Bayesian estimation of failed transfer of passive immunity IgG cut-off values for predicting pre-weaning morbidity in beef calves

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Abstract

Failed transfer of passive immunity (FTPI) has been used to predict pre-weaning disease in beef calves. However, FTPI has a wide range of reported sensitivities and specificities; therefore, the diagnostic value of testing for FTPI to predict a beef calf's disease risk is questionable. Our objective was to determine the positive and negative predictive value of FTPI classification on pre-weaning morbidity in beef calves using a Bayesian latent class analysis. Pre-weaning health records and IgG concentrations from 1,569 beef calves across 3 populations were used. Calves were classified as having FTPI using 7 IgG cut-off values (500, 800, 1,000, 1,200, 1,600, 1,800 and 2,400 mg/dL). A Bayesian latent class model assuming conditional independence between the IgG concentrations and morbidity diagnosis was used to obtain estimates of the test sensitivity, specificity and positive and negative predictive value for the IgG cut-off values using informed priors; estimated herd cumulative incidence of morbidity ranged from 3.5% to 26.1%. Immunoglobulin G had a median (95% credible interval) sensitivity ranging from 28% (22%, 36%) for 500 mg/dL to 47% (40%, 55%) for 2,400 mg/dL and a median (95% credible interval) specificity ranging from 98% (95%, 100%) for 500 mg/dL to 64% (62%, 67%) for 2,400 mg/dL. Testing for FTPI performed the best in herds with a high cumulative incidence of morbidity (> 15%). In herds with low cumulative incidence of morbidity, testing for FTPI did not aid in the detection of calves that would develop pre-weaning morbidity.

Key words: Bayesian latent class analysis, morbidity sensitivity, morbidity specificity, pre-weaning disease, failed transfer of passive immunity

Introduction

The epitheliochorial placenta of the bovine dam inhibits the transmission of immunoglobulins from the dam to the fetus in utero, resulting in neonatal calves that rely on colostrum consumption shortly after birth for the transfer of maternal antibodies. Calves that fail to absorb adequate amounts of maternal antibodies from colostrum are commonly referred to as having failed transfer of passive immunity (FTPI). Calves with FTPI have an increased, but variable, risk of disease during the pre-weaned period compared to calves without FTPI.[40]

Radial immunodiffusion assay (RID) is a common assay used to quantify absorption of maternal antibodies, specifically immunoglobulin G (IgG). A wide range of IgG cut-off values, ranging from 500 to 2,400 mg/dL, have been proposed to determine if a calf has FTPI.[3,11] Regardless, FTPI has been used as a predictive factor for determining if a calf will develop pre-weaning disease. However, FTPI has a wide range of reported sensitivities and specificities for identifying calves that develop pre-weaning morbidity.[10,25,30,34] Therefore, the diagnostic value of testing for FTPI to predict an individual beef calf's risk for disease is questionable.[4,11,45] Additionally, these previous studies attempted to compare FTPI classification with pre-weaning morbidity are complicated by differences in disease definition, detection and reporting by animal caregivers which can contribute to the variable association between FTPI and pre-weaning disease. Furthermore, the length of observation between birth to weaning is variable between and within cow-calf operations and may also contribute to the observed variability.

Due to the imprecision in disease detection, traditional methods of diagnostic test comparison, such as receiver operator characteristic curves, have a limited ability to evaluate the positive and negative predictive value of FTPI on pre-weaning morbidity. These traditional methods rely on a highly accurate diagnostic test. When a highly accurate diagnostic test is not available, a Bayesian latent class analysis can be used to combine previously reported sensitivities and specificities from imprecise tests, such as FTPI classification using an RID and pre-weaning morbidity identified by a caregiver, with additional experimental data to estimate the positive and negative predictive value of the diagnostic test.[17] Therefore, the objective of this study was to determine the positive and negative predictive value of FTPI classification on pre-weaning morbidity in beef calves using a Bayesian latent class analysis.

Materials and methods

The standards for the reporting of diagnostic accuracy studies that use Bayesian latent class models (STARD-BLCM) were followed.[24]

This was a retrospective cohort study using existing data sets from a previous study investigating IgG concentrations and calf health.[10] The target population for the current study was beef calves typically found in North American commercial cow-calf operations. The source population were apparently health calves from a university research station sampled between 24 and 72 hours after birth. Briefly, whole blood was collected from the jugular vein on each calf and allowed to clot at room temperature at the time of sampling. Clotted samples were

centrifuged and serum was aliquoted and stored in sterile 1.5 mL conical vials at -112 °F (-80 °C) the same day of collection.[11] Samples were stored at -112 °F (-80 °C) until further testing.

Caretakers were trained by herd veterinarians on disease identification prior to the study. Trained caretakers performed daily herd checks and monitored calf health using one set of standard guidelines, which included case definitions and pre-established treatment protocols. Treatment protocols were established by herd veterinarians for various disease diagnoses. These individuals were not aware of the FTPI status of the calves. Calves were monitored for signs of illness, specifically, malaise, diarrhea, dyspnea, trauma, physical deformities, mental abnormalities, nasal discharge, or bloat. If a sign was observed, a morbidity event was recorded for that calf.[11] Individual calves could have multiple morbidity diagnoses (i.e., multiple treatments).

All spring born (February-May) calves from a single university research station beef cow-calf herd born between 1996 and 1998 (Nebraska, USA) were eligible for inclusion in the study. Each year was treated as a separate population for a total of 3 populations. The cow-calf pairs were maintained on pasture with similar management practices each year. All calves were weaned between 5 and 8 months of age in the fall of the year that they were born.

Complete methods on the quantification of serum IgG concentrations are discussed elsewhere.[11] Briefly, a commercially available radial immunodiffusion was used to quantify all serum IgG[a] samples at a university laboratory within a 12-month period. Serum was pipetted onto the RID plates along with 3 standards with known IgG concentrations. Plates were allowed to sit covered at room temperature for 24 hours before the precipitin ring diameters were read. Linear standard curves were generated for each plate using the 3 standards concurrently plated to convert the precipitin ring diameter into an IgG concentration. Serum with an IgG concentration less than the lowest standard was reported as less than the lowest standard's IgG concentration (i.e. < 412 mg/dL) and serum with an IgG concentration greater than the highest standard were reported as greater than the highest standard's IgG concentration (i.e. > 3,200 mg/dL).

Calves were assigned a binary classification of having experienced a morbidity event any time prior to weaning. Calves with a recorded treatment or disease diagnosis during the pre-weaning period were classified as having a morbidity event. Multiple recorded treatments or disease diagnoses were not captured beyond the calf being classified as having a morbidity event. Calves without a recorded treatment or disease diagnosis during the pre-weaning period were classified as not having a morbidity event.

Several FTPI IgG cut-off values have been proposed for predicting pre-weaning morbidity. Seven FTPI IgG cut-off values (500, 800, 1,000, 1,200, 1,600, 1,800, 2,400 mg/dL) that have been previously associated with pre-weaning morbidity were selected to classify calves as having FTPI (Table 1). This produced 7 independent models each with 9 degrees of freedom and 7 unknown parameters.

A latent class model was fit within a Bayesian framework to estimate the sensitivity (Se), specificity (Sp) of the FTPI IgG cut-off values and the caregiver's ability to identifying pre-weaned calves with a morbidity event, and the cumulative incidence of morbidity within the 3 populations. The cumulative incidence of morbidity was modeled so that it varied between the 3 populations. A conditional independence model was used as the FTPI status of calves was not known to the caregivers. The diagnostic Se and Sp of the IgG cut-off values was assumed to be constant in the 3 populations. The diagnostic Se and Sp of disease detection by the caregivers was assumed to be the same between the 3 populations as all observers had greater than 5 years of experience with beef cow-calf herds.

Each model had 9 degrees of freedom and contained 7 parameters to estimate: IgG Se and Sp, detection of morbidity Se and Sp, and pre-weaning morbidity prevalence for each population. Informed priors were used for the Se and Sp of FTPI IgG cut-off values, the Se and Sp of morbidity detection, and the cumulative incidence of morbidity in pre-weaned beef calves (Table 1). Three literature searches were performed to determine the informed priors: 1) to locate the Se and Sp of FTPI IgG cut-off values by using pre-weaning morbidity as the reference, 2) to locate values pertaining to the Se and Sp of morbidity detection in pre-weaned calves, and 3) to locate values pertaining to the cumulative incidence of morbidity in pre-weaned beef calves. If multiple studies were located that described the same parameter, the values were plotted in a spreadsheet software to evaluate the distribution[b]. Clustering within the studies was evaluated to select the mode and the most extreme value was used to determine the value that the parameter was above or below. The alpha and beta parameters for the prior distributions were determined using a distribution package[c].

Posterior inferences (median and 95% Bayesian credible intervals [CrI]) were estimated using a Gibbons sampler[d]. Model convergence was evaluated by running 3 Markov chains starting from different initial values with a Gelman-Rubin diagnostic value[e].[13,16] Each chain was run starting at 110,000 iterations with a burn in of 10,000 iterations. Iteration and burn in were modified as needed to reach convergence and to generate an arbitrarily selected minimum effective sample size of 5,000 for all parameters. Thinning of 5 was applied to improve autocorrelation. Posterior inferences (Se and Sp) will be reported as percentages within the text for clarity.

To evaluate the robustness of the models, a sensitivity analysis was performed using perturbed priors for the Se and Sp of the FTPI IgG cut-off values (Table 1). The Se priors were perturbed by increasing the mode by 0.1 and changing the initial value by 0.3. The Sp priors were perturbed by decreasing the mode by 0.1 and changing the initial value by 0.3.[12] Informed priors for cumulative incidence and the Se and Sp of morbidity detection were maintained. Visualization of positive predictive value (PPV) and negative predictive value (NPV) outputs by IgG cutoff value was performed with a graphics package[f], further utilizing the color scaling package[g] to allow for ease of visual interpretation for individuals affected with color blindness.[23]

Additionally, the PPV and NPV of FTPI classification on pre-weaning morbidity for each IgG FTPI cut-off was calculated for each population according to the following equations:[12]

$$PPV = \frac{p(D+) * Se}{p(D+) * Se + \big(1 - p(D+)\big) * (1 - Sp)}$$

$$NPV = \frac{\big(1 - p(D+)\big) * Sp}{\big(1 - p(D+)\big) * Sp + p(D+) * (1 - Se)}$$

Table 1: Prior distributions used in the latent class models comparing IgG concentrations measured using a radial immunodiffusion to identify neonatal beef calves with failed transfer of passive immunity with pre-weaning morbidity events recorded by caregivers.

		Model				
		Informed priors		Perturbed priors		
I gG Cut-off (mg/dL)	Parameter	Mode, percentile	Distribution	Mode, percentile	Distribution	Source
500	Se*	0.2, 95th = 0.4	Beta[4.461,14.844]	0.3, 95th = 0.7	Beta[2.132,3.641]	[8,43]
	Sp†	0.9, 5th = 0.8	Beta[42.573,5.169]	0.8, 5th = 0.5	Beta[7.548,2.637]	
800	Se	0.3, 95th = 0.5	Beta[6.281,13.322]	0.4, 95th = 0.8	Beta[2.059,2.589]	[30,43]
	Sp	0.85, 5th = 0.75	Beta[46.348,9.003]	0.75, 5th = 0.45	Beta[6.985,2.995]	
1000	Se	0.4, 95th = 0.6	Beta[10.902,7.601]	0.5, 95th = 0.9	Beta[1.532,1.532]	[22,25,32,43]
	Sp	0.75, 5th = 0.55	Beta[14.222,5.407]	0.65, 5th = 0.25	Beta[3.12,2.142]	
1200	Se	0.65, 5th = 0.5	Beta[20.997,11.768]	0.75, 5th = 0.2	Beta[2.149,1.383]	[36,43]
	Sp	0.65, 95th = 0.45	Beta[7.943,9.486]	0.55, 5th = 0.15	Beta[2.057,1.865]	
1600	Se	0.65, 5th = 0.5	Beta[20.997,11.768]	0.75, 5th = 0.2	Beta[2.149,1.383]	[30,43]
	Sp	0.65, 95th = 0.45	Beta[7.943,9.486]	0.55, 5th = 0.15	Beta[2.057,1.865]	
1800	Se	0.65, 5th = 0.5	Beta[20.997,11.768]	0.75, 5th = 0.2	Beta[2.149,1.383]	[25,43]
	Sp	0.65, 95th = 0.45	Beta[7.943,9.486]	0.55, 5th = 0.15	Beta[2.057,1.865]	
2400	Se	0.8, 5th = 0.6	Beta[14.844,4.461]	0.9, 5th = 0.3	Beta[2.706,1.190]	[11]
	Sp	0.6, 95th = 0.4	Beta[7.601,10.902]	0.9, 95th = 0.5	Beta[1.532,1.532]	
	Morbidity Se	0.75, 5th = 0.55	Beta[9.628,3.876]	0.75, 5th = 0.55	Beta[9.628,3.876]	[2,5,28,38]
	Morbidity Sp	0.9, 5th = 0.6	Beta[8.304,1.812]	0.9, 5th = 0.6	Beta[8.304,1.812]	
	Cumulative incidence of morbidity	0.15, 95th = 0.4	Beta [2.704,10.656]	0.15, 95th = 0.4	Beta [2.704,10.656]	[15,20,29,44,45]

* Se= Sensitivity
† Sp= Specificity

The estimated morbidity cumulative incidence for each population is represented by p(D+) and Se and Sp represent the estimated Se and Sp for the FTPI IgG cut-off value, respectively.

To evaluate the optimal FTPI threshold, the misclassification cost term (MCT) was calculated using the estimated Se, Sp and cumulative incidence for each population according to the following equation:[18]

$$MCT = \big(1 - p(D+)\big) * (1 - Sp) + r * p(D+) * (1 - Se)$$

Where p(D+) represented the posterior estimate for the morbidity cumulative incidence for each population, Se and Sp represent the estimated Se and Sp for the FTPI IgG cut-off value, and r represents the false negative-to-false positive cost ratio. Calves with FTPI have an increased risk of morbidity compared to calves with adequate transfer of passive immunity.[40] Failed transfer of passive immunity is not routinely evaluated in neonatal beef calves; however, if it was, the authors speculate that the main cost component for a false-negative would be the costs associated with missing an increased risk of disease and the potential opportunity cost of a deceased calf. Whereas the main cost component for a false positive, might be increased management to reduce disease risk, such as increased number of acreage per cow-calf pair, managing cow-calf pairs in different groupings based on the calf's FTPI status, or metaphylaxis. Therefore, the authors speculate that the cost of a false negative would be greater than that of a false positive. Nevertheless, the MCT was estimated across IgG thresholds for false negative-to-false positive cost ratios of 5:1, 3:1, 1:1, 1:3 and 1:5. Overall threshold MCT were calculated by averaging the MCT values from each population for each IgG threshold. The ideal threshold would minimize misclassification costs.

Results

A total of 1,569 calves from 3 populations were included in the analysis. Nine calves had reported mortality events, but no reported morbidity events and were removed from the analysis. Two calves were from population 1, 5 from population 2, and 2 from population 3. Three calves had an IgG concentration less than 500 mg/dL, 2 between 2,000 and 2,400 mg/dL, and 4 greater than 2,400 mg/dL. The apparent cumulative incidence of disease ranged from 5.7% to 17.5%. Approximately 63.5% of calves (997/1,569) had an IgG concentration greater than 2,400 mg/dL. Cross-tabulation between the different IgG FTPI cut-off values and morbidity diagnosis was calculated (Table 2).

The sensitivity of the FTPI IgG cut-off values gradually increased from 23.4% (95% CrI: 19.2%, 33.9%) to 51.0% (95% CrI: 42.5%, 60.0%) as the cut-off values increased from 500 to 2,400 mg/dL (Table 3). The sensitivity of morbidity diagnosis

increased from 61.8% (95% CrI: 41.8%, 85.0%) to 76.0% (95% CrI: 55.0%, 92.0%) with the increase in FTPI IgG cut-off value. The specificity of the FTPI IgG cut-off values decreased from 90.6% (95% CrI: 88.5%, 92.9%) for 500 mg/dL to 60.5% (95% CrI: 57.8%, 63.3%) for 2,400 mg/dL. However, the specificity of morbidity diagnosis remained relatively constant between the cut-off values with median values fluctuating between 94.8% (95% CrI: 91.7%, 97.9%) and 97.5% (95% CrI: 94.5%, 99.6%).

The morbidity true cumulative incidence for population 1 remained relatively consistent between the FTPI cut-off values whereas the morbidity cumulative incidence for populations 2 and 3 decreased with the increase in FTPI cut-off values (Table 3). Regardless of the FTPI cut-off point selected, the negative predictive value was consistent with most calves with adequate transfer of passive immunity remaining healthy (Figure 1). Testing for FTPI did not aid in the detection of animals that would remain healthy. Less than half of the calves that were classified as FTPI at the 500 mg/dL cut-off value went on to develop pre-weaning disease. Additionally, increasing the FTPI cut-off value decreased the positive predictive value of FTPI classification for pre-weaning morbidity (Figure 2).

The MCT for the false negative-to-false positive cost ratio of 1:5 and 1:3 performed similarly overall and within each population (Figure 3). The MCT was lowest at the IgG threshold of 500 mg/dL for each population (population 1: 0.104 [0.083,0.123], 0.097 [0.077,0.117]; population 2: 0.123 [0.104,0.142], 0.104 [0.087,0.121]; population 3: 0.133 [0.114,0.15], 0.108 [0.092,0.124]) and overall (0.120 [0.100,0.140], 0.103 [0.085,0.121]) for the false negative-to-false positive cost ratio of 1:5 and 1:3, respectively. For the false negative-to-false positive cost ratio of 1:1, the IgG threshold with the lowest MCT was at 500 mg/dL for population 1 (0.135 [0.105,0.172]) and overall (0.203 [0.158,0.268]), but at 1,200 mg/dL for population 2 (0.209 [0.168,0.258]) and population 3 (0.237 [0.189,0.299]). The MCT was lowest at IgG threshold of 1,000 mg/dL for population 1 (0.208 [0.144,0.317]), but at 1,200 mg/dL population 2 (0.377 [0.252,0.548]), population 3 (0.482 [0.324,0.704]), and overall (0.353 [0.243,0.513]) for the false negative-to-false positive cost ratio of 3:1. For the false negative-to-false positive cost ratio of 5:1, the IgG threshold with the lowest MCT was at 1,200 mg/dL for population 1 (0.239 [0.166,0.392]), population 2 (0.545 [0.332,0.841]), population 3 (0.727 [0.455,1.111]), and overall (0.504 [0.318,0.781]). Uninformed priors (beta[1,1]) resulted in

Table 2: Cross-tabulated results of failed transfer of passive immunity (FTPI) classification using 7 IgG cut-off values and pre-weaning morbidity detected by caregivers for determining the positive and negative predictive value of FTPI classification for diagnosing pre-weaning morbidity in 1,569 beef calves from a U.S. cow-calf operation monitored over 3 years.

IgG cut-off (mg/dL)	Population	Morbidity +		Morbidity -	
		FTPI +	FTPI -	FTPI +	FTPI -
500	1	8	23	45	467
	2	19	56	48	423
	3	17	67	53	343
800	1	8	23	54	458
	2	19	56	55	416
	3	19	65	67	329
1000	1	8	23	58	454
	2	21	54	64	407
	3	24	60	74	322
1200	1	8	25	71	439
	2	23	57	67	399
	3	28	58	79	315
1600	1	11	22	106	404
	2	27	53	91	375
	3	30	56	92	302
1800	1	12	21	132	378
	2	34	46	107	359
	3	31	55	99	295
2400	1	19	14	252	258
	2	44	36	175	291
	3	33	53	112	282

Table 3: Median posterior estimates (95% credible interval) obtained for the positive and negative predictive value of failed transfer of passive immunity (FTPI) classification, using seven IgG cut-off values, on pre-weaning morbidity in 1,569 calves from a U.S. beef cow-calf operation monitored over 3 years using a conditionally independent Bayesian latent class models (each model was run to obtain a Monte Carlo simulation containing an effective size of 5,000 for each variable after thinning).

		Model					
		Informed priors			Perturbed priors		
IgG Cut-off (mg/dL)	Parameter	Median (95% credible interval) (%)	Positive predictive value (95% credible interval) (%)	Negative predictive value (95% credible interval) (%)	Median (95% credible interval) (%)	Positive predictive value (95% credible interval) (%)	Negative predictive value (95% credible interval) (%)
500	FTPI Se*	25.8 (19.2,33.9)		26.7 (19.7,35.8)			
	FTPI Sp†	90.6 (88.5,92.9)		90.6 (88.5,93.0)			
	Morbidity Se‡	61.8 (41.8,84.8)		62.0 (42.2,84.9)			
	Morbidity Sp§	97.5 (94.5,99.6)		97.4 (94.3,99.5)			
	CI Pop 1 ‖	6.3 (2.3,12.0)	15.4 (5.8,30.9)	94.8 (89.9,98.1)	6.1 (2.2,11.8)	15.4 (5.7,31.3)	95.0 (90.1,98.3)
	CI Pop 2	18.7 (11.7,29.0)	38.7 (24.0,58.4)	84.2 (74.8,90.4)	18.4 (11.5,28.7)	38.9 (24.2,58.8)	84.6 (75.2,90.9)
	CI Pop 3	25.3 (16.4,38.6)	48.1 (31.2,68.5)	78.4 (65.9,86.4)	24.9 (16.0,38.1)	48.5 (31.5,68.9)	78.9 (66.6,86.9)
800	FTPI Se	28.3 (21.3,37.0)		28.3 (21.3,37.1)			
	FTPI Sp	88.5 (86.2,91.0)		88.4 (86.2,91.0)			
	Morbidity Se	59.7 (40.1,83.6)		59.8 (39.9,83.9)			
	Morbidity Sp	97.0 (94.0,99.4)		97.0 (94.0,99.4)			
	CI Pop 1	5.9 (1.9,11.7)	13.1 (4.5,27.2)	95.2 (90.2,98.5)	5.9 (1.9,11.8)	13.1 (4.4,27.2)	95.2 (90.1,98.5)
	CI Pop 2	18.5 (11.3,28.9)	35.7 (21.7,54.2)	84.5 (75.0,91.0)	18.4 (11.2,29.1)	35.6 (21.7,54.4)	84.5 (74.9,91.0)
	CI Pop 3	25.9 (16.4,40.2)	46.1 (29.2,66.7)	78.0 (64.6,86.5)	25.8 (16.3,40.5)	46.0 (29.1,66.9)	78.1 (64.5,86.6)
1000	FTPI Se	37.5 (28.8,49.2)		33.7 (25.4,44.6)			
	FTPI Sp	87.8 (85.2,90.7)		87.7 (85.1,90.8)			
	Morbidity Se	56.3 (38.9,80.4)		55.6 (37.7,80.7)			
	Morbidity Sp	96.0 (93.0,98.9)		96.7 (93.7,99.3)			
	CI Pop 1	4.9 (1.4,10.8)	13.5 (4.2,29.2)	96.5 (91.8,99.0)	5.7 (1.8,12.0)	14.2 (4.6,30.4)	95.6 (90.5,98.7)
	CI Pop 2	17.8 (10.2,28.1)	39.9 (24.6,58.5)	86.7 (77.5,93.1)	19.2 (11.4,30.4)	39.6 (23.9,59.8)	84.8 (74.8,91.7)
	CI Pop 3	26.1 (16.0,39.7)	52.1 (33.8,71.0)	80.0 (67.5,88.7)	27.5 (17.0,42.5)	51.3 (32.1,71.9)	77.8 (64.0,87.0)
1200	FTPI Se	44.0 (34.0,57.2)		35.9 (27.3,47.7)			
	FTPI Sp	85.4 (83.0,88.1)		85.8 (83.2,88.8)			
	Morbidity Se	63.4 (44.7,85.2)		60.2 (41.2,83.7)			
	Morbidity Sp	94.8 (91.7,97.9)		96.2 (93.0,99.1)			

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Table 3 con't

		Model					
		Informed priors			Perturbed priors		
IgG Cut-off (mg/dL)	Parameter	Median (95% credible interval) (%)	Positive predictive value (95% credible interval) (%)	Negative predictive value (95% credible interval) (%)	Median (95% credible interval) (%)	Positive predictive value (95% credible interval) (%)	Negative predictive value (95% credible interval) (%)
1200	CI Pop 1	3.5 (0.09,8.5)	10.0 (2.8,22.2)	97.7 (93.8,99.5)	5.2 (1.5,11.3)	12.2 (3.7,26.1)	96.1 (91.0,99.0)
	CI Pop 2	14.9 (8.4,23.8)	34.5 (21.8,50.2)	89.7 (81.9,95.1)	18.4 (11.0,28.7)	36.3 (22.7,54.0)	85.6 (76.3,92.3)
	CI Pop 3	21.8 (13.5,33.6)	45.7 (30.8,62.9)	84.6 (74.0,91.8)	25.4 (16.1,39.4)	46.4 (30.0,66.3)	79.8 (66.9,88.2)
1600	FTPI Se	44.3 (35.4,55.9)		37.9 (29.8,48.4)			
	FTPI Sp	79.7 (77.2,82.3)		79.9 (77.3,82.6)			
	Morbidity Se	69.1 (48.7,88.5)		67.1 (45.8,87.6)			
	Morbidity Sp	95.7 (92.5,98.9)		96.8 (93.6,99.4)			
	CI Pop 1	4.4 (1.2,9.6)	9.0 (2.7,18.8)	96.9 (92.7,99.2)	5.6 (1.7,11.2)	10.0 (3.2,19.9)	95.6 (90.8,98.8)
	CI Pop 2	15.6 (9.1,24.4)	28.5 (18.3,42.0)	88.6 (80.7,94.2)	17.7 (11.0,27.6)	28.8 (18.5,43.5)	85.7 (76.7,91.9)
	CI Pop 3	20.8 (13.3,31.7)	36.4 (24.8,51.7)	84.5 (74.6,91.4)	22.9 (15.1,35.4)	36.0 (24.1,52.9)	81.2 (69.8,88.6)
1800	FTPI Se	47.1 (38.5,58.2)		42.0 (33.7,52.5)			
	FTPI Sp	75.9 (73.4,78.5)		76.1 (73.5,78.8)			
	Morbidity Se	72.2 (51.9,90.0)		70.5 (49.6,89.4)			
	Morbidity Sp	96.2 (93.0,99.1)		97.0 (93.8,99.4)			
	CI Pop 1	4.5 (1.3,9.6)	8.5 (2.6,17.1)	96.8 (92.7,99.2)	5.5 (1.7,10.9)	9.2 (3.1,17.9)	95.8 (91.3,98.8)
	CI Pop 2	15.7 (9.8,24.0)	26.7 (17.7,38.7)	88.5 (81.1,93.8)	17.2 (11.0,26.1)	26.7 (17.7,39.5)	86.4 (78.2,92.1)
	CI Pop 3	20.1 (13.1,29.9)	32.9 (22.9,46.2)	85.1 (76.0,91.6)	21.7 (14.5,32.5)	32.8 (22.5,47.1)	82.6 (72.4,89.4)
2400	FTPI Se	51.0 (42.5,60.3)		47.3 (34.2,56.7)			
	FTPI Sp	60.5 (57.8,63.3)		60.5 (56.9,63.4)			
	Morbidity Se	75.9 (54.5,92.0)		73.1 (40.6,91.0)			
	Morbidity Sp	97.2 (93.7,99.5)		97.2 (93.4,99.6)			
	CI Pop 1	5.4 (1.7,10.2)	6.9 (2.2,12.8)	95.6 (91.2,98.7)	5.6 (1.7,10.7)	6.7 (1.7,12.7)	95.1 (90.2,98.5)
	CI Pop 2	16.3 (10.5,24.2)	20.1 (13.2,28.9)	86.4 (78.3,92.1)	17.1 (11.0,27.9)	19.8 (12.5,29.5)	84.9 (71.3,90.9)
	CI Pop 3	20.0 (13.4,29.0)	24.4 (16.8,34.0)	83.2 (73.6,90.0)	21.1 (14.2,37.7)	24.4 (16.5,36.9)	81.2 (60.8,88.4)

* FTPI Se= Sensitivity of failed transfer of passive immunity classification
† FTPI Sp= Specificity of failed transfer of passive immunity classification
‡ Morbidity Se= Sensitivity of morbidity diagnosis
§ Morbidity Sp= Specificity of morbidity diagnosis
|| CI= Cumulative incidence of morbidity

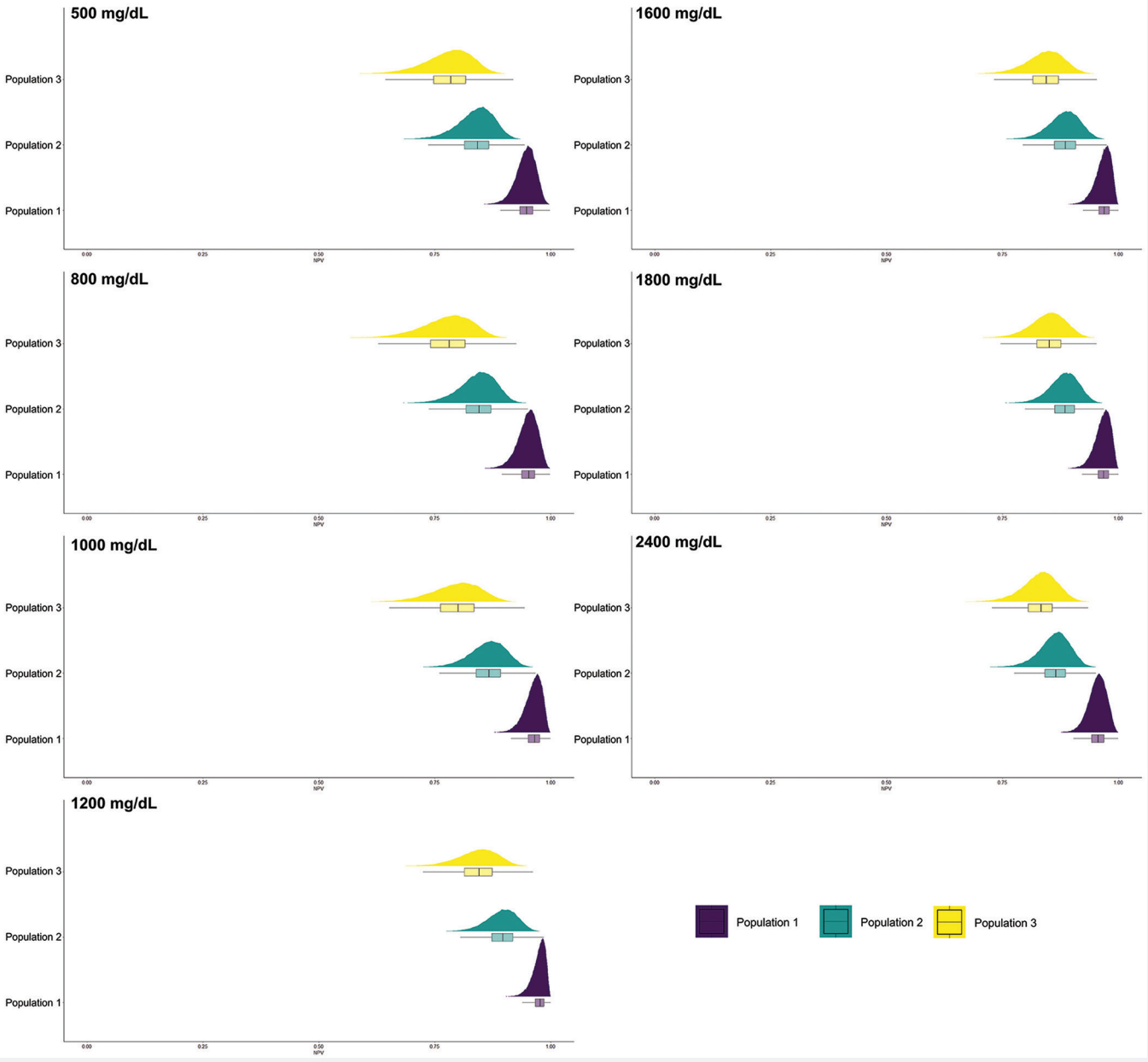
models that failed to converge, so perturbed priors were used. The 7 models with perturbed priors had minimal differences between their estimated outcomes and those estimated with the informed priors suggesting that the models were robust. All models but one (1,800 mg/dL) in the sensitivity analysis required more iterations to reach the minimum sample size. Five models (800, 1,000, 1,200, 1,600, 2,400 mg/dL) required a higher number of burn-ins to reach convergence.

Discussion

This was the first investigation to estimate the positive and negative predictive value of FTPI classification on pre-weaning morbidity in beef calves using a Bayesian latent class analysis. Immunoglobulin G concentrations were initially used to determine if neonatal calves had consumed maternal colostrum. Multiple studies noted a relationship between colostrum consumption, measured by IgG concentrations, and pre-weaning disease risk which resulted in FTPI being used as a measure of pre-weaning disease risk in calves.[25,36,45] However, we found that the FTPI cut-off values were not diagnostically useful in predicting which calves would develop disease during the pre-weaning period.

Multiple factors contribute to pre-weaning disease. Some factors that contribute to disease are infectious whereas others are not. Testing for FTPI will never capture the risk of component causes of pre-weaning disease, such as non-infectious environmental or management causes of disease, which do not rely upon colostrum consumption.[40] Additionally, the included populations denoted what disease (diarrhea, respiratory) an individual was being treated for, but due to the inconsistent nature of disease classification and quantity, all disease types were grouped together as morbidity. Using this broad definition for

Figure 1: Posterior distribution of the negative predictive values for failed transfer of passive immunity classification on pre-weaning morbidity for 7 IgG cut-off in a United Stated beef cow-calf operation monitored over 3 years.

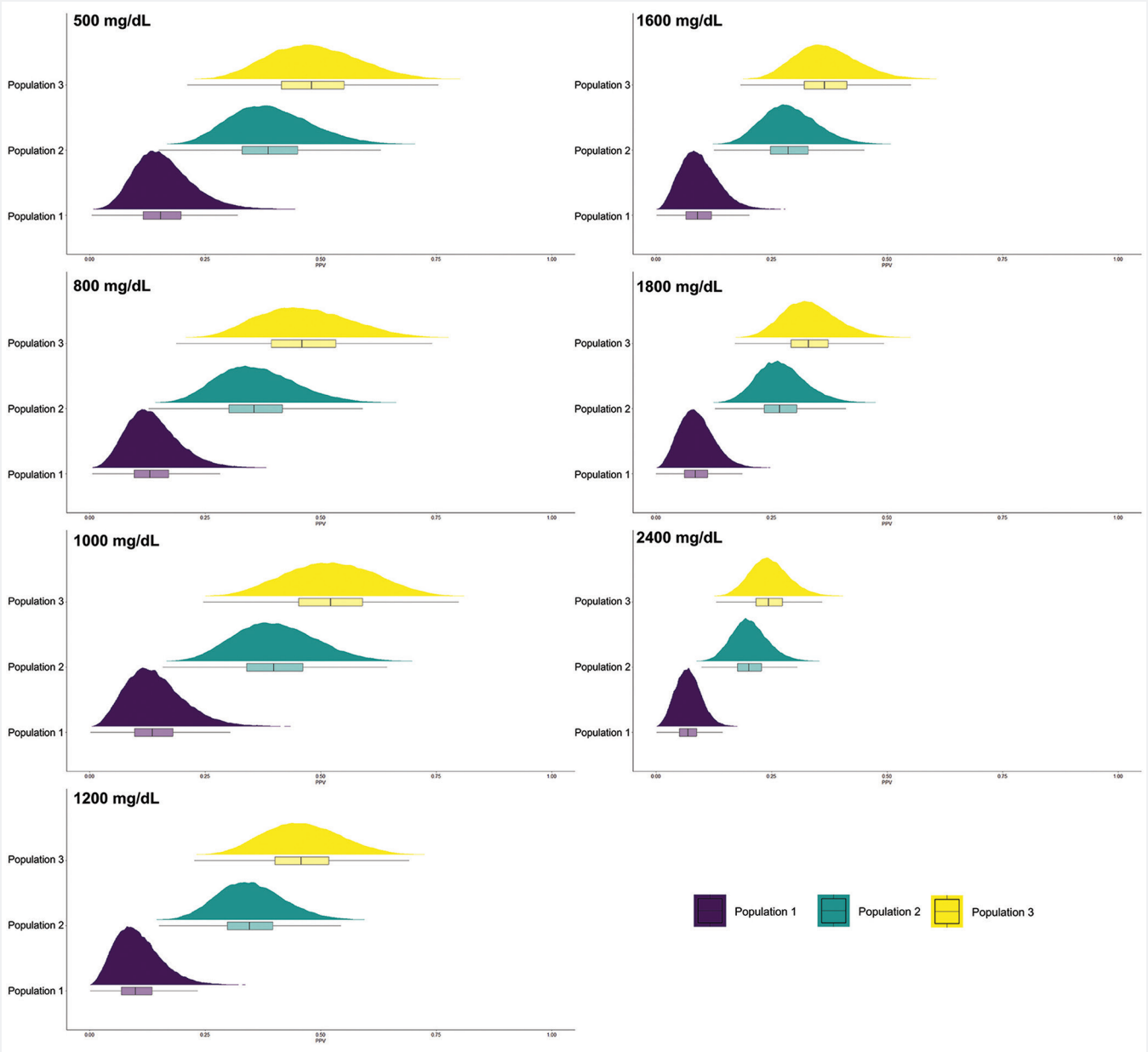


morbidity, which combines morbidity events associated with all etiologies, could contribute to the low sensitivities observed and the limited negative predictive value of the test.

Comparisons between 7 IgG cut-off values for FTPI and caregiver recorded pre-weaning morbidity showed that there was an increase in sensitivity as the IgG cut-off values increased. The true cumulative incidence of morbidity as calculated in the Bayesian models is a function of the apparent cumulative incidence of morbidity detected by the caregivers and the sensitivity and specificity of disease detection which was calculated in the Bayesian models. The sensitivity and specificity of disease detection changed as the IgG cut-off value for FTPI was altered. This change was greater in populations 2 and 3 as they had higher levels of disease compared to population 1. However, there was discordance between calves the test indicated should become diseased and the calves classified as diseased by the caregiver. Calves with FTPI are at greater risk of pre-weaning morbidity but FTPI is a component cause of pre-weaning disease and works in tandem with other factors to cause disease.[40] Furthermore, cattle are prey animals that tend to not overly show disease which makes identifying calves with disease difficult. Conversely, caregivers were better at identifying which calves would remain healthy compared to the FTPI cut-off values as indicated by median treatment specificities greater than 94% compared to the median IgG specificities that ranged from 60.5 to 90.6%. Regardless, the negative predictive values for FTPI classification did not aid in identifying which calves would remain healthy during the pre-weaning period.

The limited ability to predict pre-weaning morbidity by testing for FTPI could be related to the test. Estimating the IgG concentration in the serum of neonatal calves may not appropriately represent the individual's immune status.

Figure 2: Posterior distribution of the positive predictive values for failed transfer of passive immunity classification on pre-weaning morbidity for 7 IgG cut-off in a United Stated beef cow-calf operation monitored over 3 years.



Immunoglobulin G is measured in neonatal calves because it is the largest immunological fraction found within colostrum and contributes to the immune response by neutralizing toxins and viruses.[7] However, other immunological factors, such as T-cells, natural killer cells, and other classes of immunoglobulins also play an important role in disease prevention of the gastrointestinal tract and respiratory tract.[6,41] Also, maternal antibodies wane over time with the half-life of IgG being around 20 days.[19,26,27,31] Thus, disease that occurs close to weaning, when a calf is 4-to-6-months-of-age, may not be a result of lacking maternal antibodies.[39] Therefore, the use of a single immunological factor as a test for predicting future health events does not account for the complexity in resistance to disease and may help to explain the observed failure to appropriately assign an individual's disease risk.[1,35,37]

On beef cow-calf operations, FTPI is not routinely evaluated in neonatal calves. It has been estimated that a beef calf with FTPI would cost approximately $70 more than a calf without FTPI; however, the perceived cost of a calf with FTPI may vary between operations.[33] Therefore, a single false negative-to-false positive ratio would not be representative of the variability of costs in raising a beef calf in a U.S. cow-calf operation. This was highlighted by the varying MCT for the IgG thresholds between populations. The MCT relies on the cumulative incidence of morbidity which was not consistent between the populations or years. Therefore, a universal IgG threshold or MCT would not be consistent between operations. The false negative-to-false positive ratios of 1:5 and 1:3, which represent misclassifying more calves as falsely having FTPI, performed the most similar within a population but are probably the least representative of a typical beef cow-calf operation due to the non-tangible management costs associated with misclassifying a calf as having FTPI when, in reality, it does not.

Limitations to this analysis are primarily with disease detection. Generalized morbidity was evaluated in the present study instead of categories (digestive, respiratory) due to insufficient numbers. Additionally, practitioners and producers often evaluate overall disease risk and not necessarily a specific type. However, treatment records are only as good as the record keeping. Previous studies have found that approximately 40 to 80% of operations record when an individual is treated, but as few as 20% report an illness event that was not treated.[14,21] Therefore, some calves may have been diagnosed as diseased, but were not treated or recorded as diseased. The university herd was included in the present study due to their consistent record keeping. However, the external validity of the morbidity sensitivity and specificity may be altered for operations that have limited morbidity record keeping in calves. Additionally, an assumption of Bayesian latent class models is that the "test" sensitivity and specificity are consistent between populations, or in our case, years. We assumed that the caregiver's ability to diagnose calves with a morbidity event were consistent between years; however, their ability to diagnose the same calf as diseased was never evaluated and may be considered a limitation of the study. Another limitation with the present study is that the IgG values used were from greater than 20 years ago. Radial immunodiffusions have been used to quantify IgG concentrations in blood since the 1970s. The radial immunodiffusion assay used in this study has been discontinued but comparable assays remain on the market.[9] With the initial Bayesian analysis performed in the present study, repetition of the present study using a more current assay would validate the findings. Finally, caution should be used when extrapolating the reported sensitivities, specificities and positive and negative predictive values for pre-weaning morbidity from beef calves to dairy calves. These populations have different colostrum management strategies which may influence the sensitivity and specificity of the IgG cut-off values.[42]

Lower FTPI cut-off values were more predictive of pre-weaning morbidity and had the lower misclassification costs than higher cut-offs. However, less than half of calves with FTPI would have a morbidity event during the pre-weaning period. Most calves that did not have FTPI would remain healthy during the pre-weaning period. Testing for FTPI did not aid in the detection of calves that would remain healthy or overtly predict which calves would develop pre-weaning morbidity. Evaluation of other immune factors in tandem with IgG may be more predictive of pre-weaning disease.

End notes

[a] VMRD Inc, Pullman, WA

[b] Microsoft Excel, Microsoft Corporation, Redmond, WA

[c] epi.betabuster, v2.0.62, **https://cran.r-project.org/web/packages/epiR/index.html**

[d] r2jags, **https://cran.r-project.org/web/packages/R2jags/index.html**

[e] gelman.diag, v0.19-4, **https://www.rdocumentation.org/packages/coda/versions/0.19-4.1/topics/gelman.diag**

[f] ggdist v3.3.1, **https://cran.r-project.org/web/packages/ggdist/ggdist.pdf**

[g] viridis v0.6.2, **https://sjmgarnier.github.io/viridis/authors.html**

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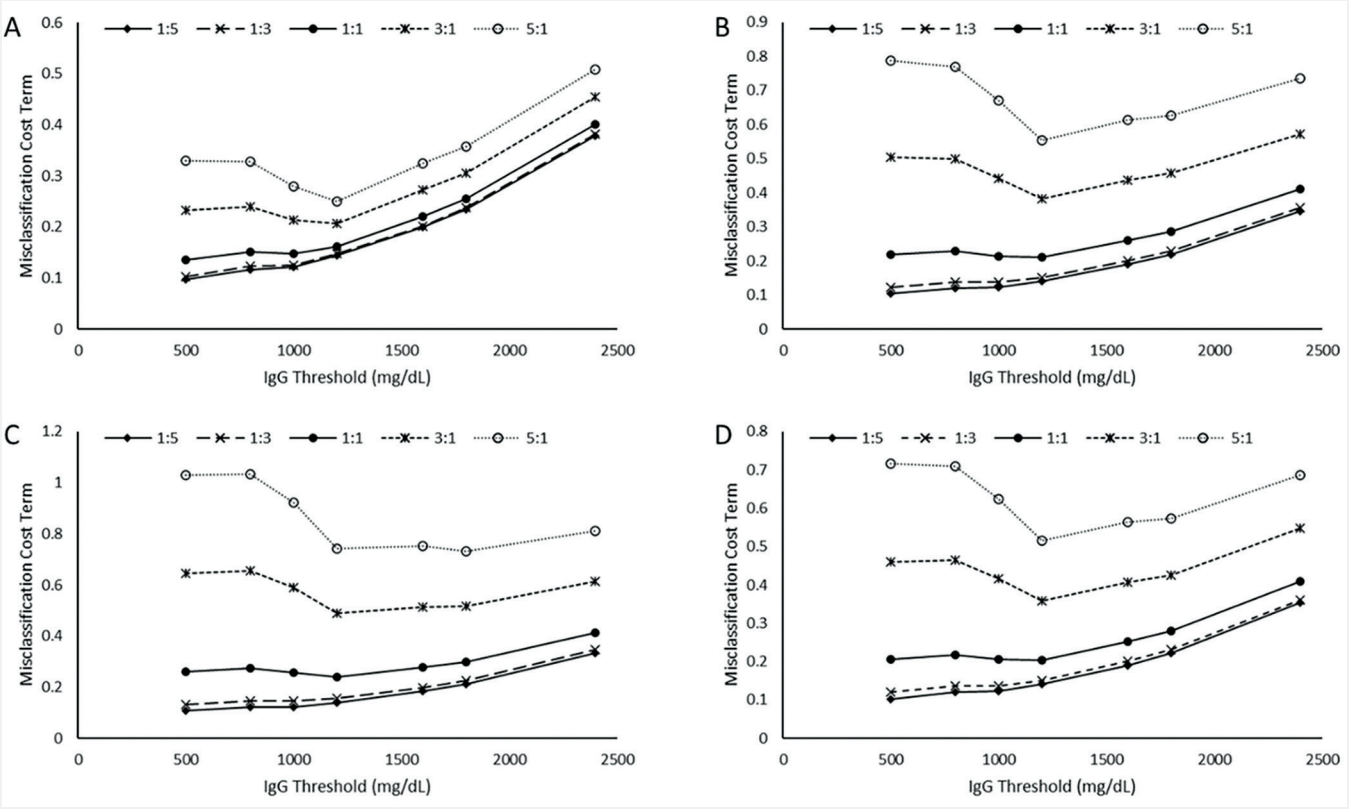
Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Conception and design, acquisition of data, analysis and interpretation, drafting of the manuscript, and approval of the final version to be published, A.T.; data analysis and interpretation, manuscript revision, and approval of the final version to be published, M.S.; acquisition of data, manuscript revision, and approval of the final version to be published, R.D; data interpretation, manuscript revision, and approval of the final version to be published, B.D.

Figure 3: Misclassification cost term (MCT) at different IgG thresholds and for different false negative-to-false positive ratio (varying from 1:5 to 5:1) to identify calves that develop preweaning morbidity in (A) population 1 (cumulative incidence of morbidity between 3.8 and 6.5%), (B) population 2 (cumulative incidence of morbidity between 15.2 and 19.2%), (C), population 3 (cumulative incidence of morbidity between 20.3 and 26.6%), and (D) overall. The MCT was calculated using a conditionally independent Bayesian latent class models (each model was run to obtain a Monte Carlo simulation containing an effective size of 5,000 for each variable after thinning).



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