Assessing the efficacy of autogenous vaccines in bovine diseases

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Abstract

Vaccination is an important tool for preventing disease. In human medicine and veterinary health, the eradication of smallpox and rinderpest are stellar examples of how effective vaccinations can be. Other outstanding examples include vaccines against measles, mumps, and rubella in humans. In animal health, most vaccines are marketed broadly for use on multiple animals and farms. However, autogenous vaccines, which are intended for use on a single farm, are also common in livestock health worldwide. For this presentation, I discuss concepts related to assessing the efficacy of vaccines and provide a summary of the publicly available evidence from the scientific literature regarding the efficacy of autogenous vaccines.

Key words: autogenous biologics, custom vaccines

Résumé

La vaccination est un outil important pour prévenir la maladie. En médecine humaine et en santé vétérinaire, l'éradication de la variole et de la peste bovine sont des cas emblématiques reflétant l'efficacité de la vaccination. D'autres exemples notoires incluent les vaccins contre la rougeole, les oreillons et la rubéole chez les humains. En santé vétérinaire, la plupart des vaccins sont largement commercialisés pour être utilisés sur plusieurs animaux dans plusieurs fermes. Toutefois, les vaccins autogènes, qui sont destinés à être utilisés dans une seule ferme, sont assez communs en gestion sanitaire du bétail à travers le monde. Dans cette présentation, je discute de concepts reliés à l'évaluation de l'efficacité des vaccins et fournit un résumé des faits disponibles publiquement dans la littérature scientifique sur l'efficacité des vaccins autogènes.

Introduction

The United States Department of Agriculture (USDA) Center for Veterinary Biologics (CVB) uses the following statement: "Autogenous biologics are custom vaccines that consist of herd specific (homologous) antigens." For this presentation, I was asked to review the publicly available evidence for the use of autogenous vaccines in cattle practice. The manuscript includes a discussion of the challenges associated with assessing the efficacy of autogenous vaccines before reviewing the publicly available data.

Framing the Problem: What are the Challenges for Assessing the Efficacy of Autogenous Vaccines in Bovine?

Asking the question "Are autogenous vaccines effective?" is potentially misleading and unanswerable. In human health, the answer to a question such as "Are vaccines effective?" would be yes for smallpox, but no for malaria and HIV. Questions about vaccine efficacy must be directed at an organism, i.e., "Are vaccines against "organism XYZ" effective?" When considering the question "Are autogenous vaccines effective in cattle practice?" we should specify the target organism.

The Target Organism and Disease

All vaccines are directed at an organism rather than a disease. For some cattle diseases, there is a clear causal organism. For example, *Clostridium tetani* is the clear causal organism of tetanus. This bacterium produces 2 exotoxins, 1 of which (tetanospasmin) is a neurotoxin that causes the symptoms of tetanus. Therefore, asking "Are (autogenous) vaccines effective against tetanus?" is equivalent to asking "Are (autogenous) vaccines effective against *Clostridium tetani*?" In this case, the vaccines are effective.

For many other diseases, like bovine respiratory disease (BRD), there is no single necessary causal organism, so asking "Are (autogenous) vaccines effective against bovine respiratory disease?" is a very different question compared to "Are (autogenous) vaccines effective against *Mannheimia haemolytica*?". For a syndromic disease such as BRD, this creates an additional challenge because both the efficacy of the vaccine and the prevalence of the organism in the sufficient causes will impact the apparent efficacy.

To illustrate this issue using an example, assume that *Mannheimia haemolytica* is causally related to the BRD and in challenge studies a *Mannheimia haemolytica* vaccine is shown to be 50% effective at preventing the challenge model of induced BRD. Now if we also we imagined there were only 2 sufficient causes for BRD in the field (obviously there are in reality hundreds of sufficient causes):

1) Sufficient Cause 1 (SC1) is the combined effect of lightweight calves, poor weather, active bovine viral diarrhea virus (BVDV) infection, and *Mannheimia haemolytica*
2) Sufficient Cause 2 (SC2) is the combined effect of lightweight calves, poor weather, active BVDV infec-

tion, and IBR infection

In these scenarios, let us imagine we had 3 feedlots of 1000 animals each and the BRD risk is always 20%, but the sufficient cause of BRD on each farm differs as follows:

- On Farm 1, Sufficient Cause 1 is the only cause of all 200 BRD cases (20% of 1000).
- On Farm 2, Sufficient Cause 2 is the only cause of all 200 BRD cases (20% of 1000).
- On Farm 3, Sufficient Cause 1 is the cause of ½ the cases (100 BRD cases) and Sufficient Cause 2 is the cause of the other ½ of the BRD cases.

As a consequence of this distribution of the sufficient causes on the farms, if we conducted a randomized controlled trial of the *Mannheimia haemolytica* vaccine at each feedlot, we would see a different effect. At feedlot 1, if we allocated 500 animals to receive the vaccine and 500 to be unvaccinated, the observed BRD risk in the unvaccinated calves will be 100 cases (20% of 500). In the vaccinated animals, the observed risk of disease will be 50 cases (0.5*20%*500), because the vaccine is 50% effective. The trial would reach the same conclusion as the challenge study; the risk ratio is 0.5. (10%/20%). However, on Farm 2, the observed BRD risk is 20% in the vaccinated (100/500) and the unvaccinated calves (100/500) because the vaccine will not work because *Mannheimia haemolytica* is not part of Sufficient Cause 2. The trial would reach the conclusion that the vaccine doesn't work and the risk ratio is 1. (20%/20%). On farm 3, the observed BRD risk in the unvaccinated calves will be 20% (100 of 500). In the vaccinated calves, vaccination will have no impact on the 50% of BRD cases caused by Sufficient Cause 2, so those 50 cases will still occur. The vaccine will prevent ½ of the cases caused by Sufficient cause 1, or 25 cases. Therefore, in total, we expect 75 BRD cases will occur in the vaccinated animals on farm 3. The risk ratio will be 0.75 (75/500 (15) divided by 100/500 (20%).

Therefore, when asked the question "Does the (autogenous) vaccine work to control a disease like BRD?", the response is a function of 2 factors: the distribution of the sufficient cause (which is unknown) and the efficacy of the vaccine in those scenarios where *Mannheimia haemolytica* is present. This complexity of sufficient causes makes the estimation of an effective vaccine very difficult.

It could be argued that scenarios 2 and 3 are less likely with autogenous vaccines because if the organism is obtained from the farm, it is likely to be part of the cause, but this cannot be proven.

Time Dependence of Interpreting Vaccines' Effects

Another question that researchers should answer while trying to synthesize study results and reach conclusions about vaccines is "How relevant to current uses is the data from older studies?". If we asked how effective Ebola vaccines were 10 years ago, then the response would have been "not effective." However, recent studies with new vaccines suggest the answer may now be "yes." Such time dependence of vaccines and lack of detailed descriptions of the specific intervention make conclusive answers about the efficacy of a vaccine difficult. As will be seen later, the evidence about the efficacy of autogenous vaccines can be old. Whether the approach to the production of the vaccines used today is represented by studies conducted years ago is often unclear based on the publicly available reports or information from CVB about the manufacturing of autogenous vaccines.

Bias in Vaccine Trials

We must have well-executed, randomized controlled studies to estimate the vaccine's effect. In a vaccine trial, we use the risk of disease in the vaccinated group to represent what would have happened to the unvaccinated group if they had been vaccinated. This is why the difference in this disease risk is called the "vaccine effect". Random allocation to groups is critical to the validity of trials. Imagine a trial where allocation to the vaccine was based on weight. Of 100 animals enrolled, the 50 heaviest animals were given the vaccine, and the lighter animals were unvaccinated. When comparing the disease risk of these groups, we cannot conclude that any difference in risk is due to the effect of the vaccine, because the groups were not exchangeable. The groups differ with respect to a characteristic (weight) that is likely related to the disease outcome. Another characteristic of trials we will be seeking is the blinding of the allocation. We have evidence in veterinary science that failure to blind the allocation is associated with a better outcome in vaccinated groups, which suggests bias in the measurement of the outcome.

The Vaccine Effect Measurements

How should we measure the "vaccine effect"? There are several ways to measure vaccine effect, which are listed in Table 1. These calculations were made in the online software OpenEpi[a] and the formula is available online.[b] Not all the effect measures are suitable for comparing information across studies. In a randomized trial, we tend to measure the vaccine effect as a risk ratio, which is the ratio of disease in the vaccinated group divided by the disease risk in the unvaccinated group. Because most vaccines are designed to reduced disease risk, we expect that risk ratio to be less than 1 if the vaccine is effective. It is also frequent to summarize vaccines as the prevented fraction. There are 2 ways to calculate prevented fraction: the prevented fraction in the entire population or the prevented fraction in vaccinated animals. In observational studies, the prevented fraction in the entire population is often relevant. However, vaccines are a unique intervention, and it is intended that all animals will receive the vaccine, therefore only the preventive fraction in the exposed (vaccinated) is relevant. In Table 1 the results of 3 trials with different characteristics are presented, and we can see that the risk ratio and the prevented fraction in

Table 1. Effect sizes for a vaccine in three trial populations of different sizes.

Trial 1	**Diseased**	**Not diseased**
Vaccinated	10	90
Unvaccinated	20	80
Risk Ratio	0.5	0.2467 to 1.014
Risk Difference	-10%	-19.8 to 0.2008
Prevented fraction in population	25%	1.312 to 39.52
Prevented fraction in the exposed (vaccinated) population	50%	-1.358 to 75.33
Trial 2		
Vaccinated	20	80
Unvaccinated	40	60
Risk Ratio	0.5	0.315 to 0.79.17
Risk Difference	-20%	-32.4 to -7.605
Prevented fraction in population	12.5%	6.502 to 17.77
Prevented fraction in the exposed (vaccinated) population	50%	20.83 to 68.42
Trial 3		
Vaccinated	20	80
Unvaccinated	120	180
Risk Ratio	0.5	0.3299 to 0.758
Risk Difference	-20%	-29.6 to -10.4
Prevented fraction in population	12.5%	6.502 to 17.77
Prevented fraction in the exposed population	50%	24.22 to 67.01

the exposed(vaccinated) population are stable effect measures. These measures of the vaccine effect are unchanged by either the prevalence of the disease, which is 20% in the unvaccinated in Scenario 1 but 40% in the unvaccinated animals in Scenario 2. These metrics also don't change with the prevalence of vaccination, which changes from 50% in Scenario 1 to 33% in Scenario 3. We want a measure of the effect size that is consistent across populations. Consistency is 1 reason why we tend to use the risk ratio. The other reason is that compared to an odds ratio, a risk ratio is easier to interpret correctly.

Knowledge Synthesis, Replication, and Random Effects

Finally, when assessing interventions such as vaccines, we have to consider the potential for random error in estimations of the vaccine effect. In Table 1 we have an estimated risk ratio of 0.5. We know that we are conducting the study on a sample of animals and have uncertainty about the estimate, which is expressed by the confidence interval. Due to this, we need multiple estimates of the vaccine effect; this concept is known as replication. We would like to know if the results are consistent or highly variable. If we only have 1 estimate of the vaccine, it could just happen to be an outlier, or it could be truly representative of the vaccine effect.

Finding Evidence about Autogenous Vaccines in Bovine Practice

To find evidence of autogenous vaccines, we used a simple search for cattle vaccines modified to be autogenous. The search strategy employed 3 concepts: cattle AND vaccination AND autogenous. The search was conducted in March 2019, updated in August 2019, and the final results of the search are below. We looked in 2 databases: Cambridge Biological Abstracts and Medline. The search string was as follows:

1) TS=("cow" OR "cows" OR "cattle" OR heifer* OR "steer" OR "steers" OR "bull" OR "bulls" OR "calf" OR "calves" OR "youngstock*" OR "young-stock*" OR "beef" OR "veal" OR "bovine" OR "bovinae" OR buiatric*)
2) TS=(vaccin* OR immunis* OR immuniz* OR innoculat*)
3) #2 AND #
4) TS= autogenous
5) #4 AND #3

The search strategies were not to be limited by date, language, or publication type. We conducted searches using each source listed in the protocol and translated the strategy appropriately to reflect the differences in database interfaces and functionality. Two undergraduate students then screened abstracts for relevant studies. We considered relevant studies ones that were available in full-text format of more than 500 words, that reported a clinically relevant disease outcome and had a concurrent comparison group. Examples of outcomes excluded because they were not clinical outcomes were antibody responses, colonization, or shedding of a pathogen.

We identified 18 potentially relevant studies[1-18] for the most clinically relevant disease outcome, the number of animals enrolled in each group, and the frequency of the disease outcome in the vaccinated and unvaccinated animals. To extract the vaccine effect for presentation as a pairwise effect

of autogenous vaccines compared to control group, several decisions about extractions were made. For 3-arm studies we excluded a negative control challenge group,[8] a peer contract control group,[13] and commercial vaccine comparator.[11] One IBK study with 3 arms included 2 active autogenous vaccine arms which differed by route of administration and 1 unvaccinated group. For this study, we reported 2 pairwise comparisons, i.e., each active arm compared to the control group.[6,7] Several relevant studies did not appear to report numerical results in an approach that made accurate extraction feasible, so these were excluded.[1,3,6] For example, 1 study administered the vaccine at the animal level and reported results at the quarter level, but did so without adjustment for clustering. These results were excluded due to difficulty interpreting the results.[3] One of the studies provided no actual estimates of effect, other than to say that there was no vaccine effect.[15] Another study reported measurements of multiple outcomes associated with respiratory disease (heart rate, respiratory rate, nasal discharge, and crackling) over multiple days (Day 1, 3, 7, 14, and 21 post-challenge).[8] The cumulative incidence could not be used because the number of unique cases was not identified. Given the potential to pick the results from 25 outcomes, we reported the outcome with the largest difference (which was nasal discharge on Day 7),[8] but it was still not significantly different.

Results

Thirteen relevant manuscripts, some with multiple trials reported, had data that could be extracted. The risk ratios for the studies are included in Figure 1. Figure 1 is a forest plot, which is an approach to graphically presenting the results from a number of studies. A forest plot is often used to present a meta-analysis and summarize the effects overall. However, in this plot, the summary information is excluded because there is too much variation in vaccines to consider a single summary effect as relevant. The data for different diseases is grouped together by subgroups such as infectious bovine keratoconjunctivitis, mastitis, respiratory disease, and warts. In this forest plot, we have data from 17 studies reported. The risk ratio is calculated with the vaccine group in the numerator; therefore, if the vaccine was effective we would expect that the risk ratio would be less than 1. On the plot, the vertical black solid line is the "null value", i.e. when the intervention has no effect. For the risk ratio the null value is 1, because it means the risk is the same in both groups. On the plot, the risk ratio in each study is represented by a dot and the horizontal line indicates the 95% confidence ratio. The size of the blue box gives a relative measure of how much weight would be given to a study if it was used to calculate a summary measure. Larger boxes suggest the study is more accurate compared to other studies in the plot. For example, the Dubek et al study has a tiny box and wide confidence interval suggesting although the risk ratio 0.25. However, this protective effect is imprecisely known because the confidence interval varies from 0.04 to 1.63, which includes highly protective effects such as 0.04 and effects that suggest vaccination might cause the disease, such as 1.63.

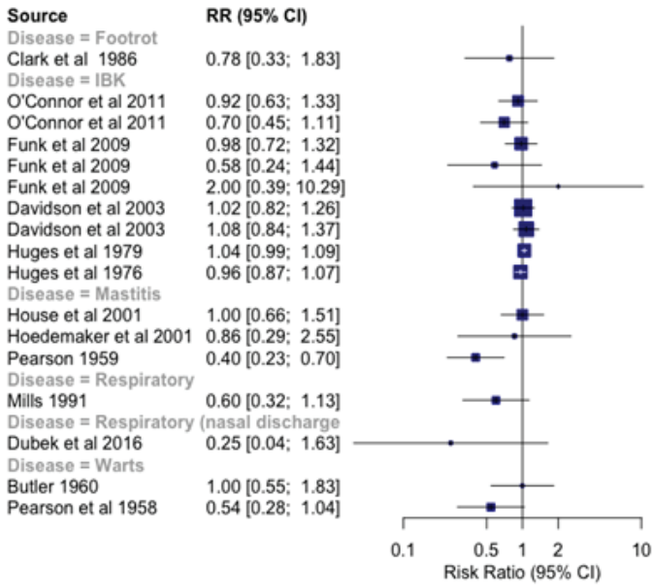

Figure 1. Risk ratio for outcomes reported for vaccine trials assessing the potential to reduce disease outcomes in cattle.

Discussion and Conclusion

Overall, the quantity of studies reporting the use of autogenous vaccines is small. The disease most frequently assessed is infectious bovine keratoconjunctivitis. For IBK, the results from the studies do seem consistent, with the conclusion that the vaccine effect seems null, i.e., no evidence of a protective effect. For the other diseases, it is not possible to draw any conclusions from the evidence because the studies were not replicated (footrot), most studies were not randomized or blinded (Table 2), and the majority of studies are very old (warts).

Autogenous vaccines are quite commonly used in veterinary science. It is difficult to know what technology is used to create the vaccines, as such information is not typically provided by companies. Further, there is almost no evidence suggesting that the vaccines, when assessed, are effective. Overall, 1 potential issue with this conclusion might be that we are missing substantial information. These omissions might have occurred due to publication bias or an incomplete search. Publication bias is a significant problem in veterinary research; however, the direction of the bias is usually in favor of the dissemination of positive results. As no results appear to be positive, this seems an unlikely explanation. Another option is that the evidence of efficacy is not needed or of interest to the individuals carrying out the studies. Alternatively, the search might have failed to capture all studies regarding the efficacy of autogenous vaccines in cattle.

Table 2. Reporting of randomization and blinding in autogenous vaccines studies in cattle

Authors	Approach to allocation to treatment group	Discussion of that assessment of clinical disease was made without knowledge of the vaccine group?
1	Allocation not described	Blinding not mentioned by authors
3	Random allocation (supporting evidence)	No- outcome assessment not blinded
4	Random allocation (supporting evidence)	Yes - outcome assessment blinded
5	Random allocation (no evidence)	Blinding not mentioned by authors
6	Random allocation (supporting evidence)	Blinding not mentioned by authors
7	Random allocation (no evidence)	Blinding not mentioned by authors
8	Random allocation (no evidence)	Blinding not mentioned by authors
9	Random allocation (supporting evidence)	No- outcome assessment not blinded
10	Random allocation (no evidence)	Blinding not mentioned by authors
11	Allocation not described	Blinding not mentioned by authors
12	Allocation not described	Blinding not mentioned by authors
13	Allocation not described	Blinding not mentioned by authors
14	Allocation not described	Blinding not mentioned by authors
15	Allocation not described	Blinding not mentioned by authors
16	Allocation not described	Blinding not mentioned by authors
17	Random allocation (no evidence)	Blinding not mentioned by authors
18	Allocation not described	Blinding not mentioned by authors

Endnotes

[a] https://www.openepi.com
[b] https://www.openepi.com/PDFDocs/TwobyTwoDoc.pdf

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References

1. Arora AK, Killinger AH, Mansfield ME. Bacteriologic and vaccination studies in a field epizootic of infectious bovine keratoconjunctivitis in calves. *American journal of veterinary research* 1976;37:803-805.
2. Butler WF. Treatment of bovine cutaneous papillomata with autogenous vaccine. *Veterinary Record* 1960;72:1016-1017.
3. CheolYong H, SonIl P, HongRyul H. Effects of autogenous toxoid-bacterin in lactating cows with *Staphylococcus aureus* subclinical mastitis. *J Vet Med Sci* 2000;62:875-880.
4. Clark BL, Stewart DJ, Emery DL, et al. Immunisation of cattle against interdigital dermatitis (foot-rot) with an autogenous *Bacteroides nodosus* vaccine. *Australian Vet J* 1986;63:61-62.
5. Connor AMO, Brace S, Gould S, et al. A randomized clinical trial evaluating a farm-of-origin autogenous *Moraxella bovis* vaccine to control infectious bovine keratoconjunctivis (pinkeye) in beef cattle. *J Vet Internal Med* 2011;25:1447-1453.
6. Daimi SGR, Waghmare SP, Bijwal DL, et al. Effect of autogenous killed vaccine against subclinical mastitis in cows. *Indian Vet J* 2006;83:15-17.
7. Davidson HJ, Stokka GL. A field trial of autogenous *Moraxella bovis* bacterin administered through either subcutaneous or subconjunctival injection on the development of keratoconjunctivitis in a beef herd. *Canadian Vet J* 2003;44:577-580.
8. Dudek K, Bednarek D, Ayling RD, et al. An experimental vaccine composed of two adjuvants gives protection against *Mycoplasma bovis* in calves. *Vaccine* 2016;34:3051-3058.
9. Funk L, Connor AMO, Maroney M, et al. A randomized and blinded field trial to assess the efficacy of an autogenous vaccine to prevent naturally occurring infectious bovine keratoconjunctivis (IBK) in beef calves. *Vaccine* 2009;27:4585-4590.
10. Hoedemaker M, Korff B, Edler B, et al. Dynamics of *Staphylococcus aureus* infections during vaccination with an autogenous bacterin in dairy cattle. *J Vet Med Series B* 2001;48:373-383.
11. House JK, Ontiveros MM, Blackmer NM, et al. Evaluation of an autogenous Salmonella bacterin and a modified live Salmonella serotype Choleraesuis vaccine on a commercial dairy farm. *Am J Vet Res* 2001;62:1897-1902.
12. Hughes DE, Kohlmeier RH, Pugh GW, et al. Comparison of vaccination and treatment in controlling naturally occurring infectious bovine keratoconjunctivitis. *Am J Vet Res* 1979;40:241-244.
13. Hughes DE, Pugh GW, Kohlmeier RH, et al. Effects of vaccination with a *Moraxella bovis* bacterin on the subsequent development of signs of corneal disease and infection with *M. bovis* in calves under natural environmental conditions. *Am J Vet Res* 1976;37:1291-1295.
14. Mills L. Cross-protection of feedlot calves against *Pasteurella* endotoxemia with an Re mutant *Salmonella typhimurium* bacterin-toxoid. *Agri-Practice* 1991;12:35-36, 38-39.
15. Olson NE. Studies on the effects of vaccination of dairy cattle against staphylococcic mastitis. *Dissertation Abstracts* 1966;26:5377-5378.
16. Pearson JKL. Autogenous toxoid vaccine in the prophylaxis of staphylococcal mastitis in cattle. *J Dairy Res* 1959;26:9-16.
17. Pearson JKL, Kerr WR, McCartney WDJ, et al. Tissue vaccines in the treatment of bovine papillomas. *Vet Rec* 1958;70:971-973.
18. Reeves HE, Lotz SB, Kennedy E, et al. Evaluation of an autogenous vaccine in cattle against *Escherichia coli* bearing the CTX-M-14 plasmid. *Res Vet Sci* 2013;94:419-424.