Efficacy of bovine viral diarrhea virus vaccination to prevent reproductive disease: A meta-analysis

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ABSTRACT

Bovine viral diarrhea virus (BVDV) is an important reproductive pathogen of cattle worldwide. The reproductive outcome of BVDV infection is largely dependent on the immune status of the dam and the stage of gestation at the time of infection. Potential sequelae include failure of conception, abortion, a variety of congenital malformations, and fetal infection. Vaccination is a possible tool in the control of BVDV, and there has been a recently renewed focus on providing fetal protection through vaccination. Consequently, the aim of this study was to evaluate the efficacy of BVDV vaccination to prevent reproductive disease by performing a quantitative synthesis of previously published studies. Pertinent articles to be included in the analysis were identified by performing a search in four relevant scientific databases (PubMed, CAB abstracts, National Agricultural Library catalog, and Web of Science) and examining the reference lists of 10 germane review articles. Inclusion criteria for the meta-analysis mandated that the studies were controlled, primary studies that included necessary data for use in the meta-analysis (e.g., group size, number of abortions). Forty-six studies in 41 separate articles matched the inclusion criteria. Risk ratio effect sizes were used in random effects, weighted meta-analyses to assess the impact of BVDV vaccination on three outcomes: risk of fetal infection, abortion risk, and pregnancy risk. Within each outcome, subanalyses were performed to evaluate the effect of a variety of interventions, including modified live, inactivated, polyvalent and monovalent vaccination, homologous, heterologous, or field challenge, and studies with only bovine subjects. The analysis revealed a decrease in abortions of nearly 45% and a nearly 85% decrease in fetal infection rate in cattle vaccinated for BVDV compared with unvaccinated cohorts. Additionally, pregnancy risk was increased by approximately 5% in field trials of BVDV vaccinates. This meta-analysis provides quantitative support for the benefit of vaccination in the prevention of BVDV-associated reproductive disease.

1. Introduction

Bovine viral diarrhea virus (BVDV) is the prototype virus of the *Pestivirus* genus and a principal viral pathogen in both dairy and beef cattle populations. Viral infection leads to a wide array of clinical signs including diarrhea, thrombocytopenia and hemorrhagic diatheses, respiratory disease, and ulcerations of the gastrointestinal tract. However, the largest economic consequence of BVDV infection may be through reproductive losses [1]. Reproductive disease as a result of BVDV infection has been recognized from the time the virus was first reported [2] and remains a major concern on dairy farms, cow-calf ranches, and breeding stock operations. The consequence

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of BVDV infection on reproduction depends largely on the immune status of the dam and the stage of gestation at the time of infection. Exposure of naive cattle to the virus at or near the time of breeding can result in reduced pregnancy rates because of decreased conception rates and early embryonic death [3,4]. Abortion is most common in the first trimester but may occur at any time during gestation, including the third trimester. Viral exposure of the fetus between 18 and 125 days of gestation may lead to immunotolerance and persistent infection. Persistently infected (PI) calves are often weak at birth but may be phenotypically normal and are important to the epidemiologic aspects of viral propagation as they consistently shed high levels of virus in the environment. Infection during crucial times of organogenesis may also result in congenital defects including cerebellar hypoplasia, microphthalmia, hydranencephaly, hypotrichosis, and brachygnathism.

Control of BVDV is currently exerted primarily through strict biosecurity, eradication efforts, vaccination, or a combination of these factors. One of the primary aims of BVDV vaccination is to prevent the creation of PI calves that act as reservoirs of the virus. Although this goal was recognized by the mid-1970s [5,6], the efficacy of early vaccines to prevent fetal infection was often incomplete [7,8]. Improper vaccine usage has also contributed to their limited efficacy [9,10]. More recently, several BVDV vaccines have been licensed that carry fetal protection claims with at least 365 days duration of immunity. Despite this, accounts of fetal infection in calves born to vaccinated dams continue to be reported in the literature [11–13] leading some to question the efficacy of BVDV vaccination to prevent reproductive disease. Consequently, the objective of this study was to analyze the published data in regard to the efficacy of BVDV vaccination to decrease the risk of abortion, the probability of fetal infection, or to prevent a decrease in pregnancy risk.

2. Materials and methods

In May 2014, a search for articles was performed in four relevant scientific databases (PubMed, Web of Science, CAB Abstracts, and National Agricultural Library catalog) using the keywords "BVDV vaccine" or "BVDV" and "vaccine." The search results were not restricted by limitations on language or year of publication. The reference lists of several review articles on BVDV and BVDV vaccination [1,14–22] were examined for further pertinent studies. Additional articles were found by cross-referencing citations in retrieved articles. Studies identified from online databases and previous publications were selected for inclusion in the meta-analysis if the following criteria were met: (1) the study was relevant to the objective of the analysis; (2) the study was a controlled, primary study; and (3) data for further analysis could be extracted for at least one of the three outcomes of interest.

From all studies meeting the inclusion criteria, data relating to the outcomes of interest were extracted. To analyze the risk of fetal infection, the number of PI animals and total animals born were noted. Alternatively, precolostral positive antibody titers to BVDV in newborn animals were used as evidence of fetal infection in studies in

which viral challenge occurred following the susceptible window for the creation of PI animals. For the abortion risk, the number of total recorded abortions and the number of pregnant animals were documented. The total number of abortions was used for the analysis rather than only those abortions confirmed to be caused by BVDV as many aborted fetuses were lost to follow-up and the etiologic cause could not be ascertained. For pregnancy risk analysis, the number of recorded pregnancies and the number of animals bred by artificial insemination or exposed to a bull were extracted from each study. Data were analyzed using a commercial meta-analysis software program (Biostat, Englewood, NJ, USA). Studies in which no events were recorded for both the treatment and control groups and studies in which the number of events equaled the group size in both groups were excluded from further analysis by the software. The risk ratio (RR) for each outcome in individual studies was used as the effect size metric. The RR compares the probability of an event occurring in an exposed (i.e., vaccinated) group with the probability of the event occurring in a nonexposed (i.e., unvaccinated) group. When there is no difference in risk between groups, the RR equals 1. If the RR is greater than 1, the event is more likely in the exposed group; when the RR is less than 1, the exposure is deemed to have a protective effect on the measured outcome. Results were presented as means bounded by 95% confidence intervals. Means were statistically different ($P < 0.05$) from the null hypothesis (i.e., no effect of vaccination) when the 95% confidence interval did not include 1. Weighted meta-analysis was performed using a random-effects model to compare mean effect sizes across treatment types. Weighting of the data is performed inherently by the commercial software and is based on the inverse of the sampling variance and by the variability across the population effects.

To examine the effect of certain vaccine and virus factors, additional quantitative syntheses were performed within each outcome of interest using a subset of the identified studies relevant to that outcome. Within each outcome, the effects of modified live (MLV), inactivated, polyvalent or monovalent vaccines, homologous, heterologous, or field challenge, and vaccination studies using only cattle were evaluated. Studies included in the analysis of homologous challenge were those reports in which the challenge genotype was known to be included in the vaccine; studies included in the analysis of heterologous challenge were those investigations in which the challenge genotype was not included in the vaccine. Consequently, studies reporting a field challenge were not included in these subanalyses as the challenge strain could not be ascertained. At least three relevant studies for each subanalysis were deemed necessary to report the results of the meta-analysis.

3. Results

A combined total of 1164 reports were returned by the four databases. After removal of duplicate citations and studies irrelevant to this meta-analysis, a total of 46 studies in 41 reports were identified for meta-analysis. One study using a vaccine subsequently found to contain a BVDV