Mastitis risk effect on the economic consequences of paratuberculosis control in dairy cattle: A stochastic modeling study

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Short Title: Modeling effect of mastitis on economics of paratuberculosis control in dairy

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ABSTRACT

The benefits and efficacy of control programs for herds infected with *Mycobacterium avium* subsp. *paratuberculosis* (**MAP**) have been investigated under various contexts. However, most previous research investigated paratuberculosis control programs in isolation, without modeling the potential association with other dairy diseases. This paper evaluated the benefits of MAP control programs when the herd is also affected by mastitis, a common disease causing the largest losses in dairy production. The effect of typically suggested MAP controls were estimated under the assumption that MAP infection increased the rate of clinical mastitis. We evaluated one hundred twenty three control strategies comprising various combinations of testing, culling, and hygiene, and found that the association of paratuberculosis with mastitis alters the ranking of specific MAP control programs, but only slightly alters the cost-effectiveness of particular MAP control components, as measured by the distribution of net present value of a representative U.S. dairy operation. In particular, although testing and culling for MAP resulted in a reduction in MAP incidence, that control led to lower net present value (**NPV**) per cow. When testing was used, ELISA was more cost-effective than alternative testing regimes, especially if mastitis was explicitly modeled as more likely in MAP-infected animals, but ELISA testing was only significantly associated with higher NPV if mastitis was not included in the model at all. Additional hygiene was associated with a lower NPV per cow, although it lowered MAP prevalence. Overall, the addition of an increased risk of mastitis in MAP-infected animals did not change model recommendations as much as failing to consider mastitis at all.

Key Words: paratuberculosis; economic model; disease control; mastitis

1. INTRODUCTION

Paratuberculosis, or Johne's Disease, is a chronic intestinal disease of ruminants caused by infection with *Mycobacterium avium* subsp. *paratuberculosis* (**MAP**). Animals are usually infected at a young age, with a variable and often extended latent period [1]. Infected animals have lower milk production [2–9], decreased reproductive performance in later stages of disease [6,10–12], and are often culled early [5,13]. It is difficult to control MAP in dairy herds; many tests have poor diagnostic sensitivity [14], MAP persists in the environment for long periods of time [15], paratuberculosis symptoms are slow to develop [16], and the available vaccines are limited in distribution due to their cross-reaction with tuberculosis diagnostics [17].

The debate over the economically optimal control method for MAP results from a wide range of models and assumptions. Some studies have found test and culling to be consistently cost-effective [18,19], while others have found that cost-efficacy of test and cull required subsidized testing costs [20] or only culling of animals with decreased milk production during MAP latency [21]. Simulation models have identified cost-effective programs, such as quarterly serum enzyme-linked immunosorbent assay (**ELISA**) testing [22], quarterly milk ELISA testing [23], risk-based testing accompanied by infection control [24], vaccination or infection control [25], testing in series with ELISA and quantitative polymerase chain reaction (**qPCR**) [26], and annual fecal culture accompanied by infection control [27]. Massaro et al. [28] found that a more sensitive ELISA test could be cost-effective in US dairy herds. Others have found that hygiene improvement was effective in decreasing transmission rate [25,29], especially in combination with testing and culling [1,30]. Our previous work found that some MAP control programs were not significantly better than no control, and that some managerial practices can produce better results than some testing and culling controls (Smith et al., 2017; Verteramo Chiu et al., 2018).

One factor that none of these studies addressed is the role of MAP infection in susceptibility to other infections. For example, higher mastitis incidence has been found in MAP positive farms in two different studies [32,33], and Rossi et al. [34] found that MAP-infected animals had significantly higher rates of clinical mastitis. As clinical mastitis is one of the most economically important diseases of dairy herds, a positive association between MAP infection and mastitis could greatly increase the cost-effectiveness of MAP and mastitis control. Even with no association, controlling for either disease may have spillover effects on the other disease.

The goal of this research is to examine the economic consequences of paratuberculosis in US dairy herds and the benefits of 123 specific control strategies involving various combinations of hygiene levels, types of testing, and decisions on culling, while accounting for the rise in mastitis cases associated with paratuberculosis infection.

2. MATERIALS AND METHODS

The infection and testing model (Figure 1) has been previously described [35], and used for an economic analysis of MAP [31]. This is a continuous-time model, simulated over 5 years after a burn-in of 50 years using values representative of US dairy herds. Details are available in the supplemental material (S1). Briefly, calves may be born susceptible or infected via vertical transmission. Susceptible calves may be infected by contact with transiently-shedding infected calves or with shedding adults. All calves age into heifers; susceptible heifers may be infected by contact with shedding adults, while infected heifers are assumed to be latently infected. All heifers age into adults. Adults infected as calves or heifers may have progressing infections, resulting in fast transition from latency, through a low-shedding phase, to high shedding and clinical disease. However, some adults infected as calves or heifers and all adults infected by contact with shedding adults experience non-progressing infections, which remain in latency for

a longer period of time and only enter the low-shedding phase. All animals may be culled or die, based on an age-appropriate mortality/culling rate.

Figure 1. Schematic of model for *Mycobacterium avium* subsp. *paratuberculosis* in a commercial dairy herd

The economic model tracks the daily milk production of all animals in the herd and calculates the net value of the herd as the value of the milk produced plus the value of any culled animals sold, minus the cost of producing milk, the cost of raising calves, the cost of raising heifers, and the cost of MAP testing.

2.1 Mastitis Risk and Milk Production

The risk of first clinical mastitis (**CM**) case, and the incidence of CM, has been found to be associated with MAP infection status in cows [34], possibly due to the immune system being affected by MAP. Clinical mastitis risk was assumed to be constant for all cows; although clinical mastitis risk is known to increase with parity, this model was not age-stratified, thereby averaging out clinical mastitis risk among all animals. Annualized risk of CM by all causes was calculated from Bar et al. [36] by averaging the monthly risk over a 10 month lactation and across the first 4 lactations, then adding the total monthly risk, $annualrisk = 10 * \sum_{p=1}^{4} \frac{\sum_{m=1}^{10} \frac{risk_{p,m}}{10}}{4}$. The range of possible values was identified by adding up the monthly risk for each lactation individually ($\sum_{m=1}^{10} risk_{p,m}$). Due to the lack of data to support modeling of secondary CM cases or subclinical mastitis, these events were not modeled.

105 In order to determine if the effect of CM on milk production would be exacerbated by MAP
106 status, we statistically analyzed milk production in animals with well-defined MAP infection
107 status as described previously [9]. Briefly, we conducted a linear regression analysis to assess the
108 effect of MAP progression (defined as progressing, non-progressing, or test-negative, where
109 progressing animals had at least one high-positive test result) and current MAP status (defined as
110 test-negative, latent, low-shedding, or high-shedding). In this analysis, a dichotomous term was
111 added to indicate whether an animal had experienced a CM event in the previous 30 days. In the
112 previous study, the linear score (log10 of the somatic cell count) was included to control for
113 subclinical and clinical mastitis; in this analysis, that variable was not included to avoid
114 collinearity with the CM variable.

115 ***2.2 Model Simulation***

116 The model was simulated under 3 different assumptions: CM association with MAP (**MA**), no
117 CM association with MAP (**NMA**), and no CM at all (**NM**). In the MA scenario, the rate of CM
118 cases was assumed to be related to MAP status. The hazard ratios from the Cox proportional
119 hazards model for MAP positive vs. negative animals [34], controlling for parity, were used to
120 inflate the CM risk for MAP positive animals. In the NMA scenario, the rate of CM cases was
121 assumed to be unchanged by MAP status. In the NM scenario, it was assumed that CM cases
122 were excluded in the model. In the MA and NMA scenarios, CM occurred in susceptible adults
123 at rate ψ, the annualized risk, and in MAP infected adults at rate $\xi_1\psi$, where ξ_1 is the hazard ratio
124 1.89 [34].

125 Upon the occurrence of a CM case, the following actions occurred: 1) remove the milk lost due
126 to CM, q_{mast}, from the period's milk production; 2) add the cost of treating CM, t_{mast}, to the

127 period's cost; 3) determine if the CM case resulted in mortality. Clinical mastitis mortality was
128 assumed to be μ_m. It was assumed that no voluntary culling occurred due to a first case of CM.

129 The net present value (***NPV***) of each scenario was calculated as

130 $$NPV = \sum_t \frac{\kappa(t)}{(1+r)^t} + \frac{\kappa(T)}{r(1+r)^{T+1}} \quad (2)$$

131 where, t is time in years, $\kappa(t)$ is the value of the herd in year t, r is the discount rate, and T is the
132 final time period. The second term represents a terminal wealth term, the NPV of the last year
133 cash flow continuing into perpetuity, to account for the value of the herd going forward past the
134 terminal year of T. Herds were simulated for 5 years, which is considered a realistic planning
135 window for commercial dairy herds.

136 ***2.3 Determining Stochastic Dominance***

137 Ranking of control programs by the distribution of NPV from 100 iterations of a five year period
138 was performed using first and second-order dominance [37]. First-order and second-order
139 stochastic dominance are methods of determining preference for an activity with variable
140 (stochastic) results; a dominant strategy by either method is to be preferred to its comparator. First-
141 order stochastic dominance is relevant for decision makers who prefer more wealth to less wealth
142 (increasing utility function), and second-order stochastic dominance is relevant for decision
143 makers who in addition to preferring more to less wealth are also risk averse (increasing and
144 concave utility function).

145 Briefly, if NPV_A is the cumulative distribution function of the NPV of control strategy A and
146 NPV_B is the cumulative distribution function of the NPV of control strategy B, first-order
147 dominance of strategy A states that

$$P\left(NPV_A \geq x\right) \geq P\left(NPV_B \geq x\right) \quad (3)$$

for all possible values of x (the range of simulated NPV values for a farm in a given scenario) and with a strict inequality for at least one value of x.

Likewise, second-order dominance of strategy A states that

$$AUC\left(NPV_A\right)\left[0:x\right] < AUC\left(NPV_B\right)\left[0:x\right] \quad (4)$$

for all possible values of x (as in equation 3), where $AUC(i)[0:x]$ is the area under the curve of the cumulative distribution function of distribution i from 0 to x.

2.4 Analyzing Dominance Results

Each of the 123 control strategies comprises four components: hygiene level, test used, test frequency, and which animals are culled (Supplemental Information S2). To estimate the effect of each of these components on dominance, we estimated a linear regression of the proportion of dominated strategies under SOSD on each of the strategies' components, measured by dummy variables. The econometric model has the following form,

$$Y_i = \alpha + \beta_i^H H_i + \beta_i^T T_i + \beta_i^C C_i + \beta_i^F F_i + \varepsilon_i \quad (4)$$

Where $Y$is the proportion that strategy i SOSD the other strategies, where the value of Y ranges from 0 to 1. H is an n x 2 matrix of hygiene level indicators (standard and high hygiene), T is an n x 4 matrix of test indicator (FC, ELISA, PCR, and hypothetical testing of calves with FC), C is an n x 2 matrix of culling policy (cull all test positive, and cull all high shedders), $F$is an n x 4 matrix of frequency of testing (annual, biannual, continuous annual, continuous biannual). Parameter α is the intercept term, which includes the effects of moderate hygiene, and culling after 2 positive tests. Parameters β^H, β^T,β^C,β^F are vectors to be estimated for each of the

components of the strategies. This regression is conducted separately for each of the three mastitis assumptions and assumes additive linear effects only. To determine which factors are most associated with changes in the NPV, this analysis was repeated using the difference between the NPV of a particular iteration and the NPV of no control from the same starting condition, expressed as an amount per cow, as the *Y*. Each of these analyses was repeated for each of the mastitis assumptions (NM, NMA, and MA) and the fitted coefficients were compared. The analysis was repeated at two different herd sizes (100 and 1000) and two different initial MAP prevalence levels (7% and 20%), but results will focus on the 1000-head herd with 20% initial prevalence.

2.5 Sensitivity Analysis

Global sensitivity analysis was performed using optimized Latin Hypercube sampling via the *lhs* package [39] with 500 parameter sets. For each parameter set, a 1000 head herd was simulated 100 times from the same randomly drawn initial population values under three generalized culling strategies (none, cull all positive adults, and cull all positive calves) with and without improved hygiene. Impact of parameters on NPV was determined using the Pearson's rank correlation coefficient. All parameters used are shown in Tables 1-3. Where variability in parameters was not provided by the source, parameters were varied by ± 10% for the sensitivity analysis. Where variability in parameters was available, parameters were varied over their interquartile ranges. Testing parameters were varied over the range of the interquartile ranges of all tests, and hygiene parameters were varied over the range of the possible additional hygiene levels. Parameters were considered significantly related to NPV at the level of $\alpha = 0.05$ with Bonferroni's correction.

Table 1. Biological parameters and interquartile ranges (IQR) used in a model of *Mycobacterium avium* subsp. *paratuberculosis* and clinical mastitis co-infection in a dairy herd.

Par.	Description	Value (IQR)	Source

μ_1	removal rate of calves (/year)	0.09 (0.08-0.1)	[40]
μ_2	removal rate of heifers (/year)	0.01 (0.008-0.015)	[40]
μ_3	removal rate of adults (/year)	0.35 (0.3-0.4)	[40]
$\mu_{b,base}$	birth rate of female calves (/adult/year)	0.45 (0.4-0.5)	[40]
$\mu_{b,H}$	birth rate of high shedding dams (/adult/year)	0.15 (0.1-0.45)	[11]
γ_E	proportion of calves of latent animals infected at birth	0.01 (0-0.04)	[40]
γ_L, γ_H	proportion of calves of shedding animals infected at birth	0.04 (0.01-0.08)	[40]
ρ_1, ρ_2	aging rate (/year)	1 (0.8-1.2)	Assumed
η	proportion of infected heifers becoming progressing adults	0.335 (0.5-1)	[40]
φ	transition rate from transient shedding to latent (/year)	2 (0.8-3)	[40]
σ_L	transition rate from latent to low shedding, low path (/year)	0.53 (0.44-0.67)	[35]
σ_H	transition rate from latent to low shedding, high path (/year)	21.5 (1.75-40)	[35]
ν_H	transition rate from low to high shedding, high path (/year)	1.08 (0.75-1.94)	[35]
α	clinical disease-related culling rate (/year)	0.67 (0.5-0.8)	[11]
β	transmission coefficient for 7% and 20% initial prevalence (/year) in a 1000-head herd	0.001, 0.003 (0.0023-0.0012)	calculated
e_β	proportional transmission effect due to improved and moderately improved hygiene	0.6, 0.98 (0.6-0.98)	[41,42] [43]
ψ	risk of clinical mastitis (/year)	0.27 (0.12-0.42)	[36]
$\boldsymbol{\xi_I}$	hazard ratio for clinical mastitis in infected cows	1.89 (1.53-2.33)	[34]
$\boldsymbol{\mu_m}$	risk of mortality during clinical mastitis	0.0175 (0.01-0.02)	[36]

Table 2. Testing parameters and interquartile ranges (IQR) used in a model of *Mycobacterium avium* subsp. *paratuberculosis* infection in a dairy herd.

Par.	Description	Value (IQR)	Source
Se_H^E	Sensitivity of ELISA for high-shedders	0.78 (0.68-0.86)	[44,45]
Se_H^K	Sensitivity of KELA for high-shedders	0.31 (0.11-0.67)	[46]
Se_L^E	Sensitivity of ELISA for low-shedders	0.24 (0.19-0.30)	[44,45]
Se_H^{FC}	Sensitivity of FC for high-shedders	0.9 (0.75-1)	[47]
Se_L^{FC}	Sensitivity of FC for low-shedders	0.5 (0.25-0.75)	[48]
Se_H^P	Sensitivity of PCR for high-shedders	0.84 (0.77-0.90)	[44,49,50]
Se_H^Q	Sensitivity of qPCR for high-shedders	0.737 (0.49-0.90)	[26]
Se_L^P	Sensitivity of PCR for low-shedders	0.47 (0.41-0.54)	[44,49,50]
Sp^E	Specificity of ELISA	0.97 (0.91-0.99)	[48,51–53]
Sp_H^K	Specificity of KELA for high-shedders	0.997 (0.952-0.999)	[46]
Sp^F	Specificity of FC	0.98 (0.92-1)	[52,53]
Sp^P	Specificity of PCR	0.94 (0.87-1)	[49,52]
Sp_H^Q	Specificity of qPCR for high-shedders	0.943 (0.80-0.99)	[26]
Se_C	Sensitivity of calf testing	0.5 (0.25-0.75)	assumed
Sp_C	Specificity of calf testing	0.98 (0.92-1)	assumed
δ_C	Culling rate of test-positive calves	$Se_CT_1+(1-Sp_C)S_1$	calculated
δ_L	Culling rate of low-positive adults	$Se_L(L_P+L_N)+(1-Sp)(E_P+E_N+S_3)$	calculated
δ_H	Culling rate of high-positive adults	$Se_HH+(1-Sp)(E_P+E_N+S_3)$	calculated

Table 3. Economic parameters and inter-quartile ranges (IQR) used in a model of *Mycobacterium avium* subsp. *paratuberculosis* and mastitis co-infection in dairy herds.

Cost	Description	Value (IQR)	Reference
prev	prevalence of MAP infection in purchased cows	0.094 (0.077-0.111)	[54]
C_{FC}	cost of fecal culture test per animal	$36 ($25-$42)	[55–58]
C_E	cost of ELISA test per animal	$6 ($4-$8)	[55–59]
C_P	cost of PCR test per animal	$32 ($32-40)	[55–59]
$\omega_{hyg,mod}$	Annual cost of implementing moderate hygiene per adult (clean milk)	$35.54	[21]
$\omega_{hyg,large}$	Annual cost of implementing improved hygiene per adult (clean milk, separate calving pens, separate housing)	$49.64	[21]
C_{cow}	Daily operating cost per kg milk produced	$0.35 (0.33-0.37)	[60]
C_{heifer}	Daily operating cost of raising a calf/heifer	$2.995 (2.662-3.403)	[61]
P_{cow}	Cull-cow price per kg	$1.9671 (1.7292-2.31)	[62]
P_{milk}	Milk price per kg	$0.444 (0.394-0.482)	[62]
P_{sale}	Sale price of replacement heifer	$2232 (2000-2500)	[61]
Q_{cull}	Average cull cow weight	680.4 kg (660-700)	[63]
$Q_{milk,S}$	Average daily milk production per uninfected cow	32.62 kg (25.45-42.73)	[9]
$Q_{milk,EN}$	Average daily milk production per latent cow (non-progressing)	32.17 kg (24.09-42.73)	[9]
$Q_{milk,LN}$	Average daily milk production per low-shedding cow (non-progressing)	30.94 kg (24.09-42.73)	[9]
$Q_{milk,EP}$	Average daily milk production per latent cow (progressing)	33.12 kg (22.27-39.09)	[9]
$Q_{milk,LP}$	Average daily milk production per low-shedding cow (progressing)	29.13 kg (22.27-39.09)	[9]
$Q_{milk,H}$	Average daily milk production per high-shedding cow	22.17 kg (12.27-32.27)	[9]
ψ_H	Proportional adjustment in cull weight for high-shedding cows	0.9 (0.75-1)	assumed
t_{mast}	Treatment cost per clinical mastitis case	$50 (35.50-73.50)	[36]
q_{mast}	Milk loss per clinical mastitis case	90.3 kg (64-183)	[64]
r	Discount rate	0.02 (0.01-0.08)	assumed

3. RESULTS

3.1 Milk Production Results

There were 31,583 monthly milk observations available for analysis, of which 537 occurred within a month of a CM event. Of those, 424 were in test-negative individuals, 97 were in non-progressing animals (85 latent, 12 low-shedding), and 16 were in progressing animals (14 latent, 2 low-shedding). Adding a variable indicating a recent CM did not improve the fit of the model including an interaction between MAP progression and status (BIC=216,536 with the term and

206 BIC=216,527 without the term), so milk loss in animals with both MAP infection and CM was
207 simulated to be additive.

208 ***3.2 Model Results***

209 For simplicity, we will present rankings of only 13 potential control options, and the results of
210 SOSD only, as SOSD implies FOSD. The base for comparison is no MAP control. If testing is
211 used, we assume that it will be based on the serum enzyme-linked immunosorbent assay
212 (ELISA) test, administered to all animals either annually or biannually. Animals may be culled
213 after any positive test, only after a test result indicating a high-positive response, or only after the
214 second positive test result. Additionally, the farm may choose to continue ELISA testing after 5
215 negative whole-herd tests, or to discontinue testing after the 5th negative whole-herd test.

216 Model results for this subset of control options are shown in Table 4 for a 1,000 head herd with
217 20% initial shedding prevalence under CM association with MAP (**MA**), no CM association with
218 MAP (**NMA**), and no CM at all (**NM**); results for other initial herd sizes and initial shedding
219 prevalence are generally similar, and are shown in Supplemental Table S3. The model predicted
220 that all control programs would decrease the median true infection prevalence of
221 paratuberculosis over 5 years, and most would decrease the median shedding prevalence (Figure
222 2).

223 **Table 4.** ELISA-based testing strategies and their NPV distribution and number of second-order
224 dominated strategies for each mastitis scenario. Results are for a 20% initial MAP prevalence in
225 a 1,000 head herd.

	Mastitis Association (MA)		**No Mastitis Association (NMA)**		**No Mastitis (NM)**	
	median NPV (range), x10^6	**SOSD**	**median NPV (range), x10^6**	**SOSD**	**median NPV (range), x10^6**	**SOSD**
No control	20.36 (16.76,23.63)	5	20.55 (16.99,23.85)	11	21.08 (14.59,26.41)	1
Annual ELISA, cull all	17.97 (13.44,21.79)	0	18.29 (12.74,22.02)	0	18.4 (10.95,23.13)	0

Annual ELISA, cull high	20.25 (15.97,24.97)	2	20.15 (15.21,23.74)	1	20.5 (16.07,24.86)	2
Annual ELISA, cull after 2	19.85 (17.14,23.82)	4	19.75 (15.52,24.48)	1	20.28 (17.22,23.36)	3
Biannual ELISA, cull all	19.95 (16.74,24.52)	2	19.96 (16.92,23.39)	3	20.58 (15.72,24.79)	1
Biannual ELISA, cull high	19.77 (16.18,23.43)	1	19.84 (16.33,23.13)	1	20.43 (16.59,23.12)	2
Biannual ELISA, cull after 2	19.69 (16.53,22.88)	1	20.43 (16.35,23.76)	5	20.11 (16.33,24.7)	2
Cont. annual ELISA, cull all	19.94 (16.69,23.82)	6	20.13 (15.92,24.22)	2	20.45 (16.19,24.51)	3
Cont. annual ELISA, cull high	20.40 (16.65,23.66)	6	20.56 (16.06,23.69)	5	20.57 (17.43,24.02)	8
Cont. annual ELISA, cull after 2	20.17 (16.69,23.79)	4	20.46 (16.76,24.22)	6	20.55 (16.95,24.85)	6
Cont. biannual ELISA, cull all	20.02 (17.53,24.17)	4	19.89 (16.52,23.81)	1	20.14 (15.9,23.58)	1
Cont. biannual ELISA, cull high	20.16 (16.35,23.74)	3	20.02 (16.17,24.6)	1	20.41 (17.62,24.56)	6
Cont. biannual ELISA, cull after 2	20.21 (15.48,23.64)	1	20.20 (15.84,24.22)	3	20.05 (16.7,23.99)	1

SOSD is the number of strategies (of the 13 presented) second-order dominated.

Figure 2. Predicted change in shedding prevalence of paratuberculosis infection after 5 years of control in a 1,000 cow herd with a median initial prevalence of 20%.

3.3 Stochastic Dominance Results

Regression results for the econometric model of SOSD rank for each of the CM scenarios and MAP prevalence are shown in Figure 3 and Table 5, using results of all 123 control combinations (S2). All six regressions have a similar set of significant variables, but their effects can be different across herds. Not testing was consistently significantly worse than annual testing, with the exception being in a herd with low initial prevalence and assuming NMA. Biannual testing was not significantly different from annual testing in most scenarios. Continuing to test after 5 negative whole-herd tests was significantly better than discontinuing

239 testing. ELISA testing was significantly better than FC or testing calves in the MA and NM
240 scenarios, but not in the NMA scenario. However, in the NMA scenario with high initial
241 prevalence, FC and PCR were significantly worse than testing calves. High levels of hygiene
242 were significantly worse than standard in all cases, and moderate levels of hygiene were
243 significantly worse than standard in most cases.

244

245 **Figure 3**. Coefficients from multivariable linear regressions for the overall second-order stochastic
246 dominance rank (1=best, 123=worst) of MAP control programs, separated by herd size, initial
247 shedding prevalence, and assumption about relationship between MAP and clinical mastitis (MA:
248 mastitis association; NMA: no mastitis association; NM: no mastitis). Central bar is estimate, box
249 shows 95% confidence interval around estimate.

250

251 **Table 5.** Linear regression results of the proportion of dominated strategies under SOSD on
252 strategy characteristics on all initial herds. Constant term includes the effects of annual
253 continuous testing of calves, culling animals after one positive test, and standard hygiene. Model
254 assumes additive linear effects.

		Mastitis Association Scenario (MA)		**No Mastitis Association Scenario (NMA)**		**No Mastitis Scenario (NM)**	
		20%	7%	20%	7%	20%	7%
Constant		42.8 (33.7,51.9)	38.8 (29.8,47.8)	41.7 (34.1,49.3)	53.7 (47,60.4)	39.1 (30.1,48.2)	39 (30.4,47.5)
Test frequency	Biannual	1.6 (-3.2,6.5)	1.7 (-3.1,6.5)	4.8 (0.7,8.8)	-2.6 (-6.2,1)	3 (-1.9,7.8)	**5 (0.4,9.5)**
	None	**44.1 (26.5,61.7)**	**46.4 (29.1,63.7)**	**26.4 (11.8,41)**	8.9 (-4,21.8)	**46.7 (29.2,64.2)**	**45.6 (29.1,62.1)**
Test discontinued after 5 negative WHT		**31.5 (26.6,36.4)**	**32.3 (27.5,37.1)**	**17.7 (13.6,21.7)**	**8.9 (5.3,12.5)**	**32.7 (27.9,37.6)**	**33.5 (28.9,38.1)**
Test type	FC	4.5 (-5.1,14.1)	9 (-0.5,18.5)	**8.8 (0.8,16.8)**	-0.4 (-7.5,6.6)	4.3 (-5.3,13.8)	5.7 (-3.3,14.7)
	ELISA	*-16.3 (-25.9,-6.6)*	*-11.7 (-21.2,-2.2)*	1.5 (-6.5,9.5)	-4 (-11.1,3.1)	*-14.7 (-24.3,-5.2)*	*-18 (-27,-9)*
	PCR	-3.5 (-13.1,6.1)	2.5 (-7,11.9)	**8.4 (0.4,16.4)**	1.3 (-5.8,8.3)	1.7 (-7.9,11.3)	-5 (-14,4.1)

Culled after	high positive	-3.2 (-9.5,3)	-4.3 (-10.5,1.9)	-5.1 (-10.3,0.2)	-3.3 (-8,1.3)	-1.9 (-8.1,4.4)	2 (-3.9,7.9)
	second positive	-0.8 (-7.1,5.5)	-6.8 (-13,-0.5)	-7.5 (-12.7,-2.3)	-3.2 (-7.9,1.4)	-2.6 (-8.8,3.7)	0.6 (-5.4,6.5)
Hygiene	Moderate	4.1 (-1.8,10)	**7.4 (1.5,13.2)**	**6.3 (1.4,11.2)**	**12 (7.6,16.3)**	**7.8 (1.9,13.7)**	3.9 (-1.7,9.4)
	High	**18.8 (12.9,24.7)**	**19 (13.1,24.8)**	**14.4 (9.5,19.3)**	**11.8 (7.5,16.2)**	**16.8 (10.9,22.7)**	**18.5 (12.9,24)**

Values in bold were associated with significantly worse SOSD ranking, while those in italics were associated with significantly better SOSD ranking.

Regression results for the econometric model of NPV for each of the CM scenarios and herds are shown in Figure 4. Biannual testing was significantly associated with a lower NPV compared to not testing, as was annual testing in almost all cases. Use of an ELISA test was significantly associated with a higher NPV than other test choices. Moderate or high hygiene levels were significantly associated with a lower NPV than standard hygiene. In a large herd, culling only high positive cows or after the second positive test was significantly associated with a slightly higher NPV; this relationship was not seen in small herds. There were few differences in coefficient values across CM scenarios.

Figure 4. Coefficients from multivariable linear regressions for change in NPV per cow by adding MAP control programs, separated by herd size, initial shedding prevalence, and assumption about relationship between MAP and clinical mastitis (MA: mastitis association; NMA: no mastitis association; NM: no mastitis). Central bar is estimate, box shows 95% confidence interval around estimate.

3.4 Sensitivity Analysis Results

The partial rank correlation coefficients of all significantly correlated parameters from the global sensitivity analysis are shown in Figure 5. Most scenarios had the same parameters consistently related with NPV, primarily economic and production-related parameters. The risk of clinical mastitis was significantly related to NPV in all scenarios.

Figure 5. Partial rank correlation coefficients (PRCC) from a global sensitivity analysis on net present value over 5 years of paratuberculosis control, assuming an association between mastitis incidence and MAP infection.

4. DISCUSSION

This research shows that consideration of interacting disease systems does not importantly change the results of an economic analysis of disease control. Adding an increased rate of CM among infected animals to an economic model of paratuberculosis control only slightly changed the ranking of control programs. Specifically, failing to include CM in the model resulted in a weaker preference for standard hygiene alone. Including CM but not its association with paratuberculosis resulted in a stronger preference for standard hygiene alone, biannual ELISA testing and culling adults after 2 positive tests, and continuous ELISA with the same culling policy. Culling for paratuberculosis should in theory have the side benefit of partially controlling for CM. However, the inclusion of an association between CM and paratuberculosis did not change the overall conclusions of this economic model. This is likely due to two factors: the high cost of MAP control and the relatively small size of the impact of MAP on mastitis.

We believe that the high cost of MAP control is the reason that few control strategies have been shown to economically dominate no control. If the cost of implementing testing or hygiene, not including costs related to culling of animals, were removed from the NPV, the distributions are somewhat similar for many control programs (Supplemental Figure, S5). However, the cost of these programs is high (Supplemental Table, S4): over a 5 year period, in a 1,000-head herd, the discounted cost of testing all adults annually via ELISA was calculated at $16,148. Testing all adult cows biannually using fecal culture or PCR was more than an order of magnitude higher. These numbers do not include the costs of culling test-positive animals, or the lower income due to smaller milking herd sizes after test-based culling in closed herds, each of which would raise the cost of control even more.

Previous studies have disagreed as to the cost-effectiveness of testing for MAP. While some models suggest that test and cull programs are effective at reducing the prevalence of MAP [30], others suggest that they are not sufficient to control MAP by themselves [23,65]. Our work here has shown that they are capable of decreasing the shedding prevalence of MAP, but are unlikely to be cost-effective. The exception would be ELISA testing, which others have also found to be potentially cost-effective [28]. This is likely due to the low cost and fast turn-around time for ELISA results.

We found here that hygiene was not cost-effective by any measure, and that this was unrelated to the relationship between MAP and mastitis. We had hypothesized that expensive control programs such as hygiene improvement (estimated here to cost a 1,000-head herd between $95,652 and $133,600 over a five year period) would become cost-effective as their effect on other pathogens was considered. The hygiene changes made to improve MAP control, however, are unlikely to directly impact CM incidence. While other models have suggested that hygiene

318 changes are indeed cost-effective [29], these may be assuming a lower base hygiene level than
319 our simulated herds. There also may be more benefits from hygiene improvement over a longer
320 time frame than the 5 years used here.

321 Our model did not show a strong effect of paratuberculosis association with CM on economically
322 optimal control. The global sensitivity analysis also showed that the hazard ratio for CM
323 incidence in MAP-infected animals was not significantly associated with NPV. Likely, this is
324 because the association between paratuberculosis and CM is so small in a practical sense. The
325 hazard ratio for first CM cases among MAP-infected animals is 1.89 (IQR: 1.53-2.33). However,
326 with an annualized rate of 0.27 CM cases/animal/year, this translates into an annual average of
327 27 extra cases of CM in a 1,000 head herd with 20% MAP infection prevalence. Given a cost per
328 case of CM of $90, not counting mortality, the additional cost to the herd is approximately
329 $2,500. Discounted over a 5 year simulation period, that results in a total cost of $11,655 due to
330 additional CM cases. This is less than the cost of the least expensive MAP control program
331 (annual ELISA testing), and, as no program can immediately eliminate MAP in the herd, not all
332 of the potential cost from the increased CM cases would be avoided by implementing control.

333 One large limitation of this model was the lack of age stratification, resulting in the necessary
334 simplification of constant clinical mastitis risk. It is known that clinical mastitis risk increases
335 with parity [66] and changes throughout the lactation [36]. However, accounting for age and
336 lactation stage in a compartmental model would cause the model to become intractable. For more
337 realistic modeling frameworks, it becomes necessary to transition to a more computationally
338 demanding modeling system, such as the agent-based model presented in Verteramo Chiu et al.
339 [67].

Regardless of the effects of MAP associations with CM, some overall preferences were determined. On average, continuing to test and cull after 5 negative whole-herd tests was always preferred. ELISA was the best-ranked test, followed by no testing. Standard hygiene was always preferred, with increasing hygiene levels associated with economically worse-ranked programs.

5. CONCLUSION

We have found that, in the setting of a typical commercial US dairy, the addition of clinical mastitis to a model for MAP control only slightly changed the ranking of individual control programs, but did not greatly change the overall cost-effectiveness of components of MAP control. These suggest that only testing by ELISA may be cost-effective.

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7. REFERENCES

1. Marcé C, Ezanno P, Weber MF, Seegers H, Pfeiffer DU, Fourichon C. Modeling within-herd transmission of Mycobacterium avium subspecies paratuberculosis in dairy cattle: a review. J Dairy Sci. Elsevier; 2010;93: 4455–70. doi:10.3168/jds.2010-3139

2. Kudahl AB, Nielsen SS, Sørensen JT. Relationship between antibodies against

Mycobacterium avium subsp. paratuberculosi s in milk and shape of lactation curves. Prev Vet Med. 2004;62: 119–134. doi:10.1016/j.prevetmed.2003.11.008

3. Aly SS, Anderson RJ, Adaska JM, Jiang J, Gardner IA. Association between Mycobacterium avium subspecies paratuberculosis infection and milk production in two California dairies. J Dairy Sci. Elsevier; 2010;93: 1030–40. doi:10.3168/jds.2009-2611

4. Nielsen SS, Krogh MA, Enevoldsen C. Time to the occurrence of a decline in milk production in cows with various paratuberculosis antibody profiles. J Dairy Sci. Elsevier; 2009;92: 149–55. doi:10.3168/jds.2008-1488

5. Lombard JE, Garry FB, McCluskey BJ, Wagner BA. Risk of removal and effects on milk production associated with paratuberculosis status in dairy cows. J Am Vet Med Assoc. 2005;227: 1975–1981. doi:10.2460/javma.2005.227.1975

6. Raizman EA, Fetrow JP, Wells SJ, Godden SM, Oakes MJ, Vazquez G. The association between Mycobacterium avium subsp. paratuberculosis fecal shedding or clinical Johne's disease and lactation performance on two Minnesota, USA dairy farms. Prev Vet Med. 2007;78: 179–195. doi:10.1016/j.prevetmed.2006.10.006

7. Gonda MG, Chang YM, Shook GE, Collins MT, Kirkpatrick BW. Effect of Mycobacterium paratuberculosis infection on production, reproduction, and health traits in US Holsteins. Prev Vet Med. 2007;80: 103–119. doi:10.1016/j.prevetmed.2007.01.011

8. Sorge US, Lissemore KD, Godkin A, Hendrick SH, Wells SJ, Kelton DF. Associations between paratuberculosis milk ELISA result, milk production, and breed in Canadian dairy cows. J Dairy Sci. 2011;94: 754–761.

9. Smith RL, Gröhn YT, Pradhan AK, Whitlock RH, Kessel JS Van, Smith JM, et al. The

effects of progressing and nonprogressing Mycobacterium avium ssp . paratuberculosis infection on milk production in dairy cows. J Dairy Sci. American Dairy Science Association; 2016;99: 1383–1390. doi:10.3168/jds.2015-9822

10. Vanleeuwen JA, Haddad JP, Dohoo IR, Keefe GP, Tiwari A, Tremblay R. Associations between reproductive performance and seropositivity for bovine leukemia virus, bovine viral-diarrhea virus, Mycobacterium avium subspecies paratuberculosis, and Neospora caninum in Canadian dairy cows. Prev Vet Med. Elsevier B.V.; 2010;94: 54–64. doi:10.1016/j.prevetmed.2009.11.012

11. Smith RL, Strawderman RL, Schukken YH, Wells SJ, Pradhan AK, Espejo LA, et al. The effect of Johne's disease status on reproduction and culling in dairy cattle. J Dairy Sci. 2010;93: 3513–3524.

12. Marcé C, Beaudeau F, Bareille N, Seegers H, Fourichon C. Higher non-return rate associated with Mycobacterium avium subspecies paratuberculosis infection at early stage in Holstein dairy cows. Theriogenology. 2009;71: 807–16. doi:10.1016/j.theriogenology.2008.10.017

13. Tiwari A, VanLeeuwen JA, Dohoo IR, Stryhn H, Keefe GP, Haddad JP. Effects of seropositivity for bovine leukemia virus, bovine viral diarrhoea virus, Mycobacterium avium subspecies paratuberculosis, and Neospora caninum on culling in dairy cattle in four Canadian provinces. Vet Microbiol. 2005;109: 147–158. doi:10.1016/j.vetmic.2005.05.011

14. Barkema HW, Orsel K, Nielsen SS, Koets AP, Rutten VPMG, Bannantine JP, et al. Knowledge gaps that hamper prevention and control of *Mycobacterium avium* subspecies

paratuberculosis infection. Transbound Emerg Dis. 2017;65: 125–148. doi:10.1111/tbed.12723

15. Moravkova M, Babak V, Kralova a, Pavlik I, Slana I. Culture and quantitative IS900 Real-time PCR-based analysis of the persistence of Mycobacterium avium subsp. paratuberculosis in a controlled dairy cow farm environment. Appl Environ Microbiol. 2012;78: 6608. doi:10.1128/AEM.01264-12

16. Ferrouillet C, Wells SJ, Hartmann WL, Godden SM, Carrier J. Decrease of Johne's disease prevalence and incidence in six Minnesota, USA, dairy cattle herds on a long-term management program. PrevVetMed. 2009;88: 128–137.

17. Garcia AB, Shalloo L. Invited review : The economic impact and control of paratuberculosis in cattle. J Dairy Sci. American Dairy Science Association; 2015;98: 1–21. doi:10.3168/jds.2014-9241

18. Pillars RB, Grooms DL, Wolf CA, Kaneene JB. Economic evaluation of Johne's disease control programs implemented in Michigan dairy farms. Prev Vet Med. 2009;90: 223–232.

19. Radia D, Bond K, Limon G, van Winden S, Guitian J. Relationship between periparturient management, prevalence of MAP and preventable economic losses in UK dairy herds. Vet Rec. 2013;173: 343-+. doi:10.1136/vr.101408

20. Groenendaal H, Wolf CA. Farm-level economic analysis of the US national Johne's Disease Demonstration Herd Project. J Am Vet Med Assoc. 2008;233: 1852–1858.

21. Wolf R, Clement F, Barkema HW, Orsel K. Economic evaluation of participation in a voluntary Johne's disease prevention and control program from a farmer's perspective-

427 The Alberta Johne's Disease Initiative. J Dairy Sci. Elsevier; 2014;97: 2822–34.
428 doi:10.3168/jds.2013-7454

429 22. Robins J, Bogen S, Francis A, Westhoek A, Kanarek A, Lenhart S, et al. Agent-based
430 model for Johne's disease dynamics in a dairy herd. Vet Res. Veterinary Research;
431 2015;46: 68. doi:10.1186/s13567-015-0195-y

432 23. Kudahl AB, Sørensen JT, Nielsen SS, Østergaard S. Simulated economic effects of
433 improving the sensitivity of a diagnostic test in paratuberculosis control. Prev Vet Med.
434 2007;78: 118–29. doi:10.1016/j.prevetmed.2006.10.004

435 24. Kudahl AB, Nielsen SS, Østergaard S. Economy, efficacy, and feasibility of a risk-based
436 control program against paratuberculosis. J Dairy Sci. 2008;91: 4599–609.
437 doi:10.3168/jds.2008-1257

438 25. Groenendaal H, Galligan DT. Economic consequences of control programs for
439 paratuberculosis in midsize dairy farms in the United States. J Am Vet Med Assoc.
440 2003;223: 1757–1763.

441 26. Aly SS, Anderson RJ, Whitlock RH, Fyock TL, McAdams SC, Byrem TM, et al. Cost-
442 effectiveness of diagnostic strategies to identify Mycobacterium avium subspecies
443 paratuberculosis super-shedder cows in a large dairy herd using antibody enzyme-linked
444 immunosorbent assays, quantitative real-time polymerase chain reaction, and bacte. J Vet
445 Diagnostic Investig. 2012;24: 821–32. doi:10.1177/1040638712452107

446 27. Cho J, Tauer LW, Schukken YH, Smith RL, Lu Z, Gröhn YT. Cost Effective Control
447 Strategies for Johne's Disease in Dairy Herds. Can J Agric Econ. 2013;61: 583–608.
448 doi:10.1111/j.1744-7976.2012.01270.x

449 28. Massaro T, Lenhart S, Spence M, Drakes C, Yang G, Agusto F, et al. Modeling For Cost
450 Analysis Of Johne's Disease Control Based On EVELISA Testing. J Biol Syst. 2013;21:
451 1340010. doi:10.1142/S021833901340010X

452 29. Dorshorst NC, Collins MT, Lombard JE. Decision analysis model for paratuberculosis
453 control in commercial dairy herds. Prev Vet Med. Elsevier; 2006;75: 92–122. Available:
454 http://www.sciencedirect.com/science/article/pii/S0167587706000547

455 30. Konboon M, Bani-yaghoub M, Id POP, Rhee N, Id SA. A nested compartmental model to
456 assess the efficacy of paratuberculosis control measures on U . S . dairy farms. 2018; 1–
457 25.

458 31. Smith RL, Al-Mamun MA, Gröhn YT. Economic consequences of paratuberculosis
459 control in dairy cattle: A stochastic modeling study. Prev Vet Med. Elsevier B.V.;
460 2017;138: 17–27. doi:10.1016/j.prevetmed.2017.01.007

461 32. Diéguez FJ, Arnaiz I, Sanjuan ML, Vilar MJ, Yus E. Management practices associated
462 with Mycobacterium avium subspecies paratuberculosis infection and the effects of the
463 infection on dairy herds. Vet Rec. 2008;162: 614–617. doi:162/19/614 [pii]

464 33. Arrazuria R, Arnaiz I, Fouz R, Calvo C, Eiras C, Diaguez F. Association between
465 Mycobacterium avium subsp . paratuberculosis infection and culling in dairy cattle herds
466 Asociación entre la infección por Mycobacterium avium subsp . paratuberculosis y las
467 causas de eliminación en rebaños de ganado lechero. Arch Med Vet. 2008;44: 39–44.
468 doi:10.4067/S0301-732X2014000100006

469 34. Rossi G, Gröhn YT, Schukken YHYHYH, Smith RL. The effect of Mycobacterium avium
470 subspecies paratuberculosis infection on clinical mastitis occurrence in dairy cows. J

Dairy Sci. American Dairy Science Association; 2017;100: 7446–7454. doi:10.3168/jds.2017-12721

35. Smith RL, Schukken YH, Gröhn YT. A new compartmental model of Mycobacterium avium subsp paratuberculosis infection dynamics in cattle. Prev Vet Med. Elsevier B.V.; 2015;122: 298–305. doi:10.1016/j.prevetmed.2015.10.008

36. Bar D, Tauer LW, Bennett GJ, González RN, Hertl JA, Schukken YH, et al. The cost of generic clinical mastitis in dairy cows as estimated by using dynamic programming. J Dairy Sci. 2008;91: 2205–14. doi:10.3168/jds.2007-0573

37. Levy H. Stochastic Dominance and Expected Utility : Survey and Analysis. Management Sci. 1992;38: 555–593.

38. Tversky A, Kahneman D. Rational Choice and the Framing of Decisions Author. J Bus. 1986;59: S251–S278.

39. Carnell R. lhs: Latin Hypercube Samples [Internet]. 2017. Available: https://cran.r-project.org/package=lhs

40. Mitchell RM, Whitlock RH, Gröhn YT, Schukken YH. Back to the real world: Connecting models with data. Prev Vet Med. Elsevier B.V.; 2015;118: 215–225. doi:10.1016/j.prevetmed.2014.12.009

41. Collins MT, Eggleston V, Manning EJB. Successful control of Johne's disease in nine dairy herds: results of a six-year field trial. J Dairy Sci. Elsevier; 2010;93: 1638–43. doi:10.3168/jds.2009-2664

42. Benedictus A, Mitchell RM, Linde-Widmann M, Sweeney RW, Fyock TL, Schukken YH,

et al. Transmission parameters of Mycobacterium avium subspecies paratuberculosis infections in a dairy herd going through a control program. Prev Vet Med. 2008;83: 215–227. doi:10.1016/j.prevetmed.2007.07.008

43. Nielsen SS, Toft N. Effect of management practices on paratuberculosis prevalence in Danish dairy herds. J Dairy Sci. 2011;94: 1849–1857.

44. Clark DL, Koziczkowski JJ, Radcliff RP, Carlson RA, Ellingson JLE. Detection of Mycobacterium avium subspecies paratuberculosis: comparing fecal culture versus serum enzyme-linked immunosorbent assay and direct fecal polymerase chain reaction. J Dairy Sci. Elsevier; 2008;91: 2620–7. doi:10.3168/jds.2007-0902

45. Sweeney RW, Whitlock RH, McAdams SC, Fyock TL. Longitudinal Study of ELISA Seroreactivity to Mycobacterium Avium subsp. Paratuberculosis in Infected Cattle and Culture-Negative Herd Mates. J Vet Diagnostic Investig. 2006;18: 2–6. doi:10.1177/104063870601800102

46. van Schaik G, Stehman SM, Jacobson RH, Schukken YH, Shin SJ, Lein DH. Cow-level evaluation of a kinetics ELISA with multiple cutoff values to detect fecal shedding of Mycobacterium avium subspecies paratuberculosis in New York State dairy cows. Prev Vet Med. Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA; 2005;72: 221–236. doi:10.1016/j.prevetmed.2005.01.019

47. Collins MT, Gardner IA, Garry F, Roussel AJ, Wells SJ. Consensus recommendations on diagnostic testing for the detection of paratuberculosis in cattle in the United States. J Am Vet Med Assoc. 2006;229: 1912–1919. Available:

http://avmajournals.avma.org/doi/abs/10.2460/javma.229.12.1912

48. Whitlock RH, Wells SJ, Sweeney RW, Van Tiem J. ELISA and fecal culture for paratuberculosis (Johne's disease): sensitivity and specificity of each method. Vet Microbiol. New Bolton Center, University of Pennsylvania, 382 West Street Road, Kennett Square, PA 19348, USA. whitlock@vet.upenn.edu; 2000;77: 387–398. Available: http://www.sciencedirect.com/science/article/pii/S0378113500003242

49. Taddei S, Robbi C, Cesena C, Rossi I, Schiano E, Arrigoni N, et al. Detection of Mycobacterium Avium Subsp. Paratuberculosis in Bovine Fecal Samples: Comparison of Three Polymerase Chain Reaction--Based Diagnostic Tests with a Conventional Culture Method. J Vet Diagnostic Investig. 2004;16: 503–508. doi:10.1177/104063870401600603

50. Leite FL, Stokes KD, Robbe-Austerman S, Stabel JR. Comparison of fecal DNA extraction kits for the detection of Mycobacterium avium subsp. paratuberculosis by polymerase chain reaction. J Vet Diagnostic Investig. 2013;25: 27–34. doi:10.1177/1040638712466395

51. Meens E, Rambaud T, Arnaud D. Evaluation of diagnostic tests to classify cattle, in control plans, according to their levels of excretion of Mycobacterium avium Paratuberculosis. 12th International Colloquium on Paratuberculosis. Parma, Italy; 2014. p. P-03.13.

52. Vitale N, Possidente R, D'Errico V, Dondo A, Bergagna S, Barbero R, et al. Estimating diagnostic accuracy of paratuberculosis (PTB) diagnostic test with latent class models. 12th International Colloquium on Paratuberculosis. Parma, Italy; 2014. p. P-02.10.

53. Sweeney RW, Gardner IA, Hines MEI, Anderson R, Byrem TM, Collins MT, et al.

536 Comparison of 3 fecal culture, 2 fecal PCR, 2 serum ELISA, and milk ELISA for
537 diagnosis of paratuberculosis in US dairy cattle. 12th International Colloquium on
538 Paratuberculosis. Parma, Italy; 2014. p. P-02.47.

539 54. Adaska JM, Anderson RJ. Seroprevalence of Johne's-disease infection in dairy cattle in
540 California, USA. Prev Vet Med. California Animal Health and Food Safety Laboratory,
541 Tulare Facility, 18830 Road 112, Tulare, CA 93274, USA. jmadaska@ucdavis.edu;
542 2003;60: 255–261.

543 55. Cornell University Animal Health Diagnostic Center. Test and Fee Schedule [Internet].
544 2015. Available: https://ahdc.vet.cornell.edu/

545 56. Collins MT, Manning EJB. Testing Services. In: Johne's Information Center [Internet].
546 2015. Available: http://www.johnes.org/testserv/index.html#tests

547 57. Besser T. New Strategies for Johne's Disease Testing. In: Washington Animal Disease
548 Diagnostic Lab [Internet]. 2015 [cited 10 Dec 2015]. Available:
549 http://waddl.vetmed.wsu.edu/animal-disease-faq/johne's-testing

550 58. Tests and Fees. In: Iowa State Veterinary Diagnostic Laboratory [Internet]. 2015 [cited 10
551 Dec 2015]. Available: http://vetmed.iastate.edu/veterinary-diagnostic-laboratory-vdl/tests-
552 and-fees#j

553 59. Indiana Animal Disease Diagnostic Laboratory. Fee Schedule [Internet]. 2015 [cited 10
554 Dec 2015]. Available: https://www.addl.purdue.edu/TestsFees/ByTest.aspx

555 60. USDA:ERS. National Milk Cost of Production. In: Milk Cost of Production Estimates
556 [Internet]. 2010 [cited 9 Sep 2015]. Available: http://www.ers.usda.gov/data-
557 products/milk-cost-of-production-estimates.aspx

558 61. Karszes J. Dairy Replacement Programs : Costs & Analysis 3 rd Quarter 2012. 2014;

559 62. USDA:NASS. Quick Stats. In: Quick Stats. 2015.

560 63. USDA. Agricultural Prices Summary 2003–2007. In: Agricultural Prices [Internet]. 2008.
561 Available: http://usda.mannlib.cornell.edu/MannUsda/view-
562 DocumentInfo.do?documentID=1003.

563 64. Bar D, Gröhn YT, Bennett GJ, González RN, Hertl JA, Schulte HF, et al. Effect of
564 repeated episodes of generic clinical mastitis on milk yield in dairy cows. J Dairy Sci.
565 2007;90: 4643–53. doi:10.3168/jds.2007-0145

566 65. Groenendaal H, Nielen M, Jalvingh AW, Horst SH, Galligan DT, Hesselink JW. A
567 simulation of Johne's disease control. Prev Vet Med. 2002;54: 225–245. Available:
568 http://www.sciencedirect.com/science/article/B6TBK-45X2PMN-
569 8/2/35a11301cbb515872fab227714a730ec

570 66. Breen JE, Green MJ, Bradley AJ. Quarter and cow risk factors associated with the
571 occurrence of clinical mastitis in dairy cows in the United Kingdom. J Dairy Sci. Elsevier;
572 2009;92: 2551–61. doi:10.3168/jds.2008-1369

573 67. Verteramo Chiu LJ, Tauer LW, Al-Mamun MA, Kaniyamattam K, Smith RL, Gröhn YT.
574 An agent-based model evaluation of economic control strategies for paratuberculosis in a
575 dairy herd. J Dairy Sci. 2018; doi:10.3168/jds.2017-13175

576

Supporting Information Captions

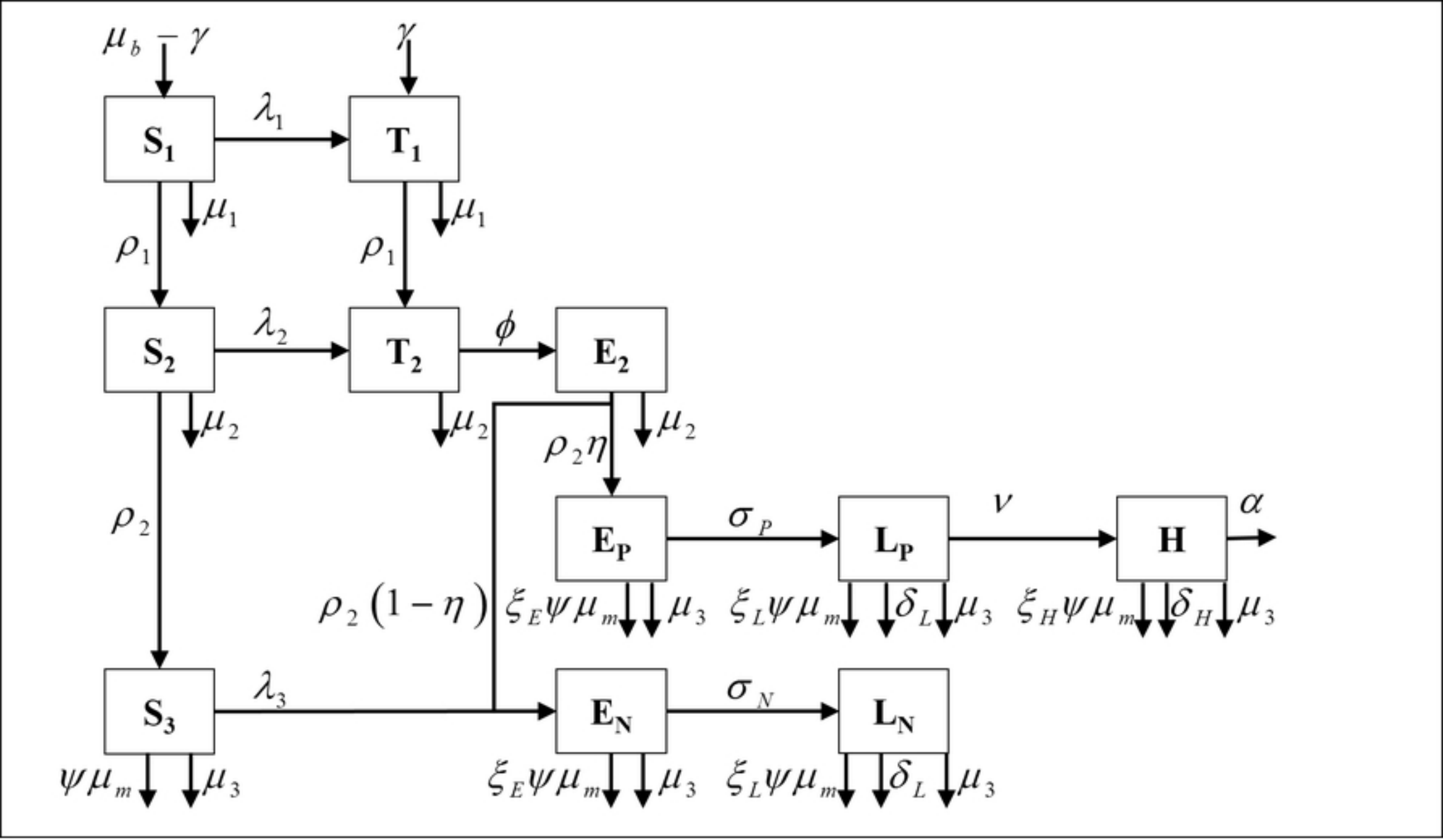
S1 Table: Events, changes, and rates used for simulation via Gillespie's direct algorithm

S2 Table: Paratuberculosis control strategy IDs

S3 Table: ELISA-based strategies and their NPV distribution and number of dominated strategies for each mastitis scenario and herd type.

S4 Table: Discounted cost of implementing different possible paratuberculosis controls, not including culling and replacement costs, over a 5 year period in a 1,000-head dairy herd

S5 Figure: Net Present Value and discounted cost of control for each paratuberculosis control strategy over 5 years in a 1,000-head dairy herd with 7% initial paratuberculosis prevalence and increased mastitis in paratuberculosis-infected cows


$\mu_b - \gamma$
γ
$\mathbf{S_1}$
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ϕ
$\mathbf{E_2}$
μ_2
μ_2
μ_2
$\rho_2\eta$
ρ_2
$\mathbf{E_P}$
σ_P
$\mathbf{L_P}$
ν
$\mathbf{H}$
α
$\rho_2(1-\eta)$
$\xi_E\psi\mu_m$ μ_3
$\xi_L\psi\mu_m$ δ_L μ_3
$\xi_H\psi\mu_m$ δ_H μ_3
$\mathbf{S_3}$
λ_3
$\mathbf{E_N}$
σ_N
$\mathbf{L_N}$
$\psi\mu_m$ μ_3
$\xi_E\psi\mu_m$ μ_3
$\xi_L\psi\mu_m$ δ_L μ_3

Figure 1

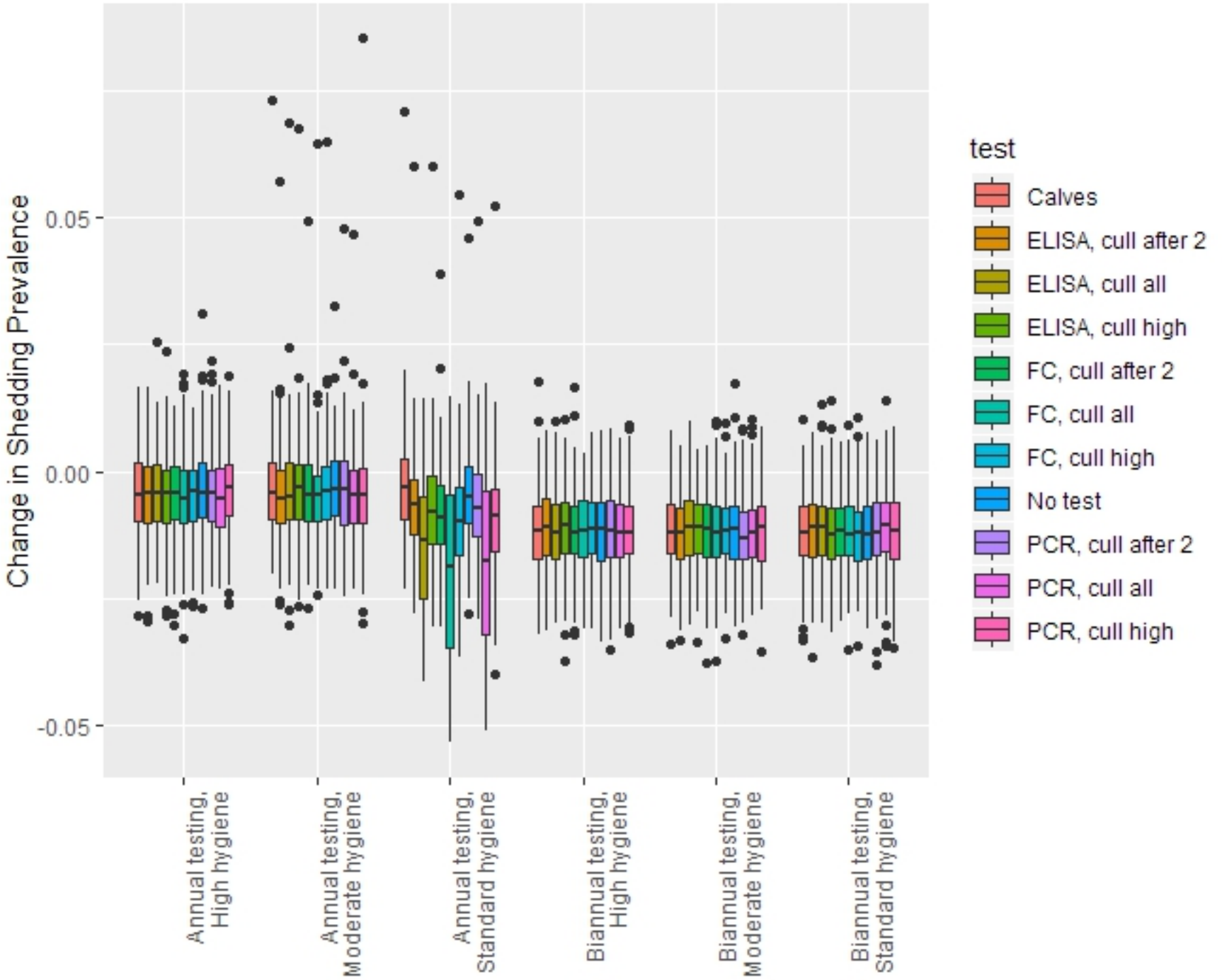
Change in Shedding Prevalence
0.05
0.00
-0.05
Annual testing, High hygiene
Annual testing, Moderate hygiene
Annual testing, Standard hygiene
Biannual testing, High hygiene
Biannual testing, Moderate hygiene
Biannual testing, Standard hygiene
test
Calves
ELISA, cull after 2
ELISA, cull all
ELISA, cull high
FC, cull after 2
FC, cull all
FC, cull high
No test
PCR, cull after 2
PCR, cull all
PCR, cull high

Figure 2

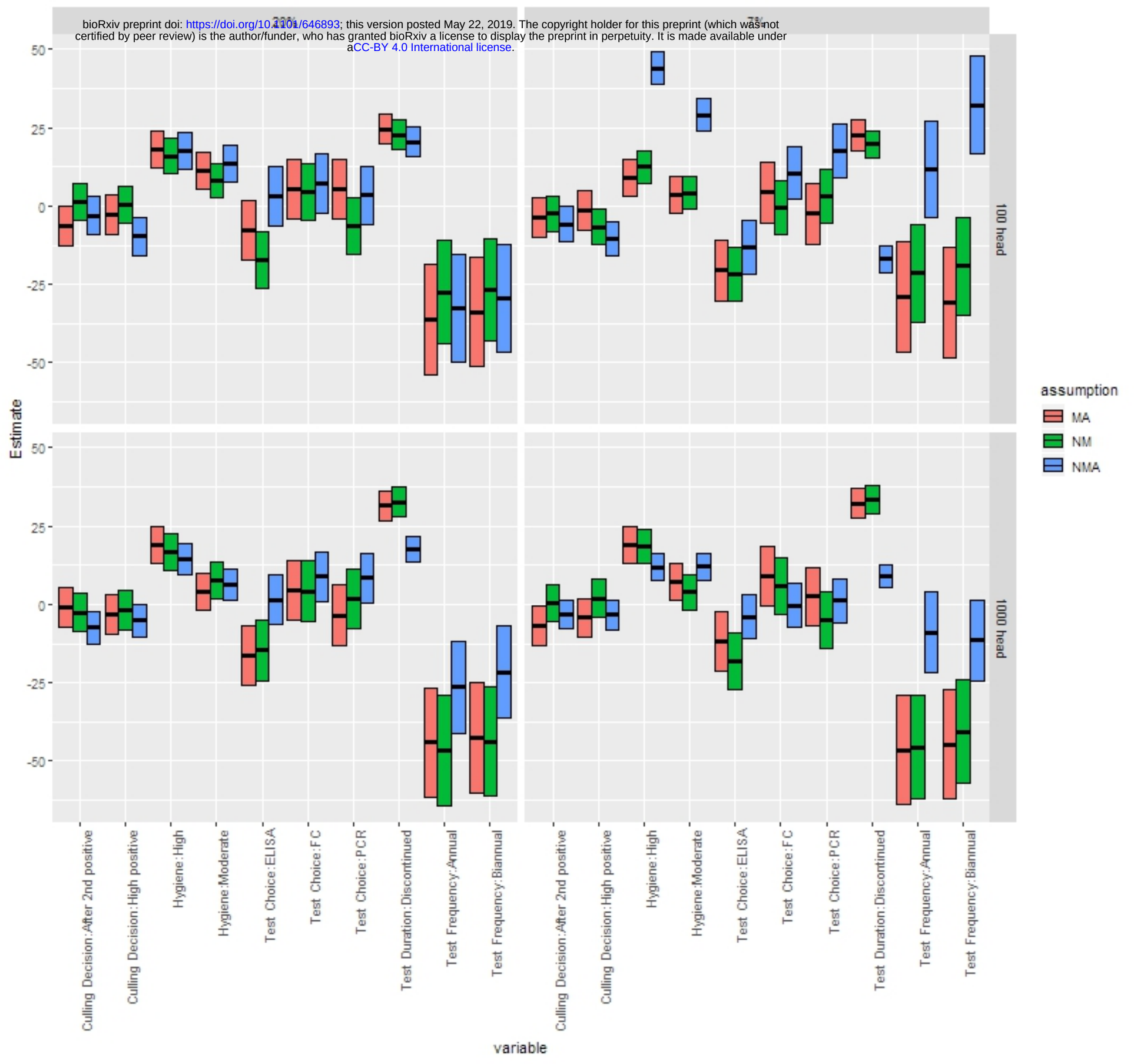

Figure 3

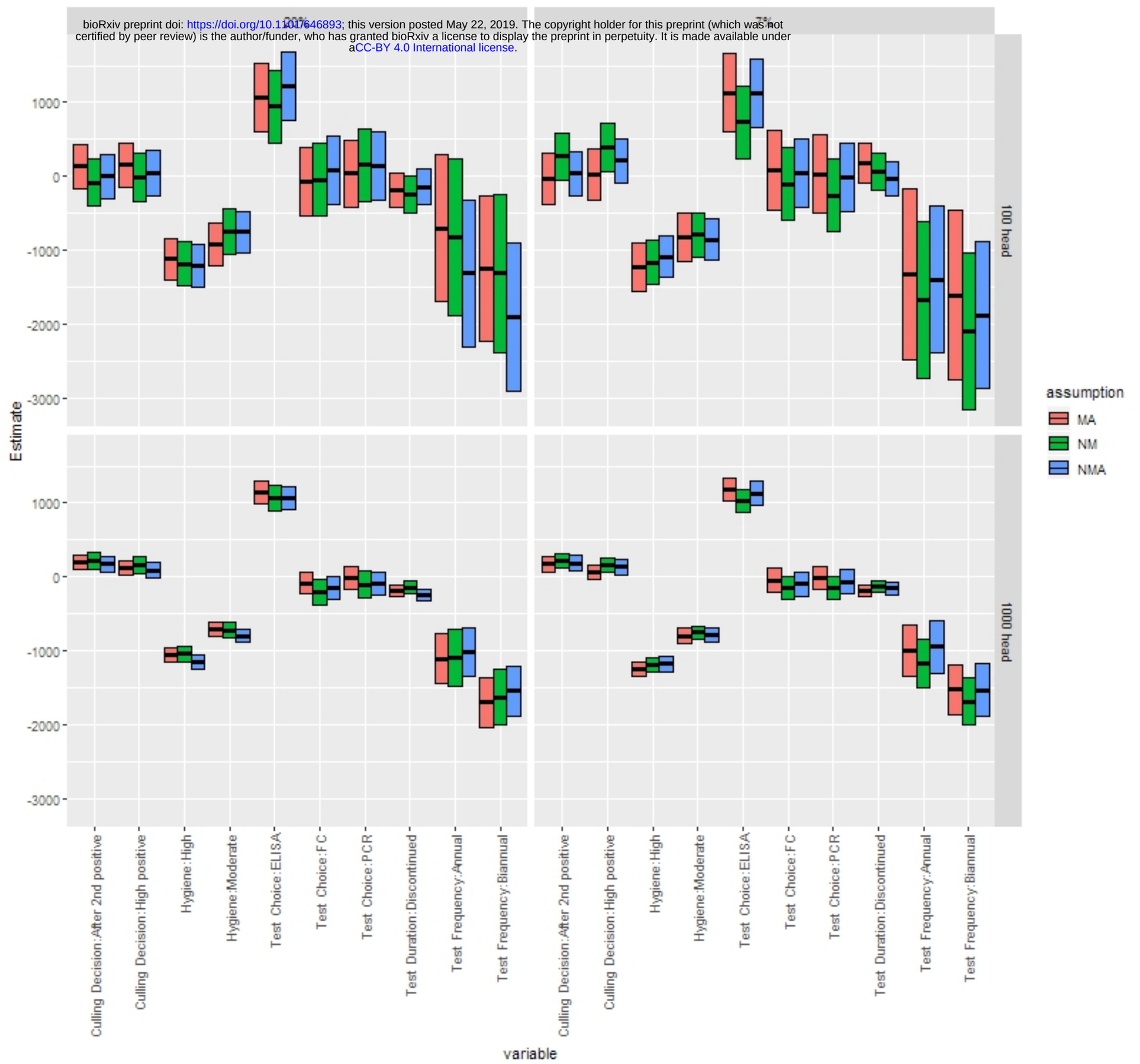

Figure 4

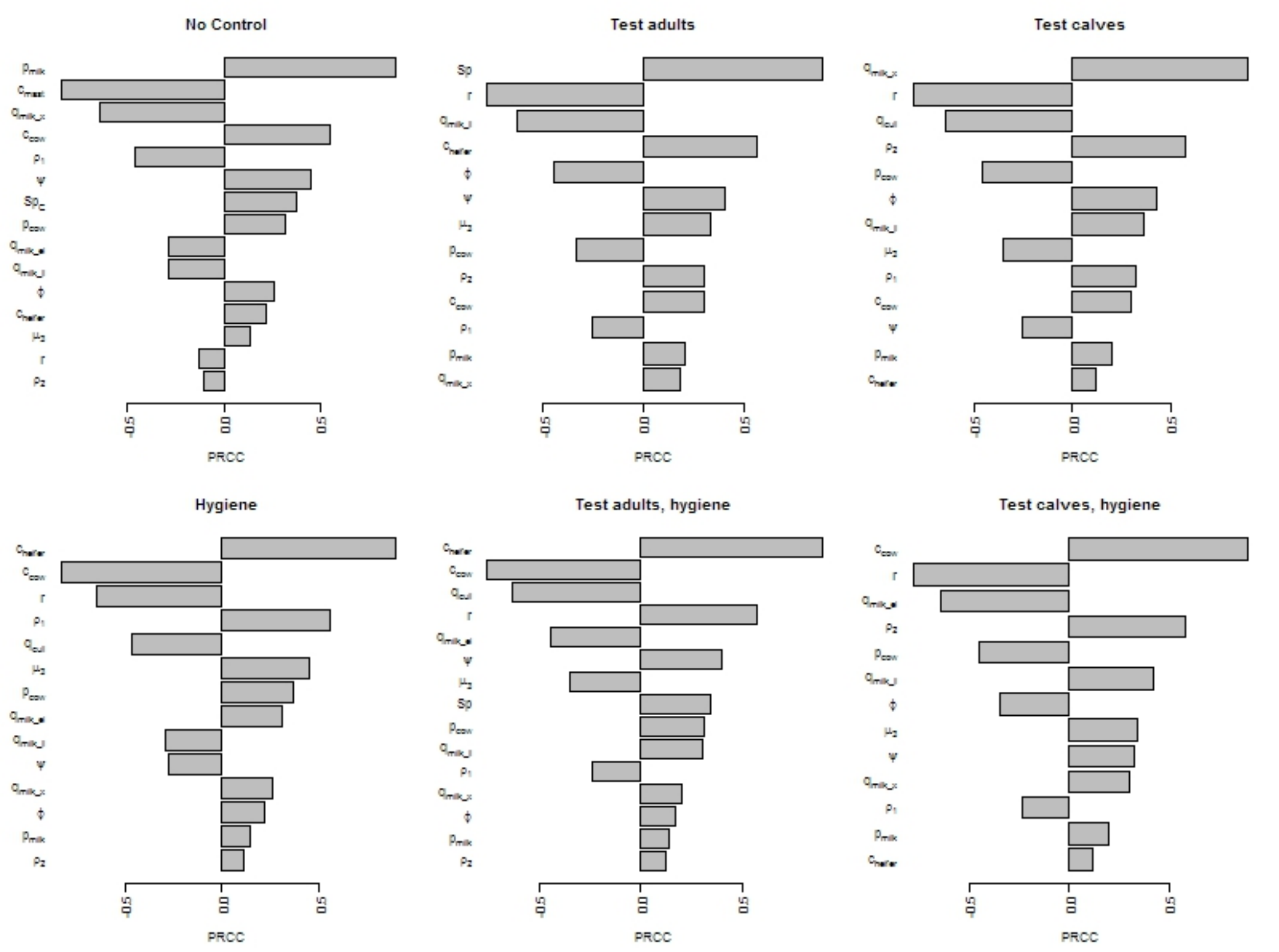
No Control
Test adults
Test calves
Hygiene
Test adults, hygiene
Test calves, hygiene
PRCC
-0.5
0.0
0.5

Figure 5