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Pritchard. The genetics of antibody response to paratuberculosis in dairy cattle

Reducing paratuberculosis incidence in dairy cattle is not only of economic importance to dairy industries worldwide but essential in accounting for the societal and environmental considerations, such as the possible link with Crohn's disease in humans, animal welfare, and greenhouse gas emissions. Testing cattle for paratuberculosis is important for its use in control programs and although the heritability of antibody response was low, breeding against the disease might be a good prospect as a preventative measure to assist together with other approaches in an overall control strategy.

GENETICS OF JOHNE'S ANTIBODY TEST RESPONSE

The genetics of antibody response to paratuberculosis in dairy cattle

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ABSTRACT

Genetic parameters were estimated for antibody response to paratuberculosis (*Mycobacterium avium* ssp. *Paratuberculosis* (**MAP**)) using milk ELISA test results, collected and analyzed by National Milk Records (**NMR**), from Holstein Friesian cows on UK dairy farms in their first three lactations. Milk ELISA test results were obtained from 2007 to 2012 and combined with milk recording data and pedigree information. The reduced dataset edited for the purposes of genetic parameter estimation consisted of 148,054 milk

ELISA records from 64,645 lactations in 40,142 cows of 908 sires, recorded in 641 herds. Milk ELISA test results were $\log_e$-transformed and univariate analysis of three alternative animal models and equivalent sire models were considered. The most appropriate model included additive genetic and permanent environmental random effects, whereas maternal effects were significant according to likelihood ratio test and Akaike's Information Criterion but not for Bayesian Information Criterion. Heritability and repeatability estimates were 0.06 and 0.37 respectively for the chosen animal model and its equivalent sire model. A subset of the data including herds with greater than 10% positive tests gave a slightly higher heritability of 0.08. Favourable but generally low significant genetic correlations were obtained between antibody response with 305-d milk yield (-0.16), 305-d protein yield (-0.16), $\log_e$-transformed lactation average somatic cell count (0.15), and the number of mastitis episodes (0.22). Thus, selection on the antibody response to paratuberculosis, should not be detrimental to production or udder health traits. Testing cattle for paratuberculosis is important for its use in control programs and although the heritability of antibody response was low, breeding against the disease might be a good prospect as a preventative measure to assist together with other approaches in an overall control strategy.

Key words: genetic parameters, paratuberculosis, milk ELISA

INTRODUCTION

Paratuberculosis (or Johne's disease), caused by *Mycobacterium avium* subspecies *paratuberculosis* (**MAP**), occurs worldwide and is a fatal chronic enteritis to which grazing ruminants (domesticated and wild) are particularly susceptible. In Europe and North America it is considered endemic in dairy cattle with herd prevalence estimates expected to be higher than 50% (Lombard et al., 2013; Nielsen and Toft, 2009), which can result in great economic losses to the dairy industry (Raizman et al., 2009) due to decreased production, weight loss, greater risk to other health problems, premature culling, reduced slaughter value, and the cost of veterinary expenses and control measures. The disease also compromises animal welfare (CHAWG, 2012) which is important to address in a society that is increasingly concerned about how animals are raised for food production. Potentially, paratuberculosis could risk the reputation of the agri-food sector due to its pathological similarities with Crohn's disease in humans (Groenendaal and Zagmutt, 2008; Sartor, 2005) together with the capability of the organism to persist in the environment and in a small number of cases it has been found to survive pasteurisation of milk (Van Brandt et al., 2011), water treatment (Aboagye and Rowe, 2011), and anaerobic digestion (Slana et al., 2011). Although there is insufficient evidence of a causal link between MAP in livestock and Crohn's Disease the UK Food Standards Agency has adopted a precautionary principle, which appeals for strategies to further minimise human exposure to MAP (Rubery, 2001).

As yet, there is no cure for the disease and control strategies are based upon timely detection and culling of infected animals together with good hygiene practices to reduce transmission (Nielsen, 2009). In some countries voluntary Johne's control programmes have been established (Bartlett and Pearse, 2012; Benedictus et al., 2000; Nielssen, 2007). However, diagnosis of MAP can prove difficult due to its long incubation period and the lack of accurate diagnostic tests (Nielsen, 2008). Diagnostic tests for the disease include serum and milk ELISA, faecal bacterial culture and PCR, skin tests, and IFN-γ assays. With a range of diagnostic tests and statistical methods used from populations of different countries with varying incidence levels several studies have indicated that antibody test response to MAP infection is heritable, with estimates ranging from 0.03 (Van Hulzen et al., 2011) to 0.23 (Küpper et al., 2012). Breeding for disease resistance might be a good candidate as a preventative measure to assist along with other approaches to control paratuberculosis, particularly since vaccination is of limited efficacy and the disease is incurable. Genetic improvement of disease resistance is a slow and long-term process; however the results are permanent and cumulative. The heritability of Johne's disease susceptibility has been estimated using milk ELISA (Mortensen et al., 2004; Attalla et al., 2010; van Hulzen et al., 2011), slaughtered animals (Koets et al., 2000), blood serum (Gonda et al., 2006; Hinger et al., 2008; Berry et al., 2010) and fecal culture (Gonda et al., 2006, Küpper et al., 2012) from a number of countries. Country-specific genetic parameter estimation is valuable as it can be influenced by disease prevalence (Kupper et al., 2012; Van Hulzen et al., 2011). The objectives of this study were 1) to estimate genetic parameters for antibody response to MAP in the UK Holstein Friesian population using milk ELISA test results and 2) to determine the genetic association between antibody response to MAP and production, health, and fertility traits.

MATERIALS AND METHODS

Data source and editing

Testing milk samples for indication of MAP infection in cows is a service available to farmers in the UK through National Milk Laboratories (NML), a division of National Milk Records (NMR), and uses the commercial milk ELISA IDEXX Pourquier* *Mycobacterium paratuberculosis* Screening Antibody Test (Idexx Laboratories Inc., Westbrook, ME) (Bartlett and Pearse, 2012). Herds enrolled in the Johne's control programme have their milking cows tested every three months during routine herd recording. Milk ELISA test results from a five year period, 2007 to 2012, were obtained from 2,478 UK herds milking cows born in years 1998 to 2010. Milk ELISA test results were combined with milk recording data (production, fertility, health, pedigree) to obtain information for genetic parameter estimation of antibody response to MAP (**AR-MAP**).

Milk ELISA test results were $\log_e$-transformed resulting in a histogram approximating a normal distribution. An earlier study performed by Hinger et al. (2008) reported that $\log_e$-transformed ELISA test resulted in higher heritability and more robust parameter estimates than treating it as a positive/negative binary trait for MAP status. The following edits of the data were used for the analysis: 1) 100% Holstein Friesian; 2) at least 50 animals per herd with tests and at least two positive tests per herd; 3) all animals required sire and dam records; 4) calving ages for lactation 1, 2, and 3 were 18 to 42 mo, 30 to 56 mo, 42 to 70 mo; 5) dams were at least 18 mo at first calving; 6) DIM at Johnes antibody testing were 6 to 305d; 7) milk test was available within 10d of milk ELISA test and also between 6 to 305d; 8) sires with at least 10 daughters and up to the first 200 daughters born in the test dataset were selected; and 9) at least 5 animals per milk herd-test-day. The ELISA tests were categorized as positive if the sample to positive control (S/P) ratio was 0.3 or higher. After editing, the dataset consisted of 40,142 cows from 641 herds with 64,645 lactations and 148,054 milk ELISA records (mean 3.7 milk ELISA tests/cow). These animals were sired by 908 bulls with records on 4,021 maternal grand-sires. The pedigrees of cows were traced up to six generations back resulting in a file containing the relationship of 166,841 animals, which was used for both animal and sire models. Table 1 provides a summary of counts for the number of animals, lactations, and tests in the edited dataset.

Joint analysis of log-transformed ELISA test was carried out with both test-day and 305-d lactational measures, which were milk weight at milk ELISA test (**TDMY**), $\log_e$ transformed somatic cell count at test (**TDSCC**), 305-d milk yield (**MY**), 305-d protein yield (**PY**), 305-d fat yield (**FY**), $\log_e$-transformed lactation average somatic cell count (**LSCC**), number of mastitis episodes (**NMAS**), number of lameness episodes (**NLAM**), calving interval (**CaI**), days to first service (**DFS**), non-return at 56d (**NR56**), and number of inseminations (**NINS**). Further editing included 1) minimum 200 DIM during a lactation; 2) animals required at least 6 SCC tests during a lactation for the calculation of LSCC; 3) CaI was between 300 and 600d; 4) DFS was not less than 20d and not later than 200 DIM; 5) 10 or more inseminations until conception were grouped as 10; and 6) at least 5 animals per herd-year-season of calving where MY records were available. As defined by Pritchard et al. (2013) NMAS and NLAM was a count of the number of unique episodes within 0 to 305 DIM. A summary of the above traits are shown in Table 2.

Statistical analysis

Univariate analysis. Genetic parameters of AR-MAP were estimated for both animal and sire models in ASReml (version Release 2.0) (Gilmour et al., 2006). Significance of fixed effects were first tested using SAS (version 9.2) to construct models. Model 1 fitted the additive direct and permanent environmental (due to repeated tests and lactations; on average 3.7 tests per cow) effects of the animal together with the residual error as random effects. The covariates, fixed and random effects for model 1 are shown in equation 1.

$$Y_{ijkl} = \mu + htd_i + birthyr_j + lact_k + \beta_1 X_{het} + \beta \;\; X_{rec} + \beta_3 X_{ageT} + \beta_4 (X_{ageT})^2 + \beta_5 X_{dim} + \beta_6 (X_{dim})^2 + \beta_7 X_{TDMY} + \beta_8 X_{ageDam} + direct_l + pe_l + e_{ijkl} \quad (1)$$

where Y_{ijkl} = is an observation for AR-MAP; μ is the overall mean of trait Y; htd_i = fixed effect of i^{th} herd-test-day (effect specific to all cows on the same TD within a herd); $birthyr_j$ = fixed effect of the j^{th} year of birth (1998 to 2010); $lact_k$ = fixed effect of k^{th} parity number at test (1, 2, 3); β_1 to β_8 = linear and quadratic regression coefficients of dependent variable Y on heterosis (X_{het}), recombination (X_{rec}), age at calving in months (X_{age}), DIM at test (X_{dim}), milk yield at test (X_{TDMY}), age of dam in months (X_{ageDam}); $direct_l$ = the random effect of animal *l*; pe_l = the permanent environmental effect of animal *l*; and e_{ijkl} = residual random error term. Heterosis (mean = 9.9%) and recombination loss (mean = 6.7%), which considered only two breeds (Holstein and Friesian), were calculated as shown in equations 2 and 3 (Wall et al., 2005):

$$\text{heterosis} = P_S(1-P_D)+P_D(1-P_S) \quad (2)$$

$$\text{recombination loss} = P_D(1-P_D)+P_S(1-P_S) \quad (3)$$

where P_S and P_D are the proportion of Holstein for the sire and dam, respectively.

In the univariate analysis, it is assumed that the residual effects are independently distributed with variance σ_e^2, therefore, var(e) = $I\sigma_e^2$ = R; var(a) = $A\sigma_a^2$ = G and cov(a,e) = cov(e,a) = 0, where I is the identity matrix, A is the numerator relationship matrix, and G and R are the (co)variance matrices for additive genetic (a) and residual (e) effects, respectively.

Further models (Models 2 and 3) tested the additive maternal genetic effect and the genetic covariance between direct and maternal genetic as additional random effects. Significance was determined using a likelihood ratio test (LRT). Models were compared that differed by one variance component and the additional effect was considered to have a significant influence when the difference between -2 log likelihood (logL) values was greater than the critical value 2.79. The test statistic follows a 50:50 mixture of chi-squared distributions with, respectively, 0 and 1 degree of freedom with a significance level of 0.05. Whilst increasing the number of parameters may increase the goodness-of-fit, there is a danger of over-parameterization (Schwarz, 1987). Therefore, to discourage over-fitting, the choice of model was also judged by Akaike's Information Criterion **AIC** = –2logL + 2k (Wada and Kashiwagi, 1990) and the Bayesian Information Criterion **BIC** = –2logL + kln(n) (Schwarz, 1987; Abney et al., 2000) where k = number of independent estimated parameters, and n = total number of observations. The preferred model chosen by AIC and BIC is that with the lowest value. The equivalent sire model to the chosen animal model was also run for comparison of variance components as it is less computationally demanding. For the sire model, heritability estimates were calculated as four times the sire variance component divided by the phenotypic variance. The ratio of permanent environmental variance to total phenotypic variance (**pe^2**) was calculated as permanent environmental variance minus three times the sire variance divided by the phenotypic variance.

Bivariate analysis. Linear animal models were employed for bivariate analyses between AR-MAP with production, health, and fertility traits. The model for AR-MAP did not include the covariate milk yield at test when analysed with 305-d production traits due to their high correlation. However, the covariate was included for health and fertility traits. Furthermore, the bivariate model for AR-MAP excluded maternal genetic effects as preliminary results from univariate analysis found these not to be significant components determined by BIC for the animal model**.** For 305-d production, health and fertility traits a single measure was given per lactation in the same lactation that an animal was milk ELISA tested. However, a repeatability model was employed as some animals had milk ELISA tests in more than one lactation. The models for test-date and 305-d traits are shown by equations 3 and 4 respectively:

$$Y_{ijkl} = \mu + htd_i + month_j + lact_k + \beta_1 X_{het} + \beta_2 X_{rec} + \beta_3 X_{age} + \beta_4 (X_{age})^2 + \beta_5 X_{dim} + \beta_6 (X_{dim})^2 + direct_l + pe_l + e_{ijkl} \qquad (4)$$

$$Y_{ijkl} = \mu + hys_i + month_j + lact_k + \beta_1 X_{het} + \beta_2 X_{rec} + \beta_3 X_{age} + \beta_4 (X_{age})^2 + direct_l + pe_l + e_{ijkl} \qquad (5)$$

where Y_{ijkl} = is an observation for production, health or fertility; μ is the overall mean of trait Y; hys_i = fixed effect of i^{th} herd-by-year-by-season (4 seasons per year) of calving; htd_i = fixed effect of i^{th} herd-test-date; $month_j$ = fixed effect of the j^{th} month of calving (12 months); $lact_k$ = fixed effect of the *k*th lactation (3 lactations); β_1 to β_6 = linear and quadratic regression coefficients of dependent variable Y on heterosis (X_{het}), recombination (X_{rec}), age at calving (X_{age}), DIM at test (X_{dim}); $direct_l$ = the random effect of animal *l*; pe_l = the permanent environmental effect of animal *l*; and e_{ijkl} = residual random error term. All bivariate analyses included the additive genetic, permanent environmental (for repeatability model) and residual variances together with corresponding covariances between both traits. It is assumed in the bivariate analyses shown in equation 6 that:

$$Var = \begin{pmatrix} a_1 \\ a_2 \\ pe_1 \\ pe_2 \\ e_1 \\ e_2 \end{pmatrix} = \begin{pmatrix} AG_{11} & AG_{12} & 0 & 0 & 0 & 0 \\ AG_{21} & AG_{22} & 0 & 0 & 0 & 0 \\ 0 & 0 & P_{11} & P_{12} & 0 & 0 \\ 0 & 0 & P_{21} & P_{22} & 0 & 0 \\ 0 & 0 & 0 & 0 & R_{11} & R_{12} \\ 0 & 0 & 0 & 0 & R_{21} & R_{22} \end{pmatrix} \quad (6)$$

Where **a**, **pe** and **e** are vector of random additive, permanent environment and residual effects for the traits respectively with correspondingly co-variances matrices **G**, **P** and **R** and **A** is the relationship matrix.

Genetic parameters for AR-MAP were also estimated using three subsets of the edited dataset where herds were categorized according to the percentage of positive tests in a herd during the time frame of the study. The three categories were ≤5% (225 herds), >5 and ≤10% (271 herds), and >10% (145 herds) positive tests.

RESULTS AND DISCUSSION

Genetic parameter estimation

Variance components, heritability, and repeatability estimates of AR-MAP for the three linear animal models with differing random effects are shown in Table 3. Permanent environmental effect contributed about 25% to the phenotypic variance and estimates barely changed with the addition of maternal effects to the model. Similarly this was the case for additive genetic variance which had minimal change; it decreased slightly with the addition of maternal effects, but increased with the further addition of the covariance between direct and maternal genetic effects. The addition of each random effect was a significant improvement on the previous model according to the LRT and AIC indicating that model 3 was the most suitable. However, determined by BIC we found that model 1 was the most suitable which included the additive direct effect and the permanent environmental effect of the animal. All models gave very similar results with heritability estimates ranging from 0.06 to 0.07 and a repeatability estimate of 0.31, and any of these models could potentially be used depending upon the criteria used.

Sire models resulted in closely similar results to the animal model with heritability estimates also ranging from 0.06 to 0.07 and repeatability estimates ranging from 0.30 to 0.31. The similarities between the results from animal and sire models confirm that the computationally less-demanding sire model can be employed if the interest is solely for bull selection (i.e., runtime for model 2 was 3 hours versus 10 minutes for the animal model and equivalent sire model respectively). The results from Hinger et al. (2008) were also virtually the same between sire and animal models (~0.10), whereas Mortensen et al. (2004) found results were slightly higher with the animal model (animal model 0.10, sire model 0.09) with both other studies using milk ELISA data, whilst Küpper et al. (2012) found higher estimates with the sire model where animals were tested by fecal culture. The heritability, based upon milk ELISA test results, provides information about the genetic ability to produce antibodies against paratuberculosis. In our study the heritability was low (~0.06) but it was in line with other similar studies that used $\log_e$-transformed optical density values from milk ELISA tests in Danish Holstein (Mortensen et al., 2004), German Holstein (Hinger et al., 2008), Dutch Holstein Friesian (Van Hulzen et al., 2011), Irish Holstein Friesian (Bermingham et al., 2010), and US Holstein (Attalla et al., 2010), which ranged from 0.03 to 0.10. Furthermore, it is comparable to other disease traits that are generally low (Bermingham et al., 2010; Pritchard et al., 2013)

Studies differ on whether the trait is measured as continuous or categorised as a binary trait (negative/positive) or categorical trait. In Israeli Holstein (Shook et al., 2012) and Irish Holstein-Friesian (Berry et al., 2010) ELISA tests from serum were analysed as a binary trait which gave heritability estimates of 0.16 and 0.15, respectively from a threshold model. Berry et al. (2010) also made the comparison between a threshold and a linear model, as well as analysing the trait as binary or continuous and obtained lower estimates from the linear model of 0.10 as a binary trait and 0.07 as a continuous trait.

The three subsets that represented different herd incidence levels gave similar values to the full dataset with heritability estimates ranging from 0.06 to 0.08 and repeatability estimates ranging from 0.28 to 0.34 (Table 4). The subset including herds with greater than 10% positive tests, which may imply higher prevalence, gave the largest heritability of 0.084 of all subsets. In Dutch Holstein-Friesian (Van Hulzen et al., 2011) and in German Holstein cows (Kupper et al., 2012) higher prevalence also resulted in higher heritability. The repeatability also increased with percentage increase of positive tests from 0.28 to 0.34. However, it should be noted that these subsets might not directly explain different prevalence levels and results could be influenced by data structure. In the subset containing herds with the highest percentage of positive tests the number of tests per cow was higher (4.1 tests) and was lowest (3.4) in the subset containing herds with least positive tests. Repeatabilities in this study were lower to those reported by Atalla et al. (2010) that ranged from 0.38 to 0.43. Repeatabilities were found to be higher in herd groups with a higher percentage of positive tests but also had a higher number of tests per cow.

Maternal effects could exist due to intrauterine infection of the fetus, although the risk is considered to be relatively small (Adaska and Whitlock, 2012; Whittington and Windsor, 2007), or the calf could be orally infected by ingesting MAP from the dam soon after birth through colostrum, milk, or feces (Nielsen et al., 2008; Sweeney, 1996). In this study the contribution of maternal effects to phenotypic variance were small in magnitude (<1%), which has been similarly reported in other studies, e.g., <1% in the study of Mortensen et al. (2004) and 1.3% in the study of Atalla et al. (2010) using linear models. Including maternal effects and the direct-maternal covariance resulted in an improved fit of the model by the LRT and AIC, however it was not the case determined by BIC. The data collected in this study is relatively recent and from a short time span. Therefore, it is very unlikely there would be many dam-daughter pairs where both dam and daughter have milk ELISA results. Future analyses with a longer duration of test results could better examine the possible transmission from dam to daughter where both generations have test data available. However, recent farm management changes may have changed the pattern of infection from a very predominant dam daughter pattern of transmission to cohorts of animals showing up as ELISA positive. This is due to management practices such as multiple calving in an area and the pooled colostrum effect of one infectious cow infecting a whole cohort of calves (Kennedy et al., 2014).

Some caution should be taken in interpreting the trait AR-MAP and its possible use as an indicator trait for selection as this study does not resolve differences between susceptibility/resistance and an animal's ability to produce a humoral response. However, results from Bermingham et al. (2010) reported a strong positive genetic correlation (0.84; SE=0.20) between serological response to MAP and susceptibility to M. avium-purified protein derivative, which suggests that selection for reduced MAP responsiveness may indirectly increase resistance to MAP. It is important though to monitor that selection for reduced MAP specific antibody response does not lead to selection of animals with an impaired humoral response.

Genetic correlations

Genetic, permanent environmental, residual, and phenotypic correlations between AR-MAP and production, health, and fertility traits and their heritability estimates are given in Table 5. Genetic correlations between AR-MAP with MY, PY, and udder health traits were significant, whereas TDSCC, FY, NLAM and fertility traits were not significant.

Genetic correlations between NMAS and LSCC with AR-MAP were positive and similar in magnitude (0.15 to 0.22). The genetic correlations between 305-d production traits and TDMY with AR-MAP were all negative and similar in magnitude (-0.14 to -0.16).

Production. The genetic correlation between AR-MAP and 305d production traits indicate that breeding for animals more resistant to paratuberculosis should not be detrimental to yields of production traits, which supports the results of previous studies (Attalla et al., 2010; Berry et al., 2010; Mortenson et al., 2004). Mortenson et al., (2004) reported low and non-significant genetic correlations between AR-MAP and daily milk yield (-0.04). Attalla et al. (2010) similarly found a non-significant correlation between sire solutions for AR-MAP and predicted transmitting abilities for milk yield whereas for fat (-0.20) and protein yield (-0.18) were significant and negative, which also suggest selection for these traits would reduce susceptibility to paratuberculosis. From a smaller dataset of 4,789 cows Berry et al. (2010) reported negative and significant genetic correlations between yield traits and AR-MAP as a binary trait, and negative but not different to zero when treated as a continuous trait. However, although with non-significant results, from another smaller dataset of 4,694 cows Shook et al. (2012) reported positive genetic correlations ranging from 0.15 to 0.22 between MAP and milk yield traits, which suggest that cows with high breeding values for milk yield would be more susceptible to MAP. Or, from another perspective, higher yielders are more likely to succumb to the effects of infection due to the greater lactational stress of high yields whereas low yielders are more capable of existing with infection. This would be consistent with findings of Norton et al. (2010) where effects of infection were likely to worsen or positive tests were more common when animals were most stressed at calving or at peak milk production. The study of Shook et al. (2012) employed a recursive model which accounted for the effect of MAP infection on yield traits, which might explain the contradictory findings. Several phenotypic association studies also correspond to results from Shook et al.

(2012) indicating that cows capable of producing higher yields are more likely to succumb to the disease if infected (Hoogendam et al., 2009; Smith et al., 2009). The phenotypic correlations in this study were low and positive with MY and PY, but negative with TDMY and FY.

Health. Few studies exist that have examined genetic associations between AR-MAP and any health traits. A significant positive genetic association was found in this study between AR-MAP and udder health traits, LSCC and NMAS, which would imply that animals predisposed to higher SCC or mastitis are also predisposed to higher antibody response, thus, breeding against paratuberculosis would in turn be favourable by improving udder health. Berry et al. (2010) however, found no significant genetic association between AR-MAP and SCC. However, these results are in line with several non-genetic studies that have found that ELISA positive cows tend to have higher somatic cell counts (Baptista et al., 2008; McNab et al., 1991). Baptista et al. (2008) reported a strong positive phenotypic association however, pointed out that a causal relationship was not apparent between high SCC and AR-MAP. A causality dilemma exists as it is possible that a cow with MAP infection is more likely to have a higher SCC because of the ‘immune energy’ expended dealing with MAP or a cow dealing with mastitis is more likely to lose control of her previously controlled MAP infection and become test positive for MAP. Previous studies have reported positive genetic correlations (i.e. unfavourable) between udder health traits and production (Pritchard et al., 2013) therefore it is unexpected to have a negative genetic correlation between AR-MAP and production since there is a positive genetic correlation between the udder health traits and AR-MAP.

Fertility. Genetic correlations between AR-MAP and fertility traits were all low, negative, and not significant, therefore genetic selection to reduce paratuberculosis should not be detrimental to fertility. Berry et al. (2010) also found low non-significant negative correlations between AR-MAP and CaI.

CONCLUSIONS

Testing of cattle for paratuberculosis is important for its use in control programs and the results of this study show that the same field data could be used to develop breeding tools as part of an overall disease control strategy. This paper presents the first genetic analysis of milk ELISA test results in the UK, which signify antibody response to MAP, including correlations with other traits in the breeding goal. Despite the low heritability (<0.10) of AR-MAP there is still potential for genetic progress to be made. For instance, there has been a turnaround in the genetic trend of fertility in the UK almost immediately after the introduction of Fertility Index in 2005, although the fertility traits included have a heritability of 1-4% (Wall et al., 2003). Genetic improvement might be a long process, but the gains are permanent and cumulative in each generation. In the case of paratuberculosis vaccination is of limited efficacy at present and the disease is incurable therefore genetic improvement is a good candidate as one of the tools for prevention. Selection for resistance to MAP reduces the likelihood of an animal becoming infected when exposed to the pathogen but also with fewer animals infected it will reduce the number of pathogens in the environment and therefore reduce exposure to the pathogen. Furthermore, genetic correlations with udder health traits were favourable and did not appear detrimental to production traits.

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Table 1 Summary of animal, lactation, and test counts in edited dataset

Lactation	n of cows	n of tests
1	25,843	61,279
2	23,479	51,346
3	15,323	35,429
Overall	40,142 (64,645 lactations)	148,054

Table 2 Summary of traits used in bivariate analysis with milk ELISA over the first 3 lactations

Abbreviation	Description	Count	Mean (sd)
Test date measures			
AR-MAP	$\log_e$ transformed milk ELISA result	148,054	0.34 (2.02)
TDMY	Milk yield (Kg) at milk ELISA test	148,054	30.8 (9.15)
TDSCC	$\log_e$ transformed SCC at milk ELISA test	148,054	10.9 (1.15)
305-day lactation measures			
Production			
MY	Kg of milk over a 305-d lactation	63,238	9148.27 (2095.21)
PY	Kg of protein over a 305-d lactation	63,238	291.45 (62.03)
FY	Kg of fat over a 305-d lactation	63,238	354.11 (81.33)
Health			
LSCC	Lactation average $\log_e$ transformed SCC	61,953	11.33 (0.94)
NMAS	n of mastitis episodes within 0 to 305-d	29,526	0.26 (0.57)
NLAM	n of lameness episodes within 0 to 305-d	20,070	0.27 (0.58)
Fertility			
CaI	n of days from calving date of present lactation to calving date of next lactation	40,629	396.29 (60.96)
DFS	n of days from calving date of present lactation to date of first service	59,545	73.00 (29.63)
NINS	n of inseminations per conception (maximum of 10 inseminations)	41,946	2.29 (1.57)
NR56	Non-return rate after 56d: 1 = a return to	57,919	1.64 (0.48)

service and 2 = no return to service

Table 3 Variance components and heritability of antibody response from three animal models (models 1 to 3) and a sire model (equivalent to model 1) with se in parenthesis

	Animal			Sire
	Model 1	Model 2	Model 3	Model 1
σ_a^2	0.18 (0.018)	0.17 (0.018)	0.19 (0.021)	0.18 (0.021)
σ_{pe}^2	0.70 (0.016)	0.70 (0.017)	0.70 (0.017)	0.69 (0.020)
σ_m^2		0.01 (0.006)	0.01 (0.007)	
σ_{am}^2			-0.02 (0.010)	
σ_e^2	1.96 (0.009)	1.96 (0.009)	1.96 (0.009)	1.96 (0.009)
σ_p^2	2.84 (0.013)	2.84 (0.013)	2.84 (0.013)	2.83 (0.013)
h^2	0.06 (0.006)	0.06 (0.006)	0.07 (0.007)	0.06 (0.007)
pe^2	0.25 (0.006)	0.25 (0.006)	0.25 (0.006)	0.24 (0.007)
m^2		0.003 (0.002)	0.00 (0.003)	
R	0.31 (0.003)	0.31 (0.004)	0.31 (0.005)	0.31 (0.003)
logL	-4738.83	-4736.97	-4734.88	-4798.58
LRT	-	3.72	**4.18**	**-**
AIC	9481.66	9479.94	**9477.76**	**-**
BIC	**9501.47**	9509.66	9517.38	-

$\sigma^2{}_a$ direct additive effect; $\sigma^2{}_{pe}$ permanent environmental variance of animal; $\sigma^2{}_m$ maternal additive genetic variance; $\sigma^2{}_{am}$ genetic covariance between direct and maternal genetic effects; $\sigma^2{}_e$ error variance; $\sigma^2{}_p$ phenotypic variance; h^2 heritability; pe^2 proportion of permanent environmental variance of animal to phenotypic variance; m^2 proportion of maternal additive genetic variance to phenotypic variance; R repeatability; LRT Likelihood

Ratio Test; AIC Akaike's Information Criterion; BIC Bayesian Information Criterion; model in bold most appropriate for LRT, AIC, or BIC.

Table 4 Variance components and heritability of antibody response for different herd groupings from an animal model with se in parenthesis

	Herd group		
	1	2	3
σ_a^2	0.18 (0.027)	0.18 (0.026)	0.23 (0.040)
σ_{pe}^2	1.99 (0.015)	1.99 (0.013)	1.85 (0.017)
σ_e^2	0.59 (0.026)	0.74 (0.025)	0.73 (0.038)
σ_p^2	2.77 (0.020)	2.91 (0.020)	2.80 (0.028)
h^2	0.07 (0.010)	0.06 (0.009)	0.08 (0.014)
pe^2	0.21 (0.009)	0.25 (0.009)	0.26 (0.013)
repeatability	0.28 (0.005)	0.32 (0.005)	0.34 (0.007)

Herd group: 1) herds with <= 5% positive tests 2) herds with >5% and <=10% positive tests 3) herds with >10% positive tests

Table 5 Estimates of heritability, genetic, permanent environmental, residual, and phenotypic correlations from an animal repeatability model between antibody response with production, health and fertility traits across the first three lactations with se

Trait	Heritability	Genetic correlation	Permanent environment correlation	Residual correlation	Phenotypic correlation
TDMY	0.13±0.009	-0.14±0.062 [s]	-0.13±0.018	-0.11±0.003	-0.12±0.003
TDSCC	0.06±0.006	0.14±0.007	0.17±0.017	0.12±0.003	0.13±0.003
MY	0.20±0.015	-0.16±0.062 [s]	-0.19±0.023	0.04±0.006	0.09±0.005
PY	0.29±0.014	-0.16±0.063 [s]	-0.16±0.023	-0.03±0.006	0.08±0.005
FY	0.20±0.014	-0.10±0.063	-0.14±0.024	-0.03±0.006	-0.06±0.005
LSCC	0.10±0.010	0.15±0.071[s]	0.21±0.026	0.03±0.005	0.08±0.004
NMAS	0.05±0.009	0.22±0.100[s]	0.05±0.040	0.00±0.007	0.02±0.006
NLAM	0.01±0.007	0.04±0.180	-0.05±0.035	0.00±0.009	-0.01±0.007
CaI	0.03±0.006	-0.11±0.106	-0.14±0.073	0.02±0.006	0.002±0.005
DFS	0.05±0.007	-0.04±0.086	-0.06±0.041	0.01±0.005	-0.002±0.004
NR56	0.01±0.003	-0.02±0.144	0.24±0.170	-0.003±0.005	0.007±0.004
NINS	0.02±0.005	-0.11±0.121	-0.07±0.046	0.018±0.006	0.004±0.005

S = significant; TDMY = test-date milk weight; TDSCC = test-date $\log_e$ transformed somatic cell count; MY = 305-d milk yield; PY = 305-d protein yield; FY = 305-d fat yield; LSCC = $\log_e$-transformed lactation average somatic cell count; NMAS = number of mastitis episodes; NLAM = number lameness episodes; CaI = calving interval, DFS = days to first service; NR56 = non-return at 56-d; NINS = number of inseminations.