Assessing Vaccine Efficacy in the Feedlot

Carl S. Ribble, *BSc, DVM, MSc*
Department of Herd Medicine and Theriogenology
Western College of Veterinary Medicine
University of Saskatchewan
Saskatoon, Saskatchewan S7N OWO Canada

Introduction

How can you decide which vaccines to recommend to your feedlot clients? The purpose of this presentation is to develop a framework for the bovine practitioner for assessing the value of a commercial bacterin, toxoid, or vaccine by examining the scientific literature. A logical approach to reading this literature would help differentiate published trials that could help you in practice from useless or entirely misleading trials. **The principles are also extremely useful for carrying out trials within feedlots in your own practice.**

To demonstrate, I will refer generally to bovine respiratory disease (BRD) vaccines, and more specifically to recent research examining the effectiveness of a particular commercial *Haemophilus somnus* bacterin. Determining the effectiveness of this bacterin could be difficult because the organism is associated with a variety of clinical diseases, referred to generally as hemophilosis,[1] and it has been implicated as one of the potential initiators of the BRD complex.[2,3] How do you decide whether to recommend the use of this bacterin, or any other vaccine, for the prevention of hemophilosis or BRD?

Quality Information

You must have some information upon which to base your decision. The first step might be to look to the licensing body which, in Canada, is Agriculture Canada. **Unfortunately, the fact that a vaccine is licensed and available does not mean that it works.** Prior to the licensing of a new BRD vaccine, the manufacturer must provide information concerning certain legal and labelling details, as well as some indication that the product is safe (will not kill animals) and "effective".[4] "Effectiveness" is usually determined in the laboratory with host challenge studies, where vaccinated animals are challenged with a "model" exposure to the specific organism. In most cases these studies involve less than 50 animals.[5] The conclusion is obvious: you *cannot* rely on the licensing procedure to ensure *field* efficacy.

The next source of information is the manufacturing company. Has the company made its trial data widely available to practitioners? Some companies are definitely more open than others, and a few show a genuine commitment to evaluating the usefulness of their vaccine products in the field. If you have access to the manufacturer's data, you can critically evaluate it. You can examine the situatons under which the product was tested, the numbers and kinds of animals used in the trial(s), and how the company measured effectivness. Then you can decide how valid and relevant the trials are for your particular clients.

If a company will not release its own data on its own product you are left with nothing but promises and promotions. **Although advertising quality will almost certainly correlate well with an increasing producer demand for a new BRD vaccine, experience teaches us that it may not correlate well with vaccine efficacy.** What do you do if you have major BRD problems in a herd using this new vaccine? Did the problems occur because your client used an improper vaccination technique? How do you distinguish this situation from one where you have used a fundamentally **useless** vaccine, and your "technique" is therefore irrevelant?

Tizard suggests that one cause of "vaccine failure" is an ineffective vaccine.[6] I maintain this is faulty logic--**a vaccine failure implies that, under "normal" conditions, the vaccine works. But if a vaccine does not work, it cannot fail!** Without SOME data to suggest the new vaccine works, a search for why it "failed" in your herds is pointless.

In the case where you have no manufacturer data to evaluate a new vaccine, I see but two alternatives: (a) tell your clients the product is "untested", the manufacturer has not provided any efficacy data, and they are better to continue with the disease control procedures they are presently using (until you can better evaluate the product); (b) test the vaccine yourself.

Assessing Clinical Research

You can develop a mental checklist of key elements to look for when examining the clinical research published for a particular vaccine (Table 1). It can be very useful to keep an actual checklist like this beside you while perusing a recently published trial to help in your critical assessment. I will briefly examine each item on the list.

Table 1. A Vaccine Assessment Checklist

1. Has the vaccine been laboratory and field-tested in randomized controlled clinical trials? If so, how many trials, and, in each case:
2. Were the control groups concurrent or historical?
3. How were the trial animals challenged?
4. Was the measure of outcome meaningful?
5. Were the biology and epidemiology of the disease considered?
6. Was the vaccine assigned randomly?
7. Were blinding techniques used to reduce bias?
8. What other potentially important biases are evident?
9. How likely was the result a chance finding?
10. What are the differences between the trial animals and the animals in your practice? Are these differences important with respect to the vaccine?

Has the vaccine been laboratory and field-tested in randomized controlled clinical trials?

Again, you need information upon which to base your decision about whether to use a particular vaccine. Has the vaccine been tested in the laboratory and the field? Do you have access to the trial reports? If you do, you can work through the rest of the checklist with each report.

Were the control groups concurrent or historical?

The crucial ingredient in any scientific evaluation of a vaccine is the presence of a *concurrent* (or parallel) control group. At the outset of a trial, animals should be assigned by some (hopefully random) procedure to one of two groups: a vaccinated group and a control (unvaccinated) group. In this way, the control group is formed at the SAME TIME as the vaccinated group. Contrast this with *historical* controls where, for example, the control group is comprised of all animals fed in previous years. Published reports containing historical controls are little more than curious bedtime stories. Too many reasons can be found for a difference in outcome between vaccinates and controls in this situation. Fortunately, these kinds of stories are becoming rare in the veterinary literature.

How were the trial animals challenged?

In a laboratory study, ask yourself how closely the challenge model approaches the natural disease: does the challenge model provide a meaningful assessment of how the vaccine will work in the field?

With field trials, note whether the controls got sick. One *Haemophilus somnus* bacterin trial looked at differences between vaccinates and controls using "serologic criteria" (immunodiffusion assay reaction) and nasal cultures, but none of the test animals (control or vaccinated) got sick.[7] The conclusion by the authors that "development of a high level of immunity . . . prevented an outbreak of *Haemophilus somnus* disease" was pure conjecture. The controls did not get sick, indicating a total *absence* of the disease. Without natural challenge, field trials like this tell us very little about the value of the vaccine.

Was the measure of outcome meaningful?

The measured outcome should be one that would provide clear evidence that the vaccine does in fact prevent *disease.* Outcomes falling into this category include mortality, morbidity, and production measures like average daily gain. Looking at serological or culture results may be interesting, but they tell little about whether or not the vaccine actually prevents disease or improves production.

Researchers may go through great trouble to set up a field trial and end up with no natural challenge--for whatever reason, none of the animals get sick. These same researchers may go on to publish their serological and culture findings. The resulting paper may be interesting, but it helps little in our assessment of the usefulness of the vaccine in the field.

I have classified "morbidity" as one of the outcome measures that could be important. Realize, however, that what is frequently measured is not true "morbidity"; instead, the actual measure is "treatment rate" or "risk of treatment". This seemingly subtle distinction becomes very important with diseases like BRD where the case definition for a pneumonic calf can vary dramatically between different feedlots. Pen riders at one feedlot may pull and treat "depressed" calves very aggressively, without making any concerted attempt to distinguish between pneumonic calves and calves suffering from other feedlot diseases. Pen riders at another feedlot may treat less aggressively and be more diligent about distinguishing pneumonic calves from calves suffering from other diseases. "Treatment rate" will refer to two very different things in these two feedlots; the treatment rate recorded at the second feedlot would likely be a closer reflection of true BRD morbidity. In trials where so-called "morbidity" was the primary measure of outcome, you should take time to determine why animals were chosen for treatment, and decide how accurately you believe the reported "treatment rate" reflects true morbidity.

Were the biology and epidemiology of the disease considered?

It may not be enough to just report crude mortality differences, or crude morbidity differences. The outcome may have to be refined to take into consideration certain particulars of the industry, the disease, or the specific trial itself. Trials which assess vaccinating with a BRD vaccine upon arrival at the feedlot offer an example for consideration. How long will it take for the vaccine to become protective? A day? A week? What do we say about animals

that get sick or die *before* this time period? Should these animals be included in the analysis? The authors should at least demonstrate an awareness of this kind of problem, and show some attempt to deal with it in the analysis.

In a trial designed to assess the efficacy of a *Haemophilus somnus* bacterin,[8] we worried about the first week after the calves' arrival at the feedlot--it was possible that a large proportion of the calves became ill before the vaccine, which was given upon arrival, could take effect. Including these animals in the analysis would contribute to background, or statistical "noise" (a form of what epidemiologists call "misclassification bias"), and interfere with our ability to determine (statistically) if the vaccine worked. We used mortality as our primary outcome measure, but we also examined "fatal disease onset" (FDO), which was the day mortalities were first treated. This gave us an indication of precisely when animals first became "fatally ill". An epidemic curve of the FDO showed that almost one-quarter of the animals became "fatally ill" during the first week in the feedlot.

We then analyzed the data on a weekly basis for the first four weeks in the feedlot, and monthly thereafter. Not suprisingly, the vaccine appeared to have no effect on fatal disease during the first week, but did have a significant "preventive" effect during the second week. This approach also provided us with a possible explanation for the puzzling finding that the bacterin appeared to reduce mortality in steers, but not heifers. The FDO pattern in heifers was dramatically different--a significantly greater proportion of heifer FDO occurred during the first week, suggesting that a larger proportion of the heifers were simply not at risk to diseases preventable by giving a *Haemophilus somnus* bacterin upon arrival at the feedlot.[8]

Was the vaccine assigned randomly?

Look to see if some kind of randomization procedure was used to assign animals to the vaccinated and control groups. By randomizing the researchers hope to prevent introducing an "entry" bias into the trial. You want to be reassured that the researchers did not leave all the animals that looked "tough" or sick at trial outset in the control group!

In many situations, authors will report that animals were assigned to vaccination on a "systematic-random" basis, where, in the feedlot for example, a coin was flipped to determine whether the first or second animal through the chute was to be vaccinated; if it turned out to be the first, then every odd animal through the chute was then "systematically" vaccinated: if it turned out to be the second, then every even animal was vaccinated. This is an acceptable procedure. The important point is that the researchers have indicated they used some kind of "fair", random or semi-random, allocation procedure.

If there is no mention of this in the paper, credibility wanes. Try to determine precisely how the groups were chosen, and how the procedure used may have biased the trial results.

Were blinding techniques used to reduce bias?

There should be some indication of "blinding", where necessary, to ensure that both the vaccinated and control groups were treated similarily.[9] At the very least, it should have been very difficult for the people handling the animals in the trial to have known which were vaccinates and which were controls. Vaccinated animals should not, for example, be identified with a brighly coloured eartag!

What other potentially important biases are evident?

Pay attention to "trial specifics" and ask yourself what other design characteristics may have biased the researchers in some way. The authors often suggest a few potential biases themselves--you may be able to find more. Having identified potential biases, you must then decide if they are significant enough to discredit the entire paper.

We noted the presence of six potential biases in one of our vaccine trials.[8] Three trial characteristics--not vaccinating until arrival at the feedlot, mixing vaccinates and controls in the same pen, and mass medicating the animals with a long acting antibiotic in 32 of 36 pens--could have biased the trial towards finding no vaccine effect. The other three mentioned--vaccinating all calves (control and vaccinated) with an IBR-PI3 vaccine on arrival, high overall mortality compared to other feedlots (not really a bias), and pushing all calves through a chute a second time two weeks after arrival--could have biased the trial towards finding a significant vaccine effect.

It is safe to say that **all field trials will contain *some* bias.** Identifying the presence of a potential bias does not itself warrant discarding the paper. You must decide how significant the bias is, and in what direction the bias is likely to have "shifted" the results.

How likely was the result a chance finding?

The reported statistics should give you a clear understanding of how likely the results were a chance finding. Traditionally, researchers have reported "p values" to indicate whether or not their results were "significant". Unfortunately, the p value is not that informative. **In clinical trials where no difference between vaccinates and controls was noted, the p value is totally meaningless.**

You will gain far more insight by looking for two things: an estimate of the magnitude of the vaccine effect, and a confidence interval for the effect.[10] This amounts to asking the researchers: "What is your best estimate of vaccine effectiveness and, based on the number of animals in your trial, how accurate is that estimate?" Assessing the efficacy of one commercial *Haemophilus somnus* bacterin, we reported an incidence rate ratio (IRR) of FDO for

steers from the 2nd to 8th week to be 1.46, with a 95% confidence interval of 1.07 to 2.00. Our IRR "best estimate" suggested that for every 3 controls becoming fatally ill during this time, only 2 vaccinates (a ratio of 1.46:1) became fatally ill. Recognizing that this is a trial carried out on only a *sample* of the total feedlot-calf population in western Canada, we are reasonably confident that the "actual" IRR lies somewhere between 1.07 and 2.00 (the 95% confidence interval).

What are the differences between the trial animals and animals in your practice?

Differences between the sample of animals used in the reported trial and those you deal with in your practice will usually exist. You should note the differences and ask yourself whether any of these differences could significantly alter the reported effectiveness of the vaccine in your clients' herds. You are essentially asking how relevant the trial results are to your specific situation.

Assessing the Process Itself

The assessment process takes time, and it is not particularly "easy"--the strong medical and scientific background of a veterinarian is extremely valuable here. And there are no absolutes--a vaccine may work in some management environments but not others. The disease itself may change over the years, rendering a previously useful vaccine impotent. Like the game of "Calvinball" invented by cartoonist Bill Watterson through his characters Calvin and Hobbes, the rules are always changing: disease is not a static entity, but an evolving dynamic system.

What trial research is there for the *Haemophilus somnus* bacterin, and what does the "checklist" approach lead *me* to conclude about its effectiveness in protecting against BRD? The authors of the Bruce County observational study in Ontario reported that using a *Haemophilus somnus* bacterin was strongly associated with no or low mortality, although the bacterin was used in only a few feedlots, making the overall importance of the bacterin difficult to assess.[11,12,13] Equivocal results were reported from three field trials carried out in the United States, using "morbidity" as the primary measure of outcome--the trials were too small to effectively assess mortality.[14,15,16] However, more recent laboratory and field trials suggest (after working through the checklist) that the commercial bacterin does have some capability for preventing BRD and mortality.[8,17]

The magnitude of the effect, when used upon arrival at the feedlot, is measurable--the attributable percent for steers was 17% in the 1988 trial--suggesting that 17% of steer mortality could be prevented by vaccination with the bacterin.[8] The effect might be greater if the bacterin were used in a preimmunization or preconditioning program; however, this is pure conjecture at present because no field trials testing such a hypothesis have been published. And the rules of the game may be changing--recent research suggests that *Haemophilus somnus* may be responsible for a variety of fatal diseases in the feedlot, like "fatal" myocarditis, which previously we may have overlooked.[1,18,19,20] Is the disease truly changing, or are researchers merely uncovering an "old" story? And what does this mean for the commercial bacterin? The research must continue, with practicing veterinarians' remaining "current", applying the relevant findings to their particular clientele.

Summary

It is no great revelation to state that the process of assessing vaccine efficacy, especially the efficacy of BRD vaccines, is not an exact science. Complexities of the cattle industry and our incomplete understanding of the BRD complex necessitate further active research in the area. Within this uncertain environment, veterinarians must develop a logical approach towards assessing the best information available so that informed recommendations can be made to cattle producers. Critically assessing manufacturer data and the scientific literature, using a checklist like that presented herein, allows you to make an informed decision about vaccine use for your clients. The process will require continual updating as the nature of your clients' operations change, technology changes, and our understanding of diseases like the BRD complex improves.

(Author's Note: An abridged version[21] of this paper appeared previously in the proceedings of a "Symposium on the use of vaccines in the control of infectious diseases of cattle" sponsored by Boehringer Ingelheim (Canada) Ltd. and published in the October 1990 issue of the Canadian Veterinary Journal).

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