Infectious bovine keratoconjunctivitis: An update

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Abstract
Infectious bovine keratoconjunctivitis (IBK, pinkeye) is cattle's most common production-limiting disease and the most common ocular disease. Despite being reported for many years, the epidemiology of IBK remains elusive. *Moraxella bovis* remains the only organism for which there is causal evidence. *Moraxella bovoculi* bacterins have been on the market for several years; however, they remain with a conditional licensed. None have been fully licensed today. Data from publicly available studies suggest that vaccine efficacy for IBK vaccines ranges from -30% to 30%, except one study published in 1976 with 32 animals that reported efficiency of ~60%. By comparison, the Moderna COVID-19 vaccine has a reported vaccine efficacy of 94%.

Key words: pinkeye, *Moraxella*, infectious bovine keratoconjunctivitis

Introduction
Infectious bovine keratoconjunctivitis (IBK) or pinkeye is one of the most common production-limiting diseases of pre-weaned calves and the most common ocular diseases of cattle. In July 2021, the *Veterinary Clinics of North American: Food Animal Practice* issue was devoted to infectious bovine keratoconjunctivitis. That special issue is ideal for a veterinarian interested in the current evidence base about IBK as it provides a comprehensive review of many topics related to IBK, including the role of *Moraxella* in IBK,[20] the role of non-*Moraxella* in IBK,[19] the role of genetics,26 and the role of environmental factors[21] in the epidemiology of IBK. The special issue also covers approaches to diagnosing,[16] preventing[22] and treating IBK.[29] The economic impact of IBK[9] and an approach to understanding the causes of IBK[26] are also discussed in papers in the special issue. Given the availability of a very recent comprehensive review, this manuscript will provide a brief overview of these topics.

Epidemiology of IBK
A 1997 USDA survey of approximately 2,700 beef production operations found 1.1% (+/- 0.1) of calves older than 3 weeks were affected with IBK. For pre-weaned calves, IBK prevalence is second only to diarrhea. Of the ~2,700 beef producers interviewed, IBK was reported for calves older than 3 weeks in 11% of operations. Elsewhere, the incidence of IBK has been estimated that as high as 30% of all beef herds are affected annually, with IBK occurring in 20-30% of calves.[5] Anecdotally, concerning IBK occurrence, there appear to be 3 types of cow-calf herds; herds that never or very rarely experience the outcome, herds that experience only sporadic outbreaks every 2- 5 years, and other herds experiencing outbreaks yearly or biannually. Unfortunately, not enough is known about the epidemiology in the United States to corroborate this anecdotal observation. However, a recent study from Australia reported in a survey of 999 producers conducted online that 5.9 % of respondents indicated that they had not seen pinkeye in their herd in the last 5 years (2014–2018).17 When asked, "How many years did you have pinkeye cases in your herd in the last 5 years?" over a third (35.5 %) reported having pinkeye every year during the last 5 years, 7.7 % had pinkeye in 4 of the previous 5 years, 13.8 % in 3 of the previous 5 years, 17.0 % in 2 of the last 5 years, and 20.1 % in 1 of the previous 5 years).17 For modern dairy calves raising facilities, there are no publicly available estimates of IBK incidence. Such estimates would be hard to compare to beef cattle as the disease frequency metric in dairy calves would be incidence rate number of cases per days at risk, rather than risk (number of cases per total at risk), which is the disease metric used in beef calves. There is undoubtedly a need for more information about IBK in dairy calves.

Disease and production impact of IBK
Based on the high prevalence and effect on production, elucidating the underlying etiologic agent(s) of IBK can have a significant economic impact on producers. IBK produces a spectrum of clinical signs that include lacrimation, photophobia, corneal edema, ocular pain, corneal ulceration, and loss of vision.[5] Data also suggests that IBK is associated with pain in calves.[10] One of the most consistent findings for IBK is decreased weaning weight with an average of 15-30lb.[11,12,28] This average can be much higher in calves bilaterally affected. It was observed that the 205-day weight of bull calves with IBK in both eyes had an average 35lb decreased weight compared to bull calves with only one affected eye.[31] In 2014, one study demonstrated that the effects of IBK on beef calves carry over after weaning. At 15 months of age, calves with IBK before weaning weighed an average of 15 lb less than unaffected calves.[11]

Causes of IBK
Historically, *Moraxella bovis* has been considered the primary casual organism associated with IBK.[20] This organism has consistently been shown in experimental models to induce IBK. The organism *Moraxella bovoculi* is also frequently isolated from the eyes of calves with IBK. It is, therefore, speculated that *Moraxella bovoculi* is a "new cause" of IBK. This is a very appealing idea as a new organism presents the opportunity to develop new vaccines, antibiotics, etc. Unfortunately, other than recovery from eyes after IBK occurrence, it has no evidence from the research studies attempted thus far that *Moraxella bovoculi* causes IBK.[25] Most importantly, in challenge models commonly used in veterinary science to establish causation, *Moraxella bovoculi* has not caused IBK. In a blinded, randomized corneal scarification challenge model, 9/10 calves inoculated with M. bovis, 0/10 with *M. bovoculi*, and 1/11 negative control calves developed IBK lesions.[13,25] Other studies have also failed to show that *M. bovoculi* is sufficient to cause naturally occurring IBK.[13] A technical report from a company that sells vaccines reports the following "It has been our experience that it is difficult to generate severe ocular lesions in calves with *M. bovoculi* alone, but severe lesions can be induced when *M. bovis* and *M. bovoculi* are both involved." The implication of this statement appears to be that combined *M. bovis* and *M. bovoculi* are a cause. However, as it is known that *M. bovis* causes severe

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IBK lesions, the observation of severe IBK lesions when both organisms were present should be expected. Those lesions would be caused by *M. bovis*, even if *M. bovoculi* played no role in disease occurrence. Without presentation of the data from the study that enables critical evaluation, in particular, data from the occurrence of disease in a study that included an appropriate positive control (*M. bovis* only), this statement does not provide evidence that *M. bovoculi* plays a role in IBK.

Future research is required to better understand the causative agent(s) and to understand why *M. bovoculi* is so commonly found after eyes have become infected, yet the case for causation remains weak after so many years of investigation.[18] It is possibly an opportunistic secondary invader but more research is needed.

Preventing IBK

One of the most common ways to prevent disease is with vaccination, and several pinkeye vaccines are on the market aimed at preventing the disease caused by *Moraxella* bacteria. Further, there has been a lot of publicity about how effective COVID-19 vaccines are, so it is a great time to ask the same question of pinkeye vaccines. Numerous randomized trials that have assessed IBK vaccines available.[2-4,6,8,11,13,24,27,28,30] A thorough review of vaccines assessed for IBK is also available in the *Veterinary Clinics of North American: Food Animal Practice* special issue.[22] Overall, the evidence for the efficacy of vaccines is poor.

Interestingly, in veterinary science, the results of vaccine trials are predominately reported as either a risk ratio or odds ratio. These are certainly standard metrics for assessing vaccine efficacy. However, during the SARS-Cov-2 pandemic, "vaccine efficacy" has been the metric used to communicate to the public the impact that SARS-Cov-2 vaccines can have on preventing disease. It is likely that at no time is the public more aware of these measures. For veterinarians, it might be worth communicating the evidence for IBK vaccines using vaccine efficacy as the metric relative to SARS-Cov-2 vaccines.

In 2020, the Moderna COVID 19 vaccine was assessed in a large vaccine trial. Rather than report the results as a risk ratio or odds ratio, as is standard for veterinary vaccines, the vaccine was reported to be 94% effective (95% confidence interval of 89% to 97%). The summary of data from the Phase 3 Clinical Trial on the Moderna website, reports that the study enrolled 28,207 participants who received two doses 28 days apart of either Moderna COVID 19 Vaccine (n=14,134) or placebo (n=14,073). There were 11 COVID 19 cases in the Moderna COVID 19 vaccine group and 185 cases in the placebo group. How are these data used to obtain an estimate of 94% effective? Vaccine efficacy was calculated as follows:

In a randomized controlled trial, the placebo group represents what happens without the vaccine. At the end of the Moderna trial, 185 cases of COVID-19 occurred in the 14,073 unvaccinated people. That represents 1.31% of people in the unvaccinated group became COVID-19 cases.

Now imagine that the vaccinated people didn't get vaccinated (or the vaccine did not work at all); if that were the case, the researchers should expect around 1.31% of the 14,134 vaccinated people to become cases. The researcher should have expected 186 COVID-19 cases in the vaccinated group if the vaccine did not work (1.31% of 14,134=186). At the end of the trial, 11 cases of COVID-19 occurred in the vaccinated group. Eleven is only 6% of 186, so the vaccine prevented 94% of the expected COVID-19 cases in the vaccinated group. Looking at the Moderna study, because the vaccinated and unvaccinated groups were large, the enrolled people were unaware of their vaccine status, and people were randomized to the groups; we can attribute the decrease in COVID-19 cases to the vaccine. This is how we obtain the estimate that the Modern COVID-19 vaccine was 94% effective. Vaccine efficacy would normally range between 0 and 100%. For example, if 186 cases of COVID-19 had occurred in the 14,134 vaccinated people, then the vaccine would have been 0% effective i.e., vaccination prevented no cases. Normally we would not expect vaccine efficacy to be negative i.e., less than 0% because we would hope previous research phases would prevent harmful vaccines from reaching large Phase 3 trials, but if a higher percentage of cases than expected occurred in the vaccinated group than the unvaccinated, then the vaccine efficacy percentage (%) would be negative, implying the vaccinated did not prevent cases but caused cases.

Other numbers reported with vaccine efficacy are an interval that expresses how sure we are that the vaccine efficacy is 94%. In lay terms, this can be view as expressing uncertainty about the vaccine's effects. For the Moderna COVID 19 trial, that uncertainty range is 89% to 97%; this narrow range suggests the trial results were certain we have a highly effective vaccine. What we don't want is a confidence interval that is very wide – which means we don't really know how the vaccine will work or an interval that includes zero, which would suggest the vaccine might not work at all or an interval that includes negative percentages, which would suggest more disease in the vaccinated group.

Given the comfort level the public now has with vaccine efficacy, we can obtain similar numbers for pinkeye vaccines conducted in the field, and ask what do they tell us about how effective the pinkeye vaccines are. The data used to calculate the vaccine efficacy for pinkeye vaccines are reported in Table 1. These data are also presented in Figure 1, the squares represent the percentage of vaccine efficacy, and the lines represent the uncertainty (95% confidence interval). The first blue dot on the left-hand side is the Moderna-COVID 19 vaccine ~ 94% effective. The other studies labeled 2-15 are various pinkeye vaccines conducted in the field with different vaccination schedules. The takeaway from these data is that 13 of the 14 studies do not show the pinkeye vaccines were effective, and several studies suggest the vaccines can make things worse, i.e. negative vaccine efficacy (studies: 4,12,13,14). Only one publicly available field trial has reported positive vaccine effectiveness and it was conducted 50 years ago.[4]

Based on these data, there is little evidence that pinkeye vaccines are effective, and there is no evidence that pinkeye vaccines are highly effective. Certainly, these data are not new, however, presenting the available data as vaccine efficiency, a metric that the public is very comfortable with now, might be a good way to communicate with producers about the reported effect in the scientific literature, and the comparison to Moderna COVID-19 results might provide a reference value for understanding the characteristics of pinkeye vaccines.

Other options

Other options for prevention include clipping grass or fly control measures. There is no data available on grass clippings. Recently, a report was published about treating calves for flies that failed to show a protective effect. There was no significant difference in the number of IBK cases (24 vs. 30 respectively)

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between the 2 treatment groups (TAG and PON) (OR 0.7, 95% CI 0.4–1.4, p = 0.362, n = 195). The TAG calves were given two Cypermethrin impregnated ear tags (Flectron Tag, containing 935 mg Cypermethrin on turnout.) The PON calves were treated with Alphacypermethrin pour-on preparation at 10 mL per animal (Dysect Cattle 15 g/L Pour-on Solution, containing alphacypermethrin) every 6 weeks.[1] This study did not include a negative control, i.e. a group with any treatment, therefore it is unclear if TAG or PON were better than no treatment. This area of intervention still requires investigation because there are some promising data.[21]

Finally, anecdotally, there has been discussion that supplementation with Vitamin A might prevent IBK, especially in the organic community. The Iowa State University team conducted a small, randomized trial of injectable Vitamin A. The product assessed was a commercially available Vitamin AD3 injectable (Vitamins A and D3). Each mL contained 500,000 I.U. of Vitamin A propionate and 75,000 I.U. of Vitamin D3. There was no evidence of efficacy. The incidence of IBK was 69% in the supplemented calves and 63% in un-supplemented calves. The risk ratio was 1.1 (95% confidence interval =0.8- 1.5, Fisher's Exact P = 0.68). This study did not evaluate if the product was bioavailable or if calves were actually vitamin A-deficient. This study has not been submitted for peer review and is available only the ISU digital depository.

Treatment of IBK

In the U.S., long-acting oxytetracycline and tulathromycin are currently approved antibiotics to treat IBK in cattle. These products have been shown to be effective when compared against a placebo. There is no evidence that injection of antibiotic into the subconjunctiva is effective.[7] No data is available on the usefulness of using third eye flaps, eye patches or closing the eyelids with sutures.

Conclusion

Progress on IBK has been slow. Despite recognition of new organisms and some outstanding new microbiological studies that help us understand the organisms involved, we still do not understand the epidemiology of IBK, and we still do not have approaches to effectively prevent IBK. The effort to understand IBK should continue as this is a painful disease of cattle that has economic consequences for farms with high levels of disease. Further, without effective vaccines, IBK is a major driver of the use of antibiotics on cow-calf herds.

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Figure 1: Forest plot of vaccine efficacy and 95% confidence intervals for the Moderna COVID-19 vaccine study and 14 publicly available field-based pinkeye vaccination studies aimed at Moraxella bacteria. 100% efficiency means all cases are prevented, an interval that includes zero suggests a vaccine that is not effective and includes negative percentages would suggest more disease in the vaccinated group.

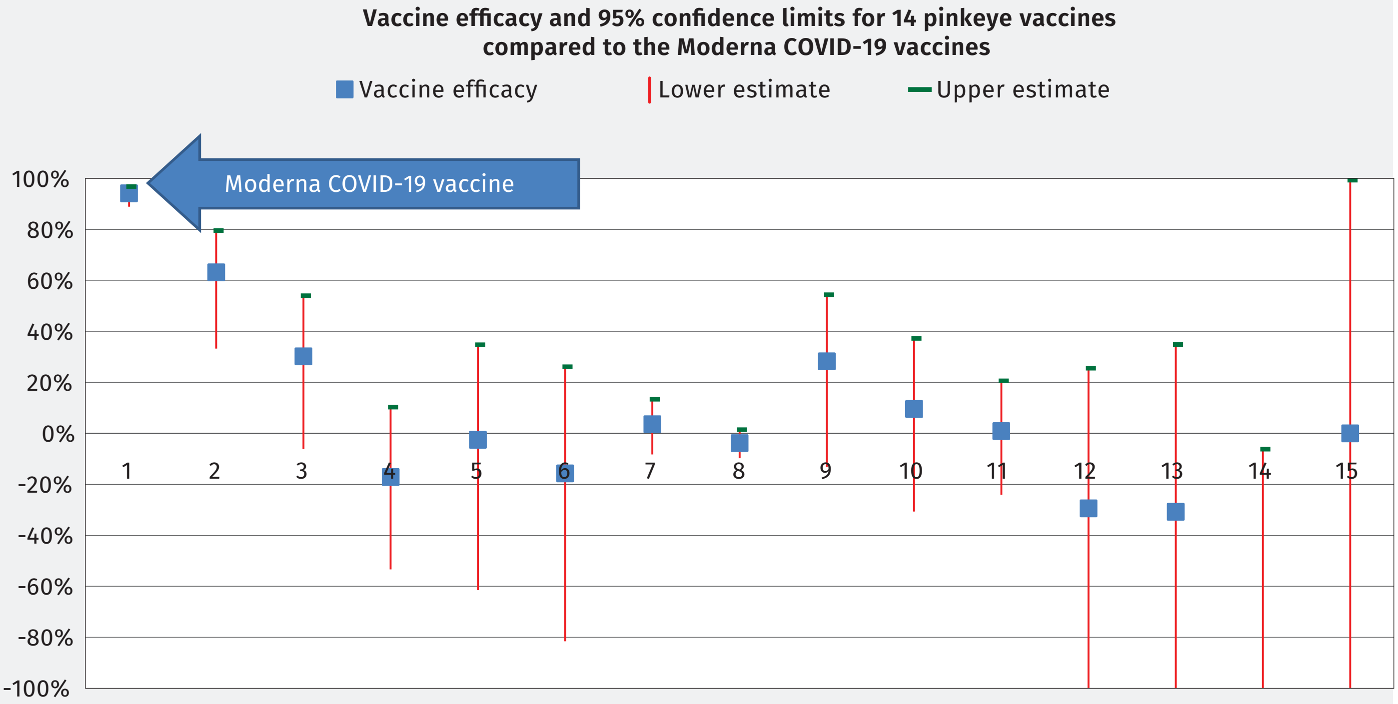

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Table 1: Results of the MODERNA COVID-19 vaccine study and 14 publicly available field-based pinkeye vaccination studies aimed at *Moraxella* bacteria

Vaccine type	Vaccinated		Not vaccinated		Vaccine efficacy	Lower estimate	Upper estimate
	Cases	Not cases	Cases	Not cases			
1. MODERNA COVID-19	11	14123	187	13886	94%	89%	97%
2. *M. bovis* autogenous vaccine[4]	7	12	13	0	63%	34%	80%
3. *M. bovis* autogenous vaccine[8]	21	49	49	65	30%	-6%	54%
4. *M. bovis* autogenous vaccine [8]	72	71	49	65	-17%	-53%	10%
5. *M. bovis* autogenous vaccine [8]	57	82	14	21	-3%	-61%	35%
6. *M. bovis* autogenous vaccine [8]	56	65	14	21	-16%	-81%	26%
7. *M. bovis* autogenous vaccine[15]	54	6	56	4	4%	-8%	13%
8. *M. bovis* autogenous vaccine[14]	54	0	52	2	-4%	-9%	1%
9. *M. bovis* autogenous vaccine[28]	23	68	31	57	28%	-13%	54%
10. *M. bovis* autogenous vaccine [28]	35	59	35	50	10%	-30%	37%
11. *M. bovis* commercial vaccine[6]	65	45	62	42	1%	-24%	21%
12. *M. bovoculi* commercial vaccine[23]	22	59	17	64	-29%	-125%	26%
13. *M. bovoculi* commercial vaccine[23]	16	88	12	90	-31%	-163%	35%
14. *M. bovis* commercial vaccine[30]	11	4	4	10	-157%	<-200%	-6%
15. *M. bovis* commercial vaccine[30]	1	5	1	5	0%	<-200%	99%

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