groups was recorded. With one exception, the total number of abortions was used for the analysis rather than only those abortions confirmed to be caused by BoHV-1 as many aborted fetuses were lost to follow-up and the etiologic cause could not be ascertained. In the lone study involving multi-pathogen challenge, abortions definitively caused by other pathogens and not BoHV-1 were not included in the abortion count for the current analysis.

Data was analyzed using a commercial meta-analysis software program (Comprehensive Meta-analysis, Biostat, Englewood, NJ, USA). The relative risk (RR) for each individual study was used as the effect size metric. The RR compares the probability of an event occurring in an exposed (i.e., vaccinated) group to the probability of the event occurring in a non-exposed (i.e. unvaccinated) group. When there is no difference in risk between groups the RR equals one. If the RR is greater than one, the event is more likely in the exposed group; when the RR is less than one, the exposure is deemed to have a protective effect on the measured outcome. Results were presented as means bounded by 95% confidence intervals (CI). Means were statistically different ($p < 0.05$) from the null hypothesis (i.e., no effect of vaccination) when the 95% CI did not include 1. Weighted meta-analysis was performed using a random-effects model to compare mean effect sizes across treatment types. Weighting of individual studies was performed using the default weighting algorithm of the meta-analysis software program for a random-effects model. Heterogeneity was evaluated informally in this meta-analysis due to the small number of studies included in the meta-analysis. Publication bias was visually assessed using a funnel plot of the standard error by log risk ratio. In addition to the overall meta-analysis, subgroup analyses were performed using specific subsets of the identified studies to assess the type of vaccine (MLV or inactivated) and the type of viral challenge (field study or experimental challenge).

3. Results

The initial database searches yielded a total of 1724 articles that matched the search terms (Fig. 1). Following removal of duplicate citations and studies irrelevant to the current meta-analysis (i.e., did not evaluate the efficacy of BoHV-1 vaccination in the prevention of abortion), 41 full-text articles were assessed for study eligibility. After exclusion of 26 reports for incompatibility with the study objectives or design, 15 total studies in 10 manuscripts were identified for inclusion in this study (Table 1). The 15 studies included in the assessment comprised 7536 total pregnancies between the treatment (vaccinated) and control (unvaccinated) groups. When all studies were included in the meta-analysis, risk of abortion was decreased by 60% (RR = 0.40; CI = 0.28–0.58) in vaccinated animals compared to unvaccinated cohorts (Fig. 2). Seven of the 15 studies analyzed did not demonstrate a significant decrease in abortion risk but the decrease resulting from the combined analysis was highly significant ($p < 0.001$). Visual assessment of the funnel plot demonstrated an approximately symmetric inverted funnel shape distribution of the data points which is the pattern expected when publication bias is unlikely (data not shown).

Nine studies included in the meta-analysis utilized vaccines containing MLV BoHV-1 vaccines, the vaccines used in the remaining six studies were inactivated. Studies using MLV vaccines involved 1469 study animals; animals involved in the studies utilizing inactivated vaccines totaled 6067. In both groups, vaccination significantly decreased the abortion of risk. In the analysis of the MLV studies, the RR of abortion was 0.42 (CI = 0.26–0.68) (Fig. 3). The RR of abortion in studies employing inactivated vaccines was similar (0.37; 0.21–0.67) (Fig. 4). In a separate subanalysis, studies involving field challenge or challenge with multiple viral pathogens were excluded from the evaluation, leaving only studies with an intentional, controlled BoHV-1 challenge. Seven studies were included in this analysis which yielded a RR of 0.18