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1 GENETIC EVALUATION FOR TUBERCULOSIS

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3 **Genetic evaluation for bovine tuberculosis resistance in dairy cattle**

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19 **INTERPRETIVE SUMMARY**

20 Bovine Tuberculosis (bTB) is a chronic disease of grave consequences to the dairy and beef
21 cattle sector. A genetic evaluation platform was developed to estimate the genetic merit of
22 animals with regards to bTB resistance. The presence of significant genetic variation rendered
23 the distinction between genetically susceptible and resistant animals possible. Genetic
24 evaluations for bTB resistance are now official in Great Britain.

25 **ABSTRACT**

26 Genetic evaluations for resistance to bovine tuberculosis (bTB) were calculated based on British
27 national data including individual animal tuberculin skin test results, post-mortem examination
28 (presence of bTB lesions and bacteriological culture for *Mycobacterium bovis*), animal
29 movement and location information, production history and pedigree records. Holstein cows
30 with identified sires in herds with bTB breakdowns (new herd incidents) occurring between the
31 years 2000 and 2014 were considered. In the first instance, cows with a positive reaction to the
32 skin test and a positive post-mortem examination were defined as infected. Values of zero and
33 one were assigned to healthy and infected animal records, respectively. Data was analyzed with
34 mixed models. Linear and logit function heritability estimates were 0.092 and 0.172,
35 respectively. In subsequent analyses, breakdowns were split into two-month intervals to better
36 model time of exposure and infection in the contemporary group. Intervals with at least one
37 infected individual were retained and multiple intervals within the same breakdown were
38 included. Healthy animal records were assigned values of zero, and infected records a value of
39 one in the interval of infection and values reflecting a diminishing probability of infection in the
40 preceding intervals. Heritability and repeatability estimates were 0.115 and 0.699, respectively.

41 Reliabilities and across time stability of the genetic evaluation were improved with the interval
42 model. Subsequently, two more definitions of “infected” were analyzed with the interval model:
43 (i) all positive skin test reactors regardless of post-mortem examination; (ii) all positive skin test
44 reactors plus non-reactors with positive post-mortem examination. Estimated heritability was
45 0.085 and 0.089, respectively; corresponding repeatability estimates were 0.701 and 0.697.
46 Genetic evaluation reliabilities and across time stability did not change. Correlations of genetic
47 evaluations for bTB with other traits in the current breeding goal were mostly not different from
48 zero. Correlation with the UK Profitable Lifetime Index was moderate, significant and favorable.
49 Results demonstrated the feasibility of a national genetic evaluation for bTB resistance. Selection
50 for enhanced resistance will have a positive effect on profitability and no antagonistic effects on
51 current breeding goal traits. Official genetic evaluations are now based on the interval model and
52 the last bTB trait definition.

53

54 **Key words:** Genetic evaluation, bovine tuberculosis resistance

55

INTRODUCTION

56 Bovine tuberculosis (bTB) is a chronic bacterial disease of cattle caused by *Mycobacterium bovis*
57 (*M. bovis*) infection primarily involving the respiratory tract. The disease affects animal health
58 and welfare, causing substantial financial strain to the dairy cattle sector worldwide through
59 involuntary culling, animal movement restrictions and the cost of control and eradication
60 programs (Allen et al, 2010). Furthermore, bTB is considered a zoonotic disease with
61 considerable public health implications in countries where it is not subject to mandatory
62 eradication programs.

63 In Great Britain, the majority of bTB cases are recorded in south western England and Wales. A
64 bTB control and eradication program has been in place in these areas since 1950 comprising
65 primarily routine and targeted surveillance of cattle herds, culling of positive animals and
66 movement restrictions on infected herds. Surveillance is based on the administration of the single
67 intradermal comparative cervical tuberculin test (skin test) involving two separate injections of
68 sterile purified mixtures of *M. avium* and *M. bovis* antigens (tuberculins) in the deep layer of the
69 skin of the neck, followed by examination of the skin for localized allergic reactions after 72
70 hours (de la Rua-Domenech et al, 2006). When reaction to the *M. bovis* tuberculin injection is
71 deemed to be less than or equal to that to the *M. avium* tuberculin injection, then the skin test is
72 considered negative (non-reactor). A positive skin test result (known as a reactor) is declared
73 when the reaction to *M. bovis* tuberculin exceeds that to *M. avium* tuberculin by more than 4 mm,
74 according to the standard international interpretation (de la Rua-Domenech et al, 2006). In all
75 other cases the test is considered inconclusive and repeated 60 days later. If one or more animals
76 in a herd react positively to the skin test then a new bTB incident, also known as breakdown, is
77 declared prompting animal movement restrictions, suspension of the official bTB free (OTF)
78 status of the herd, and systematic testing of all animals in the herd at 60-day intervals. Animals
79 with a positive or two consecutive inconclusive skin tests are compulsorily slaughtered and
80 examined at the abattoir for visible lesions of bTB in their organs. Tissue samples from a
81 representative number of infected animals from each herd are submitted to the laboratory to
82 isolate *M. bovis* in bacteriological culture. A positive post-mortem examination result (presence
83 of lesions and/or positive *M. bovis* culture) signals a downgrading of the herd's OTF status from
84 "suspended" to "withdrawn". The breakdown remains open and skin testing continues in the herd

85 until one or two (depending on the post-mortem results and location of the herd) consecutive
86 negative tests at minimum intervals of 60 days are obtained on all remaining animals.

87 Implementation of bTB control and eradication programs incurs significant costs to taxpayers on
88 an annual basis. During 2010-2011, these costs amounted to £152 million in Great Britain and
89 £23 million in Northern Ireland (Abernethy et al, 2013). However, despite the investment and
90 good control efforts, the incidence and prevalence of bTB cases in Great Britain constantly
91 increased between the mid-1980s and 2012, although they have leveled-off in more recent years.
92 Even so, just over 4,800 new breakdowns were declared in cattle herds and more than 36,000
93 animals had to be slaughtered for bTB control purposes in 2015 (Department for Environment
94 Food and Rural Affairs - DEFRA, 2016). This has been partly attributed to a reservoir of
95 endemic *M. bovis* infection in wildlife, especially badgers, in large parts of England and Wales.
96 All these facts hinder progress towards achieving the DEFRA's goal for Great Britain to be OTF
97 by year 2038.

98 The presence of genetic variation among individual animals in their immunological response to
99 *M. bovis* exposure was documented by Pollock et al (2002). This genetic variation was
100 subsequently quantified and moderate heritability estimates were reported in cattle (Bermingham
101 et al, 2009; Brotherstone et al, 2010; Tsairidou et al, 2014). The amount of genetic variation and
102 the level of estimated heritability render resistance to bTB amenable to improvement via genetic
103 selection. Breeding for enhanced bTB resistance could complement existing control and
104 eradication programs. However, relevant tools have not been widely available as no formal
105 genetic evaluation systems have been put in place.

106 The objective of the present study was to assess the feasibility of a national genetic evaluation
107 for bTB resistance in dairy cattle based on British population data. We combined data from

108 various sources and developed automated data handling procedures suitable for a routine
109 commercial process. We investigated different models and trait definitions.

110 **MATERIALS AND METHODS**

111 *Data*

112 Population surveillance data were made available from the Animal and Plant Health Agency
113 (APHA) of the Department for Environment, Food and Rural Affairs (DEFRA). Data consisted
114 of tuberculin skin test and post-mortem examination records of dairy and beef cattle from Great
115 Britain (predominantly England and Wales), spanning the period 1957-2014 although more than
116 90% of the recorded data were post 2000. Skin tests had been applied to individual animals every
117 two months within a given breakdown (defined as the period of disease surveillance in a herd
118 prompted by the first detection of an infected animal and ending with the lifting of herd
119 movement restrictions). Animals were classified as non-reactors, inconclusive reactors and
120 reactors as described by de la Rua-Domenech et al (2006).

121 Negative skin test results for individual animals (non-reactors) were not being systematically
122 recorded in the APHA database prior to 2011. Therefore, the British Cattle Movement Service
123 (BCMS) database was used to identify contemporaries of reactors and inconclusive reactors in
124 the APHA database that were present in the same herd during each breakdown. All
125 contemporaries found in the BCMS database that were not included in the APHA data were
126 considered to be non-reactors. The combined APHA-BCMS data was merged with milk
127 recording data to derive information about the date of calving and parity number of the animals.
128 A final match with the national pedigree dataset (including data from the official Herdbooks)
129 maintained by the Edinburgh Genetic Evaluation Services on behalf of the Agriculture and

130 Horticulture Development Board (Dairy), retrieved the identification of the sire of each cow.
131 Figure 1 illustrates the combination of data from various sources. A total of 5,358,308 cow
132 records were included in the initial project database.

133 *Trait Definition*

134 The health status of each animal was defined as follows:

135 1. Infected; three definitions were examined:

136 a. Reactors to the skin test with positive post-mortem examination results
137 comprising visible lesions of bTB and/or positive *M. bovis* culture (R+PM); this
138 conservative definition required that a positive skin test be confirmed post-
139 mortem and is consistent with the current formal APHA definition of a confirmed
140 case as well as a previous study based on similar data (Brotherstone et al, 2010).

141 b. All reactors to the skin test regardless of post-mortem examination results (R);
142 this definition was based on the very high specificity (ca. 99%) and positive
143 predicted value of the skin test (de la Rua-Domenech et al, 2006; Goodchild et al,
144 2016) implying a very small percentage of false positives (positive skin test
145 reactors that were not actually diseased).

146 c. As in (b) plus non-reactors and inconclusive reactors to the skin test who had been
147 subsequently slaughtered and had positive post-mortem examination results
148 (RandNPM); this definition aimed at capturing all information available that
149 could be indicative of infection including possible false negative skin test reactors
150 in the analysis (Allen et al, 2010).

151 2. Healthy: live non-reactors to the skin test or slaughtered non-reactors with negative post-
152 mortem examination results (i.e. absence of lesions and a negative *M. bovis* culture).

153 Based on the above, three trait definitions of the animal's bTB infection status were considered
154 according to the three definitions of "infected". The "healthy" animal definition was the same in
155 all cases.

156 *Data Edits*

157 More than 90% of the records in the database were from breakdowns that started in the year
158 2000 or later. The latter data were also more complete in terms of post-mortem examination
159 results. Therefore, breakdowns that started before 2000 were removed from further analyses.
160 This edit was consistent with a previous study conducted on similar data (Brotherstone et al,
161 2010). Additional edits kept only milking cows of the Holstein breed with an identified Holstein
162 sire in breakdowns that were not shorter than two months. A final edit required that breakdowns
163 have at least five observations of which at least one pertained to an infected cow. According to
164 the three trait definitions, data from 424,843; 642,995 and 660,762 daughters of 15,211, 19,050
165 and 19,325 sires, respectively, were kept in the analysis.

166 *Genetic Evaluation*

167 In the first instance, the following animal model was used to analyze animal bTB infection status
168 as defined above:

$$169 \quad Y_{ijkmn} = \mu + B_i + R_j \cdot M_k + L_m + b_1dur + b_2age + b_3phol + A_n + e_{ijkmn} \quad (1)$$

170 where

171 Y = bTB infection status record of animal n in breakdown i (0/1)

172 μ = population mean

173 B = fixed effect of the breakdown i

174 R·M = fixed effect of the interaction between calendar year j and month k of breakdown
175 onset

176 L = fixed effect of lactation number m (m=1 for primiparous cows, 2 for multiparous
177 cows)

178 dur = linear regression on duration of the breakdown (b_1 =regression coefficient)

179 age = linear regression on age of animal at breakdown onset (b_2 =regression coefficient)

180 phol = linear regression on percentage of Holstein genes of the animal (b_3 =regression
181 coefficient)

182 A = random additive genetic effect of animal n including pedigree (6,398,839 animals)

183 e = random residual

184 Although data were restricted to only Holstein cows, the percentage of Holstein (vs. British
185 Friesian) genes was available in the national dairy pedigree and was included in the model,
186 consistent with the national genetic evaluations for other traits (Edinburgh Genetic Evaluation
187 Service, 2016).

188 In a separate analysis, a logit function was fitted to model 1 to account for the binary nature of
189 the trait.

190 In model 1, the entire breakdown irrespective of length represented a contemporary group
191 (cohort of animals). Although the model adjusted for different breakdown duration, the time of
192 exposure and actual infection could vary considerably within and across breakdowns, thereby
193 affecting the true definition of the contemporary group and possibly impacting on results. In an
194 alternative design, breakdowns were split into equally-sized (two months) intervals that would
195 better capture the specific prevailing conditions and dynamics at a given time, and model

196 exposure and infection consistently within and across breakdowns and herds. The interval
 197 duration of two months was chosen in connection with bimonthly surveillance testing of herds
 198 during open breakdowns. As before, a breakdown interval was required to have at least one
 199 infected animal and a minimum size of five to be included in the analysis. Data from multiple
 200 intervals within the same breakdown were included, resulting in repeated records per individual
 201 cow. Specifically, animals defined as healthy in a given interval were assumed to have been
 202 healthy in all previous intervals within the same breakdown and were assigned repeated records
 203 of zero. An animal found to be infected in a given interval was assigned a record of one in this
 204 interval. In previous intervals within the same breakdown, this infected animal was assigned a
 205 value reflective of a diminishing probability of infection manifested as a record of $(0.40)^n$, where
 206 n was the time distance from the interval of infection; for example, the infected animal record
 207 was 0.40 in the immediately previous interval, 0.16 in the interval before that, 0.064 in the third
 208 preceding interval and so on. The probability of infection chosen (0.40) is consistent with a
 209 sensitivity estimate of 0.60 of the skin test as diagnostic tool for bTB. Sensitivity reflects the
 210 proportion of negative skin test reactors (non-reactors) that were truly healthy; thus the value of
 211 0.40 represents the proportion of diseased non-reactors (false negatives). Reported sensitivity
 212 estimates of the tuberculin skin test range in literature from 0.51 to 0.81 (Downs et al, 2011;
 213 Álvarez et al, 2012; Karolemeas et al, 2012). Varying the assumed sensitivity and probability of
 214 infection between these values had only trivial impact on the genetic evaluation results (data not
 215 shown).

216 The model of analysis under the interval design was revised as follows:

$$217 \quad Y_{ijklmno} = \mu + B_i + R_j \cdot M_k + L_m + D_l + b_1age + b_2phol + A_n + PE_n + e_{ijklmno} \quad (2)$$

218 *where*

219 Y = bTB infection status record of animal n in breakdown interval i (repeated records)
 220 B = fixed effect of the breakdown interval i
 221 R·M = fixed effect of the interaction between calendar year j and month k of breakdown
 222 interval onset
 223 D = fixed effect of breakdown interval duration l (l=1 for a two-month interval, 2 for a
 224 possibly shorter interval leading to the end of the breakdown)
 225 age = linear regression on age of animal at breakdown interval onset (b₁=regression
 226 coefficient)
 227 PE = random permanent environment effect associated with animal n
 228 All other effects were as in model (1).

229 In all cases, variance component and parameter estimates were derived using the software
 230 ASReml (Gilmour et al, 2009) and genetic evaluations (estimation of breeding values) with the
 231 software MiX99 (Vuori et al, 2006). Reliability estimates of the genetic evaluations, reflecting
 232 the squared correlation between the estimated and true breeding values, were based on the
 233 approximation proposed by Jamrozik et al (2000). Variance component estimation was based on
 234 a subset of data pertaining to sires with 20 to 500 daughters in the data. This edit resulted in
 235 about one third of the data being used in variance component estimation, in each case.

236 Separate genetic evaluations were calculated after removing the last two years of data and
 237 repeating the analyses on the reduced dataset. Results from the reduced and full data analyses
 238 were compared to test the stability of the genetic evaluation across time by emulating conditions
 239 of consecutive genetic evaluations with updated data. Additional model validation was
 240 conducted based on Interbull's method 3 for national genetic evaluations, which entails

241 regression of current (full) on the previous (reduced) genetic evaluation and on a function of the
242 number of new daughters per sire since the previous evaluation (Boichard et al, 1995). This
243 function combines the number of new daughters by year of first calving with the total number of
244 daughters in the current evaluation (Boichard et al, 1995).

245 **RESULTS AND DISCUSSION**

246 *Descriptive Statistics*

247 Table 1 summarizes the three datasets considered in the present study, depending on trait
248 definition. In the breakdown design (model 1) each cow had a single record whereas repeated
249 records were included in the interval design (model 2). It should be noted that these proportions
250 reflect only breakdowns with infected cases included in the present study and are not
251 representative of the entire national herd.

252 As expected, the conservative definition of infection (R+PM, requiring a positive post-mortem
253 examination of skin test reactors) resulted in the lowest proportion of infected animals (3.57%).
254 There was minimal difference between the other two datasets which were mainly based on all
255 skin test reactors regardless of post-mortem results (8.28% vs. 8.29%). The last dataset also
256 included non-reactors and inconclusive reactors that had been slaughtered and tested positively
257 post-mortem. However, there were very few such cases; in fact, of all infected cases in the third
258 dataset (RandNPM), 97.3% were skin test reactors, 2.6% were inconclusive and only 0.1% were
259 non-reactors to the skin test.

260 *Breakdown vs. Interval Model*

261 Results from the breakdown design (model 1) and the interval design (model 2) were compared
262 using the first trait definition (R+PM), where skin test reactors with positive post-mortem were

263 considered to be infected. The heritability estimates were 0.093 (± 0.009) and 0.115 (± 0.014) for
264 the two models, respectively. Heritability estimate after fitting a logit function to model 1 was
265 0.172 (± 0.018), reflecting the genetic variation in the underlying liability scale. These estimates
266 are in agreement with results of previous studies on British (Brotherstone et al., 2010) and Irish
267 (Bermingham et al., 2009) bTB data considering the same trait definition. Presence of significant
268 ($P < 0.01$) genetic variance signifies the amenability of the trait to improvement via selective
269 breeding. Model 2 also yielded a repeatability estimate of 0.699 (± 0.005) indicative of the
270 definition of repeated records of the same cow within a breakdown in the present study.

271 Figure 2 shows the histogram of sire estimated breeding values (EBVs) by models 1 and 2. In
272 accordance to industry preference, positive numbers were associated with higher resistance to
273 bTB. Both models yielded normally distributed sire EBVs. The average proportion of infected
274 daughters among the top and bottom 20 bulls from the evaluation based on the breakdown model
275 was 2% and 23%, respectively. Corresponding proportions for the interval model were 2% and
276 24%, respectively. Thus the two models fared equally well at distinguishing sires whose
277 offspring have a higher degree of resistance from those that are more susceptible.

278 Table 2 summarizes the reliability estimates of sire EBVs obtained by the two models. Results
279 are expressed as the cumulative percentage of sires falling within each reliability range. For
280 example, 78% and 90% of the sires had EBV reliability greater than or equal to 0.30 based on the
281 breakdown and interval model, respectively. Proportionally, more than twice the number of sires
282 had EBV reliability of at least 0.50 based on the interval compared to the breakdown model,
283 whereas this proportion was trebled for higher reliabilities (≥ 0.60). The average sire EBV
284 reliability was 0.40 and 0.54 for the breakdown and interval model, respectively. These results

285 attest to the increased accuracy on the interval model, reflecting a more appropriate definition of
286 the contemporary group and a larger amount of data in the genetic evaluation.

287 Figure 3 illustrates the relationship between sire EBVs and proportion of infected daughters in
288 the genetic evaluation. In both models, sire EBVs were reflective of the infection rate among
289 their daughters, with somewhat stronger correlations for the interval than the breakdown model
290 (-0.68 vs. -0.64). These correlations are expectedly negative as a higher EBV is indicative of
291 increased resistance to bTB manifested by a lower infection rate.

292 Stability of genetic evaluations across time is illustrated in Figure 4. In both cases, sire EBVs
293 based on a reduced data set were very good predictors of EBVs based on full data, the latter
294 emulating a future genetic evaluation including new records. In this research case, new records
295 were from an additional two full years of bTB surveillance, adding more than 30% of new data
296 to the genetic evaluation. Official national genetic evaluations in the UK are calculated three
297 times per year meaning new data will be included more gradually leading to even higher
298 correlations and stability between successive evaluation runs. High EBV correlations and
299 stability across time are crucial for the acceptability of genetic evaluation results by the industry.

300 Validation with Interbull method 3 yielded a significantly greater than zero ($P < 0.01$) regression
301 on the function of new daughters for the breakdown model but a non-significant one ($P = 0.29$) for
302 the interval model. If a genetic evaluation is unbiased, this regression is expected to be zero
303 (Boichard et al, 1995). Furthermore, Interbull require the regression to not exceed 0.02 genetic
304 standard deviations in order to include a national genetic evaluation in their international
305 comparisons (www.interbull.org). In the present study, the regression in question was 0.0338 and
306 0.0053 genetic standard deviations for the breakdown and the interval model, respectively,
307 making the latter acceptable for national genetic evaluations.

308 The above results collectively demonstrate an overall superiority of the interval over the
309 breakdown model in the analysis of bTB data. Therefore, further analyses were based on the
310 former.

311 *Comparison of Trait Definitions*

312 The interval model was used to analyze data based on the other two trait definitions, where all
313 skin test reactors (R) and all skin test reactors plus non-reactors with positive post-mortem
314 (RandNPM), respectively, were considered to be infected.

315 Table 3 summarizes the variance component and heritability estimates from the three interval
316 model analyses. All estimates were statistically greater than zero ($P < 0.01$). Slightly higher
317 heritability was estimated for the conservative definition of infected (R+PM), which can be
318 attributed to the lower estimates for residual and permanent environmental variance (Table 3).
319 The latter may be due to the definition of the trait, which, combined with the requirement to
320 include breakdown intervals with at least one infected record, resulted in fewer records per cow
321 compared to the more relaxed definitions (R and RandNPM). In fact, the average number of
322 records per cow increased from 2.45 in R+PM to 3.38 and 3.47 for the other two definitions,
323 respectively (Table 1). In all cases, genetic variance was of equal size and significant ($P < 0.01$)
324 attesting to the amenability of all traits to genetic improvement via selection.

325 The distribution of sire EBV based on the R and RandNPM trait definitions was similar to those
326 in Figure 2 for the interval model (R+PM). Table 4 illustrates differences between the top 20 and
327 bottom 20 sires, by EBV, in the three genetic evaluations. Sires with a minimum EBV reliability
328 of 0.30 and daughters in at least 10 breakdowns were considered in this Table. The distinction
329 between the best and worst sires was more pronounced in the R and RandNPM cases compared
330 to the conservative definition (R+PM). This can be attributed to the more relaxed definition in

331 the last two cases, allowing more infected individuals to be included in the analysis. Enhanced
332 capacity to distinguish sires by their genetic merit is expected to facilitate genetic progress.

333 Average reliability of sire EBV was 0.54, 0.54 and 0.55 for the three trait definitions (R+PM, R
334 and RandNPM), respectively. The distribution of sires across ranges of EBV reliability was very
335 similar to the interval model results shown in Table 2 for the conservative definition (R+PM).
336 The advantage of the larger amount of data and increased progeny group size in the last two
337 definitions (33.8 and 34.2 daughters per sire, respectively) compared to R+PM (27.9) was
338 seemingly offset by the increased heritability of the latter (Table 3).

339 Product moment correlations between sire EBVs based on the three trait definitions are shown in
340 Table 5. As expected, correlations were strongest between the last two definitions considering all
341 skin test reactors (R and RandNPM). Weaker correlations with R+PM can be primarily attributed
342 to the number of diseased animals that reacted positively to the skin test and were culled without
343 having had the time to develop and exhibit post-mortem lesions.

344 The stability of genetic evaluations across time was tested for all trait definitions and results
345 were very similar to those in Figure 2. Correlations between reduced and full model EBV were
346 0.94, 0.95 and 0.95 for R+PM, R and RandNPM, respectively. Validation with the Interbull
347 method 3 yielded very similar results in R and RandNPM analyses to those for R+PM described
348 above. In all cases, the genetic evaluations were shown to be unbiased as far as this method is
349 concerned.

350 Correlations between sire EBV for bTB with the interval model and official EBV for other traits
351 in the current national breeding goal are shown in Table 6. Sire EBV with a minimum reliability
352 of 0.30 and daughters in minimum 10 herds (2,039-2,996 sires, depending on trait definition)

353 were considered for this purpose. These results illustrate the generally weak and favorable
354 correlation between genetic evaluations for bTB and other important traits. The strongest
355 correlation estimates (0.15) was with the overall Profitable Lifetime Index (£PLI), which
356 effectively combines all economically important traits in one single value (Agriculture and
357 Horticulture Development Board, 2016). Significant ($P < 0.05$) correlations were also observed
358 with lifespan, which describes the functional longevity of a cow, reflecting the probability of
359 being involuntarily culled after adjusting for milk yield. Relatively stronger correlations
360 pertaining to R and RandNPM can be attributed to losses of animals that react positively to the
361 skin test and have to be culled, regardless of the outcomes of post-mortem examination. These
362 estimates indicate that selection for increased resistance to bTB may have small favorable effects
363 on £PLI and cow longevity. In general, Table 6 suggests that no antagonistic effects on animal
364 traits already in the breeding program should be expected from sire selection for enhanced bTB
365 resistance. This is consistent with the UK £PLI placing over 65% of its emphasis on health traits.
366 The availability of bTB resistance genetic evaluations provides the industry with a number of
367 options to add to the existing control measures. Farmers may choose to avoid particularly poor
368 bulls when another bull of similar £PLI is available. Breeding companies may make only
369 desirable bulls available in high risk areas and may incorporate bTB in their bull dam choices
370 where possible. These choices combined and made over time would be expected to lead to a
371 general reduction in the infection rate in UK herds.

372 The bTB evaluations are now being used to create genomic breeding values. At the cow level,
373 genomic breeding values would allow farmers to exclude young animals at an early age if they
374 were predicted to be particularly susceptible to bTB. For example, if farmers removed the worst
375 5% of their animals each year before they had a chance to infect the remainder of the herd, the

376 expectation would be that the overall level of herd infectivity would decrease over time and,
377 therefore, the potential of each animal to infect another would be reduced. Similarly, the
378 potential of a herd to pass infection to wild reservoirs would be reduced, thereby further
379 decreasing the overall level of infectivity in the population. The genetic epidemiology of such a
380 proposed policy warrants further study to determine an optimal strategy for the use of genetic
381 evaluations in reducing overall bTB infection.

382 **CONCLUSIONS**

383 The feasibility of a genetic evaluation for enhanced bTB resistance using nationally available
384 data was demonstrated in the present study. Results have shown that selective breeding can
385 potentially make a positive contribution (when used alongside other interventions such as cattle
386 movement restrictions and biosecurity improvements) to DEFRA's stated aim for Great Britain
387 to be OTF by 2038.

388 As of January 2016, the interval model has been applied in the official national genetic
389 evaluation of Holstein sires considering all reactors to the skin test plus non-reactors and
390 inconclusive reactors with positive post-mortem results as infected individuals. Further work is
391 planned to address bTB resistance in the other dairy breeds as well as beef cattle.

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396 Cattle Movement Service, and Edinburgh Genetic Evaluation Services. Ian Archibald compiled
397 the datasets.

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455

Table 1. Three datasets in the genetic evaluation according to bTB trait definition¹.

	R+PM	R	RandNPM
No. cows	424,843	642,995	660,762
No. records*	1,040,891	2,170,322	2,294,859
No. sires of cows	15,211	19,050	19,325
No. breakdowns	4,365	8,158	8,397
No. breakdown intervals*	7,585	18,079	18,822
Prop. infected cows	0.0357	0.0828	0.0829

¹R+PM: bTB infected = skin test reactors with positive post-mortem results; R: bTB infected = all skin test reactors regardless of post-mortem results; RandNPM: bTB infected = as R plus non-reactors and inconclusive reactors with positive post-mortem results.

*Interval model only.

Table 2. Reliability of sire genetic evaluations¹ based on the breakdown and interval models; cumulative percentage of sires per reliability range.

Reliability range	Breakdown model	Interval model
< 0.10	100%	100%
0.10 - 0.19	94%	97%
0.20 - 0.29	89%	94%
0.30 - 0.39	78%	90%
0.40 - 0.49	42%	73%
0.50 - 0.59	22%	53%
0.60 - 0.69	12%	37%
0.70 - 0.79	7%	25%
0.80 - 0.90	4%	13%
≥ 0.90	2%	6%

¹bTB infected = skin test reactors with positive post-mortem results.

Table 3. Variance components and parameter estimates (est.) and standard errors (s.e.)¹ from the interval model analyses.

	R+PM		R		RandNPM	
	est.	s.e.	est.	s.e.	est.	s.e.
Genetic variance	0.006	0.001	0.006	0.001	0.007	0.001
Permanent environment variance	0.032	0.001	0.047	0.001	0.046	0.001
Residual variance	0.016	<0.001	0.023	<0.001	0.023	<0.001
Phenotypic variance	0.055	<0.001	0.076	<0.001	0.076	<0.001
Heritability	0.115	0.014	0.085	0.007	0.089	0.007
Repeatability	0.699	0.005	0.701	0.002	0.697	0.002

¹R+PM: bTB infected = skin test reactors with positive post-mortem results; R: bTB infected = all skin test reactors regardless of post-mortem results; RandNPM: bTB infected = as R plus non-reactors and inconclusive reactors with positive post-mortem results.

Table 4. Differences between top 20 and bottom 20 sires in genetic evaluations based on three datasets¹ and the interval model; sires with minimum reliability of 0.30 and daughters in at least 10 herds were considered.

	R+PM	R	RandNPM
Difference in % of infected daughters	22%	33%	35%
Difference in estimated breeding values	0.17	0.21	0.21

¹R+PM: bTB infected = skin test reactors with positive post-mortem results; R: bTB infected = all skin test reactors regardless of post-mortem results; RandNPM: bTB infected = as R plus non-reactors and inconclusive reactors with positive post-mortem results.

Table 5. Product-moment correlations between genetic evaluations (above diagonal) and number of common bulls (below diagonal) based on three data definitions¹ and the interval model.

	R+PM	R	RandNPM
R+PM		0.62	0.64
R	14,998		>0.99
RandNPM	15,201	19,050	

¹R+PM: bTB infected = skin test reactors with positive post-mortem results; R: bTB infected = all skin test reactors regardless of post-mortem results; RandNPM: bTB infected = as R plus non-reactors and inconclusive reactors with positive post-mortem results.

Table 6. Genetic evaluation correlations between bovine tuberculosis¹ and other traits.

Trait	R+PM	R	RandNPM
Milk Yield	0.00	0.05	0.06
Fat Yield	-0.02	0.08*	0.08*
Protein Yield	0.01	0.10*	0.10*
Fat %	-0.02	0.02	0.01
Protein %	0.02	0.07*	0.06
Milk Somatic Cell Count	-0.04	-0.05	-0.06
Fertility Index ²	0.03	0.05	0.05
Calving Interval	0.00	-0.03	-0.03
Conception Rate	0.06	0.06	0.05
Calving Ease (direct)	0.06	0.08*	0.08*
Calving Ease (maternal)	0.04	0.06	0.07*
Lifespan	0.07	0.10*	0.11*
Profitable Lifetime Index	0.06	0.15*	0.15*

¹R+PM: bTB infected = skin test reactors with positive post-mortem results; R: bTB infected = all skin test reactors regardless of post-mortem results; RandNPM: bTB infected = as R plus non-reactors and inconclusive reactors with positive post-mortem results.

²Combination of calving interval and non-return in 56 days.

*P<0.05. Positive correlations are favorable except for Milk Somatic Cell Count and Calving Interval.

468 **Figure 1.** Combination of data from different sources in the genetic evaluation for bTB
469 resistance; APHA=Animal and Plant Health Agency; BCMS=British Cattle Movement Service;
470 EGENES= Edinburgh Genetic Evaluation Services.

471

472 **Figure 2.** Histogram of sire estimated breeding values (EBV) based on the breakdown and
473 interval models; bTB infected = skin test reactors with positive post-mortem results.

474

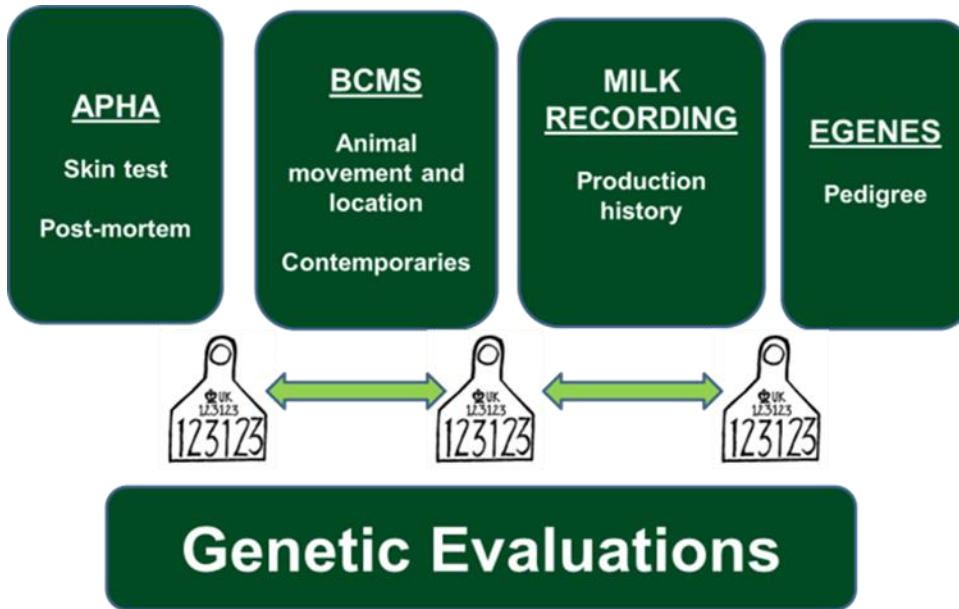
475 **Figure 3.** Sire estimated breeding values (EBVs) plotted against the proportion of infected
476 daughters on which EBVs were based, using the breakdown and interval models; r =correlation;
477 bTB infected = skin test reactors with positive post-mortem results.

478

479 **Figure 4.** Sire genetic evaluations based on the full dataset (vertical axis) plotted against genetic
480 evaluations based on the reduced dataset (minus last two years, 30% less), using the breakdown
481 and interval models; r =correlation between genetic evaluations; bTB infected = skin test reactors
482 with positive post-mortem results.

483

484 Banos Figure 1

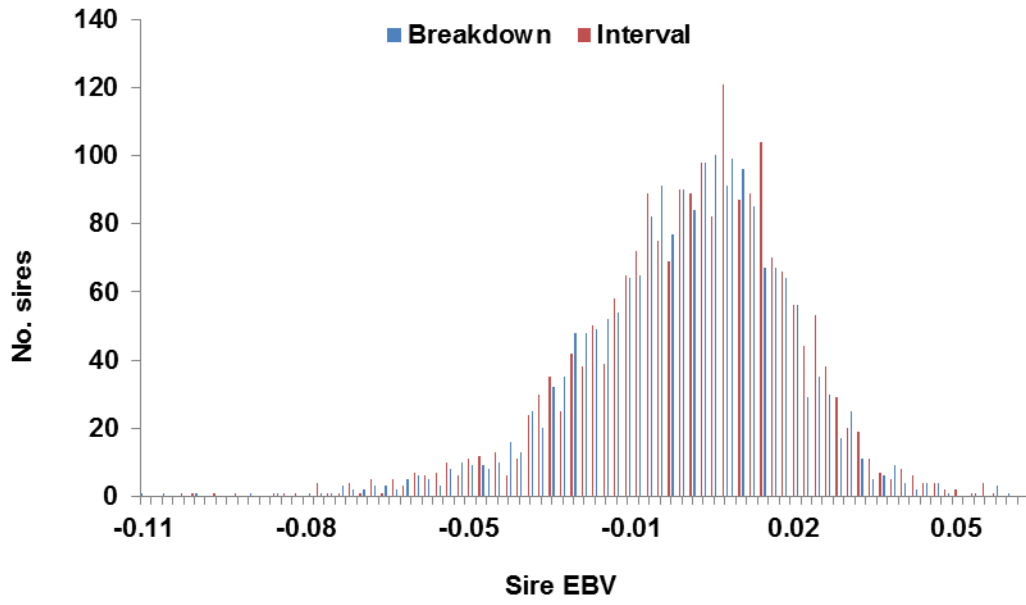


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487 Banos Figure 2

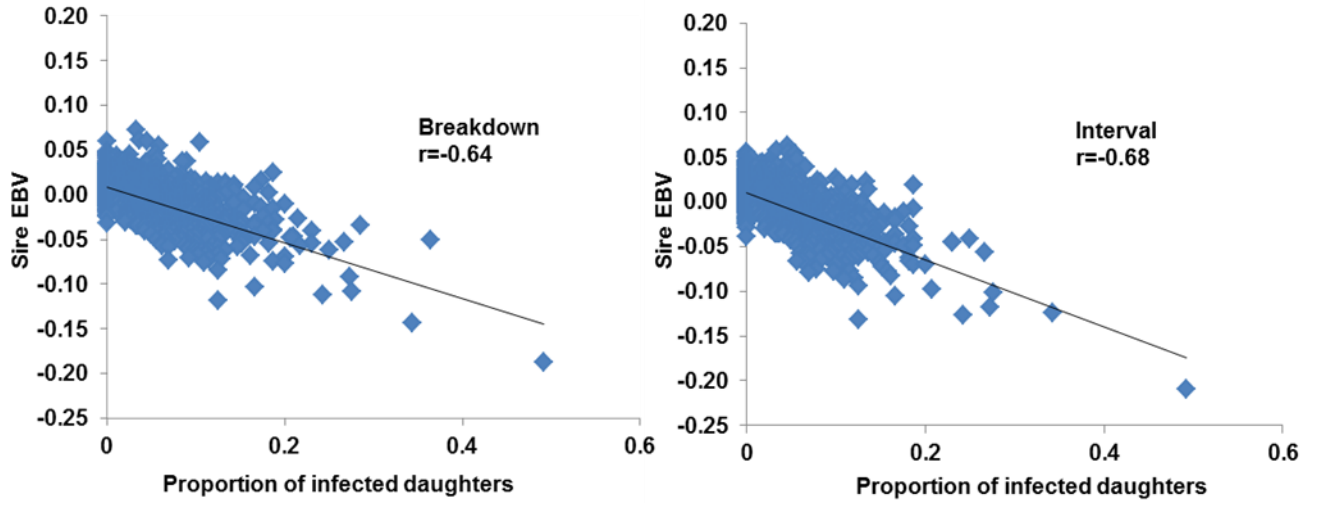
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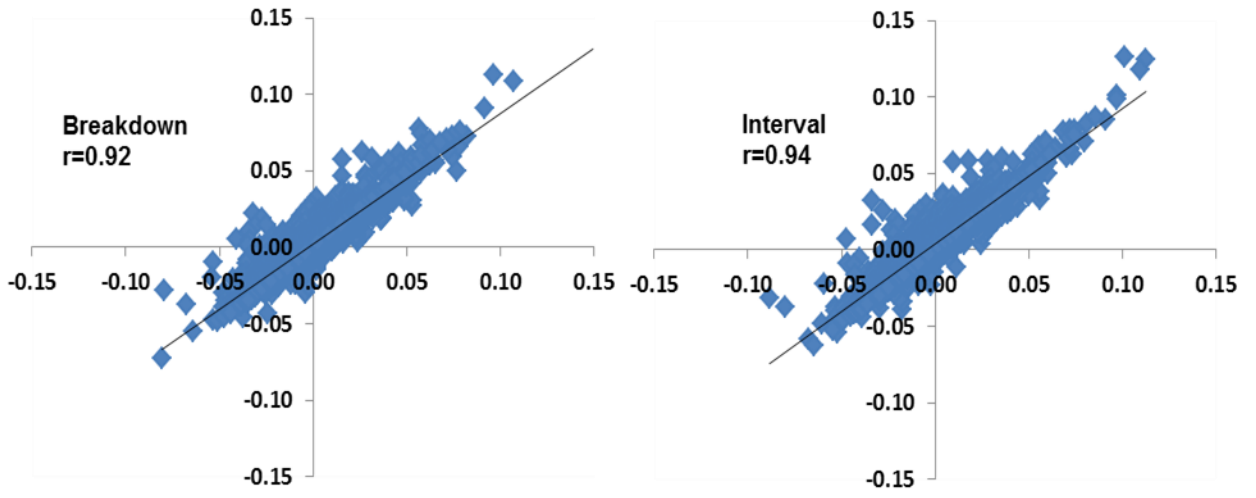
491 **Banos Figure 3**



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494 **Banos Figure 4**



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