Genetic correlations between endo-parasite phenotypes and economically important traits in dairy and beef cattle[1]

Alan J. Twomey,[†,‡] Rebecca I. Carroll,[‖] Michael L. Doherty,[‡] Noel Byrne,[†] David A. Graham,[‖] Riona G. Sayers,[†] Astrid Blom,[§] and Donagh P. Berry[†,2]

[†]Animal and Grassland Research and Innovation Centre, Teagasc, Moorepark, Fermoy, Co. Cork, Ireland; [‡]School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland; [‖]Animal Health Ireland, Carrick on Shannon, Co. Leitrim, Ireland; [§]Irish Cattle Breeding Federation, Highfield House, Bandon, Co. Cork, Ireland

ABSTRACT: Parasitic diseases have economic consequences in cattle production systems. Although breeding for parasite resistance can complement current control practices to reduce the prevalence globally, there is little knowledge of the implications of such a strategy on other performance traits. Records on individual animal antibody responses to *Fasciola hepatica*, *Ostertagia ostertagi*, and *Neospora caninum* were available from cows in 68 dairy herds (study herds); national abattoir data on *F. hepatica*–damaged livers were also available from dairy and beef cattle. After data edits, 9,271 dairy cows remained in the study herd dataset, whereas 19,542 dairy cows and 68,048 young dairy and beef animals had a record for the presence or absence of *F. hepatica*–damaged liver in the national dataset. Milk, reproductive, and carcass phenotypes were also available for a proportion of these animals as well as their contemporaries. Linear mixed models were used to estimate variance components of antibody responses to the three parasites; covariance components were estimated between the parasite phenotypes and economically important traits. Heritability of antibody responses to the different parasites, when treated as a continuous trait, ranged from 0.07 (*O. ostertagi*) to 0.13 (*F. hepatica*), whereas the coefficient of genetic variation ranged from 4% (*O. ostertagi*) to 20% (*F. hepatica*). The antibody response to *N. caninum* was genetically correlated with the antibody response to both *F. hepatica* (−0.29) and *O. ostertagi* (−0.67); a moderately positive genetic correlation existed between the antibody response to *F. hepatica* and *O. ostertagi* (0.66). Genetic correlations between the parasite phenotypes and the milk production traits were all close to zero (−0.14 to 0.10), as were the genetic correlations between *F. hepatica*–damaged livers and the carcass traits of carcass weight, conformation, and fat score evaluated in cows and young animals (0.00 to 0.16). The genetic correlation between *F. hepatica*–damaged livers in cows and milk somatic cell score was 0.32 (SE = 0.20). Antibody responses to *F. hepatica* and *O. ostertagi* had favorable genetic correlations with fertility traits, but conversely, antibody response to *N. caninum* and *F. hepatica*–damaged livers were unfavorably genetically correlated with fertility. This study provides the necessary information to undertake national multitrait genetic evaluations for parasite phenotypes.

Key words: carcass, *Fasciola hepatica*, fertility, milk, *Neospora caninum*, *Ostertagia ostertagi*

© The Author(s) 2018. Published by Oxford University Press on behalf of the American Society of Animal Science. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

J. Anim. Sci. 2018.96:407–421
doi: 10.1093/jas/sky008

INTRODUCTION

Animal parasites are a growing concern in dairy and beef cattle production systems, with reported associated significant economic losses

[1]Funding from the Irish Department of Agriculture, Food and the Marine STIMULUS research grants HEALTHYGENES and FLUKELESS is greatly appreciated.

[2]Corresponding author: donagh.berry@teagasc.ie

Received November 3, 2017.
Accepted January 8, 2018.

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

(Schweizer et al., 2005). Milk production (Charlier et al., 2005; Mezo et al., 2011), reproductive performance (Sanchez et al., 2002; Haddad et al., 2005; Charlier et al., 2007), and meat yield (Barling et al., 2000; Charlier et al., 2009a) have all been documented as compromised in cattle herds infected with *Fasciola hepatica*, *Ostertagia ostertagi*, or *Neospora caninum*. The high prevalence of infection in cattle with both *F. hepatica* and *O. ostertagi* (Sekiya et al., 2013; Twomey et al., 2016) suggests that current control practices (e.g., anthelmintic treatment; Bloemhoff et al., 2014) are sub-optimal. On the other hand, effective *N. caninum* control strategies (i.e., herd biosecurity and the culling of infected animals; Dubey et al., 2007) can be costly.

Using animal-level data for *F. hepatica*–damaged livers on >95,000 Irish dairy and beef cattle, Twomey et al. (2016) reported the presence of significant underlying genetic variability suggesting that breeding strategies could be used as a supplementary control for *F. hepatica*. A limited number of studies exist in cattle that documented genetic parameters for phenotypes based on the other two endo-parasites of interest, *O. ostertagi* (n = 2; Morris et al., 2003; Coppieters et al., 2009) and *N. caninum* (n = 1; Pan et al., 2004). These previously published studies consist of few animals, with the study by Pan et al. (2004) being the largest with 9,723 animals.

The present study will be the first, to our knowledge, to quantify the genetic correlations between these parasitic diseases and economically important traits in cattle, as well as among the antibody responses to parasites. The objective of this study was to provide the necessary information to facilitate evaluation of the potential to breed for resistance to parasitic diseases in cattle.

MATERIALS AND METHODS

Parasitic data available to the present study consisted of: 1) information on *F. hepatica*–damaged livers which originated from the national database managed by the Irish Cattle Breeding Federation; and 2) enzyme linked immunosorbent assay (ELISA) results for *F. hepatica*, *O. ostertagi*, and *N. caninum* generated from a cross-sectional study of 68 Irish dairy herds. Individual animal pedigree and breed composition information, 305 d milk production records (dairy cows only), reproductive records (i.e., service dates, pregnancy diagnoses, and calving dates) as well as information pertaining to the slaughter of animals (i.e., carcass weight, conformation, and fat score) were also available for all animals from the national database. Individual cow body condition score (BCS) data from the cross-sectional study of the 68 dairy herds were also available.

Study Herd Data

In 2015, two trained technicians collected individual cow BCS twice, where possible, for each cow in the spring (n = 10,853 cows) and summer (n = 10,456 cows), in the 68 study herds. Cow BCS was measured on a scale of 1 (thin) to 5 (fat) in increments of 0.25 (Edmonson et al., 1989). Blood samples from 10,879 of these cows were collected in Autumn 2015 from the study herds as part of the voluntary Irish national Johne's disease control program (http://www.animalhealthireland.ie) coordinated by Animal Health Ireland. All blood samples were tested separately for the presence of antibodies to *F. hepatica*, *O. ostertagi*, and *N. caninum* using the Svanovir *F. hepatica*-Ab ELISA kit, the Svanovir *O. ostertagi*-Ab ELISA kit, and the Svanovir Neospora-Ab ELISA kit (Boehringer Ingelheim Svanova, Uppsala, Sweden), respectively. ELISA tests for all blood samples were carried out by the same commercial laboratory (FarmLab Diagnostics, Co. Roscommon, Ireland). All parasite ELISA records were treated as either a continuous or a binary (i.e., positive/negative) trait in the analyses, as described later. Records were discarded if, at blood sampling, the cow resided in a different herd to the one in which it had been present at 90 d of age. Only 9,240 cows remained for the analysis.

F. hepatica. ELISA results were reported as optical density values which were expressed relative to a positive control provided in the test kit, known as an optical density ratio (**ODR**). An ODR ≥ 0.4 has previously been shown to lead to milk production losses in dairy cows (Charlier et al., 2012), and this cut-off was, therefore, regarded as the positive threshold for antibody response to *F. hepatica* in the current study; animals with recorded ODR levels of <0.4 were assumed to be negative, which is consistent with the definition used previously by Twomey et al. (2016) for these animals. Only data from herds with more than five cows with a positive antibody response to *F. hepatica* (i.e., ODR ≥ 0.4) and a within-herd prevalence of ≥5% with a positive antibody response to *F. hepatica* on the day of the blood test were retained. The positively skewed ODR data were transformed using the natural logarithm to approximate a normally distributed

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

variable. Data from 6,949 cows in 48 herds remained for the analysis.

O. ostertagi. Optical density values were also expressed as ODR. The test used in the present study has not been validated on blood samples, so the test manufacturer had no known threshold to indicate positives. Therefore, the median of all the ODR results in the dataset was used as the threshold to differentiate a high result from a low result; based on that, an ODR ≥ 1.27 was regarded as a high result, while an ODR < 1.27 was regarded as a low result. It is documented that the majority of cattle grazing pasture are exposed to *O. ostertagi* (Sanchez and Dohoo, 2002; Forbes et al., 2008; Bloemhoff et al., 2015). Thus, all study herd cows were deemed potentially exposed to *O. ostertagi*, as cows in the study herds were known to be grazing pasture for the vast majority of the year.

N. caninum. Blood results for *N. caninum* were calculated as per cent positivity (**PP**), which is the optical density of each sample expressed as a percentage of the optical density of the positive control. The ELISA test manufacturer stated that a PP ≥ 20 indicates a positive result for *N. caninum* and was thus treated as such in the present study. Therefore, a PP < 20 was deemed to represent a negative result in the present study. The positively skewed PP data were normalized using a reciprocal transformation. Cows were defined as potentially exposed if there was a within-herd cow prevalence of >1% positive (i.e., PP ≥ 20) for antibody response to *N. caninum*. Only cows defined as potentially exposed were retained. Only 5,804 cows from 37 herds remained for the analysis. All progeny from dams that had a positive result for *N. caninum* were discarded (86 cows were discarded), as there is a high likelihood that progeny from a cow infected with *N. caninum* will also be infected with *N. caninum* (Dubey and Schares, 2011).

F. hepatica–Damaged Liver

A detailed description of the generation of the *F. hepatica*–damaged liver phenotypes from the available slaughter information has been documented in Twomey et al. (2016). In brief, liver damage caused by *F. hepatica* was diagnosed by veterinarians on the kill-line of seven Irish abattoirs between February 2012 and May 2016, as either "live *F. hepatica* observed in the liver at the time of slaughter" or as "liver exhibits *F. hepatica* damage without the identifiable presence of live *F. hepatica*." Using the national dataset on all slaughtered animals, animals slaughtered with no recorded *F. hepatica*–damaged liver phenotype were defined as "negative for *F. hepatica*–damaged liver" if there was at least one other animal slaughtered in that abattoir on the same day with a phenotype for *F. hepatica*–damaged liver. Data on 1,042,929 slaughtered singleton dairy and beef cattle from 29,412 herds were available.

Animals were identified as having been potentially exposed to *F. hepatica*, as described by Twomey et al. (2016), depending on the *F. hepatica*–damaged liver phenotype of their slaughtered contemporaries. Animals that moved herd after 90 d of age were not considered further in the analysis. Cows (i.e., females with at least one recorded calving event) in Irish dairy and beef herds generally graze together as a single group. Therefore, cows were deemed to have been potentially exposed if they were resident in the herd 100 d prior to the date of slaughter of a cow herd-mate with recorded live *F. hepatica* at slaughter. However, if a cow was recorded with observed liver damage but no observable live *F. hepatica*, an additional criterion was imposed to define cow contemporaries as being potentially exposed; as well as residing in the herd 100 d prior the date of slaughter of the cow with liver damage, only cows born within 100 d of the date of birth of the cow with liver damage were regarded as exposed.

Similarly, young cattle (i.e., males and females <1096 d of age that were not a registered sire or had no recorded calving event) in a herd generally graze a common pasture which is sometimes separate to the cows. Therefore, an identical definition was used for classifying young cattle as being exposed based on the recorded diagnoses of their herd-mates at slaughter, except that an animal had to be at least 365 d old at the time of a diagnosis of a herd-mate with live *F. hepatica* to be considered potentially exposed. Subsequently, a total of 229,014 animals remained.

For purpose of the present study, liver damage caused by *F. hepatica* was dichotomized; animals were either deemed infected (i.e., observation of live *F. hepatica* or *F. hepatica* damage in the liver) or not infected with *F. hepatica* (i.e., no observation of live *F. hepatica* or *F. hepatica* damage in the liver). All analyses were undertaken in young cattle and cows, separately.

Carcass Data

As well as receiving a *F. hepatica*–damaged liver phenotype at slaughter, all animals had a recorded carcass weight (kg), conformation

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

score (scale: 1–15), and fat score (scale: 1–15). Carcass weight was measured, on average, 2 h after slaughter following the removal of the head, legs, thoracic and abdominal organs, and internal fats and hide. As described by Pabiou et al. (2011), carcass conformation and fat scores were graded using video image analysis and were graded under the European Union beef carcass classification system (EUROP). The resulting EUROP classification grades were transformed into a 1 to 15 scale as outlined in Englishby et al. (2016). Only carcass traits from animals in the *F. hepatica*–damaged liver dataset were retained for the analysis.

Milk production data

Individual lactation records for 305-d milk yield (kg), fat yield (kg), protein yield (kg), fat percentage (%), protein percentage (%), fat-to-protein ratio and somatic cell count (SCC) from 3,133,555 lactations on 1,321,572 dairy cows calving between the years of 2010 to 2015, inclusive, were available. Somatic cell count (SCC) values were normalized to somatic cell score (SCS) using the natural logarithm transformation of SCC/1000. Lactation records were discarded if the 305 d milk yield was >4 standard deviations from the parity mean or if the recorded lactation length was either <100 or >500 d. There were 2,904,669 lactation records remaining. Milk records were discarded if the cow calved in a different herd to where it resided since 90 d of age. Only milk records from cows in herds that contained at least one animal with a record for antibody response to any of the three parasites or a *F. hepatica*–damaged liver phenotype, from either study herd data or abattoir data were considered. Consequently, following all edits, 452,774 lactation records remained.

Fertility Data

Data were available, between the years of 2010 and 2016, inclusive, on 6,300,278 artificial and 558,006 natural insemination records as well as 1,673,348 pregnancy diagnoses and 13,647,743 calving records from 4,589,153 dairy and beef cows. Where two insemination records for the same cow were within 5 d of each other, the earlier of the two was discarded. Fertility data from herd-years where >80% of cows were recorded as having only one insemination were not considered further, as these herds are likely to have only recorded the last insemination.

Several alternative fertility phenotypes were defined similar to those described in detail by both Berry et al. (2013) and Berry and Evans (2014) in dairy cows and beef cows, respectively. Calving to first service interval (**CFS**) was defined as the number of days from calving to first insemination; CFS records were discarded if <20 or >250 d. Also, CFS was only defined using artificial insemination records. Calving interval (**CIV**) was defined as the number of days between consecutive calving events. Only CIV records >300 d were retained; CIV records >600 d were discarded unless the CFS record for that lactation was <150 d, otherwise CIV records >800 d were discarded (Berry et al., 2013). Age at first calving was defined as the age, in days, when the heifer calved for the first time; only records between 660 and 1400 d of age were retained. Number of services was defined as the number of times a cow was inseminated per lactation; lactations with >10 inseminations were given a value of 10.

Dairy and beef cows are generally bred and calve within a strict time period in seasonal calving/breeding herds, which predominate in Ireland (Berry et al., 2013; Berry and Evans, 2014). The start date of a herd's breeding period was chosen to be the date when five or more cows were inseminated within the subsequent 14 d in that herd; the end date of the breeding period was when the last cow in the herd was inseminated with no reported insemination in the herd for the subsequent 21 d (Berry et al., 2013). Only breeding periods between 35 and 140 d in length with ≥20 cows were retained. Likewise, for the calving period (i.e., defined separately for primiparous cows and multiparous cows), the start date of the calving period for a herd was the first calendar date, which was followed by five or more calving events within the subsequent 14 d; the end date of a calving period was that last calving date which was not followed by a subsequent calving in that herd for the following 21 d. Only calving periods between 35 and 200 d in length were retained. Also, calving periods for primiparous cows and multiparous cows with <6 calving primiparous cows and <20 calving multiparous cows, respectively, were discarded.

The defined breeding and calving periods were used to derive the three fertility traits: submission rate, calving rate, and pregnancy rate. Using only first insemination records within a predefined breeding period, submission in the first 24 d of the breeding period (SR24) was defined as whether or not a cow was inseminated for the first time in the first 24 d of the breeding period. Calving in the first

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

42 d of the herd calving period (CR42) was defined as whether or not a cow calved in the first 42 d of the defined calving period described previously; cows were not considered if they did not calve in a predefined calving period.

The binary trait of pregnant/not pregnant in the first 42 d of the breeding period (**PR42**) was defined as whether or not a cow was pregnant in the first 42 d of the breeding period. Only breeding periods >42 d in length were used for defining PR42. Cows inseminated in the first 42 d of the breeding period, without any further insemination, and with a subsequent calving date recorded within 265 and 295 d of the insemination date (i.e., mean gestation length in dairy cows is reported to be 279 d with a standard deviation of 5 to 6 d; Norman et al., 2009; Nogalski and Piwczyński, 2012), were deemed pregnant in the first 42 d; cows with no recorded subsequent calving or insemination date, but which were diagnosed pregnant using the pregnancy diagnosis information, where available, were also deemed pregnant in the first 42 d of the breeding period. Cows that were inseminated after day 42 of the breeding period or cows that had a calving date between 320 and 500 d after their insemination date in the first 42 d of the breeding period were deemed not pregnant in the first 42 d of the breeding period. If there were no subsequent calving or insemination dates recorded, but the cow was diagnosed as "not pregnant" using the pregnancy diagnosis information, where available, the cow was deemed not pregnant in the first 42 d of the breeding period. Pregnant to first service (**PRFS**) was defined as whether or not a cow was pregnant to her first insemination. Cows were deemed not pregnant to first service if there was a second insemination recorded. Subsequent calving dates and pregnancy diagnoses were used, similar to that defined for PR42, to ascertain PRFS status for cows with only one insemination record.

Survival was defined as whether or not a cow successfully reached the next lactation. A cow was deemed to have survived lactation n if she had a subsequent calving date for lactation n+1 within 600 d of the cow's calving date for lactation n. A cow that did not have a calving date for lactation n+1 and was either slaughtered or there was >200 d between her last milk recording date and the last milk recording date of the herd the cow was residing in was deemed to have not survived lactation n. Survival was only defined for lactations ≤5.

Fertility phenotypes were discarded if the cow calved in a different herd to where it resided since 90 d of age. Only fertility phenotypes from cows in herds that contained at least one cow with a record for antibody response to any of the three parasites or a *F. hepatica*–damaged liver phenotype were considered further. Also, only fertility phenotypes from lactations between the years of 2010 and 2015, inclusive, were retained. There were 605,828 lactation records remaining.

General Data Edits

Cow parities of >10 were discarded and parity was subsequently categorized as 1, 2, 3, 4, 5, 6, and 7+. Young cattle were partitioned into an age group at slaughter of either between 366 and 730 d, or between 731 and 1,096 d (Twomey et al., 2016); young animals were discarded if they were not assigned to either age group. Cow age at calving relative to the median age at calving of the respective parity was calculated. Cow age at blood sampling relative to the median age at blood sampling of the respective parity was calculated, as was animal age at slaughter relative to the median age at slaughter of the respective parity and age group for the cows and young cattle, respectively. Only animals sired by a known sire that had at least one progeny recorded with any one of the four parasite phenotypes (absent or present) were considered further.

General heterosis and recombination loss coefficients for each animal were calculated as $1-\sum_{i=1}^{n} sire_i \cdot dam_i$ and $1-\sum_{i=1}^{n} \frac{sire_i^2 + dam_i^2}{2}$, respectively where $sire_i$ and dam_i are the proportion of breed i in the *sire* and *dam*, respectively.

Contemporary group for all traits was defined as herd-year-season of calving for cows and herd-year-season of birth for young cattle. All herd-year-season contemporary groups were generated for each trait phenotype separately using an algorithm described in detail by Berry and Evans (2014). The algorithm was used to group cows that calved around the same period of the year within each herd. Similarly, the algorithm was used to group young animals born around the same period of the year within each herd. Contemporary groups with less than five animals were discarded for all datasets, with the exception of cows in the *F.* hepatica–damaged liver dataset where contemporary groups with less than four cows were discarded. Only contemporary groups with >1 sire represented in the contemporary group were retained for all datasets. Only 2,036 contemporary groups containing beef cows remained in the *F. hepatica*–damaged liver dataset. These records were discarded and thus no analysis included beef cows.

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

In the study herds, 9,271 cows with at least one record for an antibody response to a parasite remained (Table 1). In the study herds, 18,586 BCS records were included in the analysis, as well as 37,980 and 183,368 lactation records for milk production and fertility traits (Table 2). A total of 19,542 cows and 68,048 young animals remained that had both a *F. hepatica*–damaged liver phenotype (absent or present) and a respective carcass phenotype. For computational reasons, in herds that contained at least one cow in the *F. hepatica*–damaged liver dataset, milk and fertility lactation records were only retained from the years 2013 to 2015, inclusive. Furthermore, a random sample of the remaining contemporary groups in herds that contained at least one cow in the *F. hepatica*–damaged liver dataset were chosen to result in a dataset with, where possible, approximately 100,000 records per trait. The dataset contained 105,531 and 202,829 lactation records for milk production and fertility traits (Table 2), respectively.

Statistical Analyses

For the purposes of analyses, the data were separated into two groups: 1) data from the study herds and 2) data from herds with at least one cow in the *F. hepatica*–damaged dataset. For the analyses of the study herd dataset, variance components were estimated for the individual antibody response to each of the three parasites, as a binary or a continuous trait (i.e., normalized for *F. hepatica* and *N. caninum*), as well as covariances amongst the antibody response to *F. hepatica*, *N caninum* and *O. ostertagi*. Also, covariance components between antibody response to parasites and performance traits (i.e., milk, fertility, and BCS) in the study herds were estimated. For the analyses of data with at least one cow in the *F. hepatica*–damaged dataset, covariance components were estimated between the binary trait of *F. hepatica*–damaged liver (i.e., absent or present) of cows and the performance traits (i.e., milk and fertility), as well as between the *F. hepatica*–damaged liver trait and

Table 1. Prevalence (Prev), additive genetic standard deviation (σ_a), and heritability (h^2; SE in parenthesis) for antibody response traits treated as a binary or a continuous trait for *F. hepatica* (n = 6,892 records), *N. caninum* (n = 5,289 records), and *O. ostertagi* (n = 9,260 records), as well as the inter-trait genetic (below the diagonal; SE in parenthesis) and phenotypic (above the diagonal; SE in parenthesis) correlations

				Correlations		
Trait	Prev (%)	σ_a	h^2	*F. hepatica*	*N. caninum*	*O. ostertagi*
Binary						
F. hepatica (1/0)	37	0.114	0.09 (0.022)	—	0.01 (0.153)	0.10 (0.012)
N. caninum (1/0)	4	0.000	0.00 (0.000)	−0.49 (0.759)	—	0.00 (0.014)
O. ostertagi (1/0)	49	0.123	0.08 (0.018)	0.66 (0.172)	−0.76 (0.612)	—
Continuous						
F. hepatica (ODR level)	—	0.328	0.15 (0.027)	—	−0.10 (0.015)	0.17 (0.013)
N. caninum (PP level)	—	0.030	0.09 (0.027)	−0.29 (0.175)	—	−0.06 (0.015)
O. ostertagi (ODR level)	—	0.061	0.10 (0.020)	0.91 (0.103)	−0.67 (0.160)	—

Table 2. Number of cows, contemporary groups (CG), and records (N), as well as the sample population mean and heritability (h^2),s for the different fertility traits in either the study herds or the herds that had at least one cow with *F. hepatica*–damaged liver

	Study herds					*F. hepatica*–damaged liver herds				
	Cows	CG	N	Mean	h^2	Cows	CG	N	Mean	h^2
Age of first calving (d)	10,786	912	10,786	744	0.01	47,385	4,915	47,385	774	0.01
Calving to first service interval (d)	13,728	1,600	31,760	77	0.02	62,489	7609	107,644	76	0.02
Calving interval (d)	13,886	1,750	33,269	373	0.01	71,315	8500	109,574	376	0.02
Number of services (number)	13,728	1,600	31,760	1.59	0.02	62,489	7609	107,644	1.54	0.01
Submission rate in 24 d (1/0)	13,261	1,539	30,177	0.86	0.03	56,663	6620	95,395	0.79	0.02
Calving rate in first 42 d (1/0)	14,565	2,444	35,424	0.79	0.01	69,878	9,000	102,074	0.70	0.01
Pregnancy rate in first 42 d (1/0)	12,025	1,382	25,780	0.68	0.02	48,402	5537	77,213	0.63	0.02
Pregnancy rate to first service (1/0)	12,904	1,491	28,929	0.57	0.02	52,706	6101	87,112	0.56	0.01
Survival (1/0)	14,408	1,726	32,197	0.92	0.01	68,364	8,500	110,912	0.90	0.02

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

its respective carcass traits, separately for cows and young animals.

Covariance components in all analyses were estimated using a series of univariate and bivariate animal linear mixed models in ASReml (Gilmour et al., 2009). The models varied per trait and were

$$W = \mathrm{CG} + \mathrm{Het} + \mathrm{Rec} + \mathrm{age} + \mathrm{group} + \mathrm{stage} + \mathrm{a} + \mathrm{e}$$

$$X = \mathrm{CG} + \mathrm{Het} + \mathrm{Rec} + \mathrm{age\_calve} + \mathrm{group} + \mathrm{a} + \mathrm{PE} + \mathrm{e}$$

$$Y = \mathrm{CG} + \mathrm{Het} + \mathrm{Rec} + \mathrm{a} + \mathrm{e}$$

where W is the dependent variable for all four parasite traits and the three carcass traits; X is the dependent variable representing the milk traits or fertility traits (with the exception of age at first calving); Y is the dependent variable of age at first calving; *CG* is the fixed effect of contemporary group; *Het* is the fixed effect of a general heterosis coefficient (0.0, >0.0 to <0.1, ≥0.1 to <0.2,…≥0.9 to <1.0, 1.0); *Rec* is the fixed effect of a general recombination loss coefficient (0.00, >0.00 to <0.05, ≥0.05 to <0.10,…≥0.45 to <0.50, 0.50, >0.50); *age* is the fixed effect of age at slaughter/diagnosis in months relative to the median age of the parity for cows or age group (i.e., 366 to 730 d of age and 731 to 1096 d of age) for young cattle, *group* is the fixed effect of parity in cows or age group in young cattle; *stage* is the fixed effect of stage of lactation for cows only (0 to ≤50 d, >50 to ≤100 d,…>450 to ≤500 d, >500 d); *age_calve* is the fixed effect of age at calving in months relative to the median age of the parity for cows; *PE* is the random permanent environmental effect for each cow, where $PE \sim N(0, I\sigma_{PE})$ with σ_{PE} representing the permanent environmental standard deviation; a is the direct additive genetic effects, where $a \sim N(0, A\sigma_a)$ with σ_a representing the additive standard deviation; and e is the random residual effect, where $e \sim N(0, I\sigma_e)$ with σ_e representing the residual standard deviation. Gender was included as a fixed effect when more than one gender was included in the analysis. The date and abattoir of the slaughtered animal was also included as a fixed effect for all traits recorded in abattoirs (i.e., carcass traits and *F. hepatica*–damaged liver trait). CFS was fitted as a quadratic fixed effect when the dependent variable was PRFS (Berry et al., 2011a). The pedigree of each animal was traced back to the founder population which was allocated to 11 genetic groups based on breed. Breed effects were estimated as the mean estimated breeding value of purebred (i.e., ≥0.875 of the breed) animals in each breed born between 2007 and 2015; only means from breeds with >1,000 animals are presented. The breed mean was only estimated for *F. hepatica*–damaged liver, as the other dataset mainly contained just Holstein-Friesians.

RESULTS

Parity was associated ($P < 0.001$) with the binary and continuous trait of antibody response to *O. ostertagi,* in that there was an inverse relationship between mean antibody response to *O. ostertagi* and parity. General recombination loss coefficient was also associated with antibody response to *O. ostertagi* ($P < 0.001$), although there was no obvious trend. Parity ($P < 0.01$) and age at diagnosis in months relative to the median age of the parity for cows ($P < 0.001$) were both associated with antibody response to *N. caninum* as a binary trait; no obvious trend was detected. Stage of lactation was associated ($P < 0.01$) with antibody response to *O. ostertagi* as a binary trait, but the estimated stage effects were erratic. Fixed effect estimates for *F. hepatica* phenotypes are reported in Twomey et al. (2016). The mean breed estimated breeding value for *F. hepatica*–damaged liver of Holstein Friesian, Limousin, Charolais, Hereford, and Aberdeen Angus was −0.001 (SE = 0.00009), −0.015 (SE = 0.00029), 0.008 (SE = 0.00038), 0.047 (SE = 0.00042), and −0.007 (SE=0.00031), respectively. The coefficient of genetic variation estimated using the univariate model was 0.21, 0.05, and 0.10 for antibody responses to *F. hepatica*, *O. ostertagi*, and *N. caninum* when analyzed as a continuous trait. The additive genetic standard deviation in antibody responses to the three parasitic diseases varied from 0.000 (*N. caninum*) to 0.123 (*O. ostertagi*) when treated as a binary trait (Table 1). Heritability estimates for antibody responses to the different parasite traits varied from 0.00 (*N. caninum*) to 0.09 (*F. hepatica*) and from 0.09 (*N. caninum*) to 0.15 (*F. hepatica*) when analyzed as a binary or a continuous trait, respectively (Table 1). Heritability estimates for the milk production traits ranged from 0.27 to 0.36 for the yield traits and from 0.46 to 0.68 for the milk composition traits; the heritability of SCS was 0.13. The heritability estimates ranged from 0.01 to 0.03 for the fertility traits (Table 2). The heritability and repeatability for BCS were 0.28 and 0.35, respectively. The heritability for the carcass traits ranged from 0.46 to 0.63 in young cattle and from 0.18 to 0.40 in cows.

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

Genetic correlations

Antibody response to *N. caninum* was negatively genetically correlated with antibody response to both *O. ostertagi* (−0.76 to −0.67) and *F. hepatica* (−0.49 to −0.29; Table 1). Antibody response to *O. ostertagi* and antibody response to *F. hepatica* were positively genetically correlated (0.66 to 0.91). The phenotypic correlations were similar in sign to their respective genetic correlations, albeit the former were close to zero (Table 1). The within-trait genetic correlations between the binary and continuous trait for *F. hepatica*, *O. ostertagi*, and *N. caninum* were 0.92 (0.052), 0.95 (0.038), and 0.80 (0.570), respectively. The binary trait therefore accounted for 85%, 90%, and 64% of the genetic variation in the continuous trait for *F. hepatica*, *O. ostertagi*, and *N. caninum*, respectively (i.e., r_g^2). Genetic correlations between performance traits and antibody response to parasitic diseases were very similar irrespective of whether they were analyzed as a binary or a continuous trait. As a result, only genetic correlations between performance traits and antibody responses to parasitic diseases analyzed as a continuous trait are reported herein.

Milk production and carcass traits. The genetic correlations between antibody responses to the three parasite diseases and milk production traits for cows in the 68 study herds are in Table 3; the phenotypic correlations were all close to 0 (ranged from −0.03 to 0.03) and are, therefore, not reported. All genetic correlations between antibody response to *F. hepatica* and the milk production traits, including SCS, in the study herds were unfavorable (−0.14 to -0.03), but, only the genetic correlations with fat yield, protein yield and fat percentage were different from zero (Table 3). The genetic correlations between antibody response to *O. ostertagi* and the different milk production traits, including SCS, were close to zero (−0.05 to 0.14; Table 3). The genetic correlations between antibody response to *N. caninum* and the different milk production traits, including SCS, ranged from −0.02 to 0.13. The genetic correlations between *F. hepatica*–damaged liver in cows and the milk production traits were all close to zero (−0.06 to 0.10; Table 4) with the exception of SCS (0.32 SE = 0.195).

Table 3. Genetic correlations (SE in parentheses) between antibody response to parasites, when treated as continuous traits, and milk production traits in the study herds

Trait	*F. hepatica*	*O. ostertagi*	*N. caninum*
Milk yield	−0.07 (0.060)	−0.04 (0.062)	−0.01 (0.052)
Fat yield	−0.12 (0.061)	−0.01 (0.064)	0.04 (0.084)
Protein yield	−0.14 (0.063)	−0.05 (0.065)	0.02 (0.086)
Fat percentage	−0.09 (0.045)	0.00 (0.047)	0.02 (0.062)
Protein percentage	−0.09 (0.046)	−0.04 (0.047)	0.02 (0.062)
Fat-to-protein ratio	−0.04 (0.051)	0.04 (0.052)	0.01 (0.069)
Somatic cell score	−0.05 (0.082)	0.07 (0.084)	0.13 (0.110)

Table 4. Genetic correlations (SE in parentheses) between *F. hepatica*–damaged liver and performance traits in herds that had at least one animal with *F. hepatica*–damaged liver

Trait	Correlation	Trait	Correlation
Milk production traits		Fertility traits	
Milk yield	0.10 (0.159)	Age of first calving	−0.18 (0.375)
Fat yield	0.00 (0.163)	Calving interval	0.48 (0.217)
Protein yield	0.05 (0.175)	Calving to first service interval	0.36 (0.245)
Fat percentage	−0.06 (0.138)	Number of services	0.21 (0.250)
Protein percentage	−0.08 (0.128)	Survival	−0.41 (0.228)
Protein: fat ratio	−0.07 (0.143)	Submission rate in 24 d	−0.30 (0.260)
Somatic cell score	0.32 (0.195)	Calving rate in 42 d	0.00 (0.000)
Carcass traits—cows		Pregnancy rate in 42 d	−0.41 (0.248)
Weight	0.16 (0.195)	Pregnancy rate to first service	−0.30 (0.266)
Conformation	0.12 (0.211)		
Fat cover	0.00 (0.222)		
Carcass traits—young cattle			
Weight	−0.01 (0.063)		
Conformation	0.13 (0.061)		
Fat cover	0.07 (0.063)		

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

Although not more than twice the respective standard error, the genetic correlations between the carcass traits in cows and *F. hepatica*–damaged liver in cows ranged from 0.00 to 0.16 (SE = 0.195 to 0.222). Genetic correlations between carcass traits in young cattle and *F. hepatica*–damaged liver in young cattle were also close to zero (i.e., favorable; -0.01 to 0.13), albeit the correlation with conformation score was different from zero (0.13; SE=0.061)

Fertility and BCS traits. The genetic correlations between antibody responses to the three parasites diseases and fertility traits, including BCS, for cows in the 68 study herds are shown in Table 5. Antibody response to *F. hepatica* was genetically correlated with both CFS (−0.46; SE = 0.138) and survival (0.36; SE = 0.180); the genetic correlations between antibody response to *F. hepatica* and the other analyzed fertility traits were not different from zero (ranging from −0.25 to 0.26). A negative genetic correlation (−0.38; SE = 0.144) existed between antibody response to *O. ostertagi* and CFS; the genetic correlations ranged from −0.11 to 0.15 between antibody response to *O. ostertagi* and the other fertility traits, albeit none were more than twice their SE. Antibody response to *N. caninum* was genetically correlated with CFS (0.56; SE = 0.175), PR42 (−0.73; SE = 0.182), and PRFS (−0.43; SE = 0.208); the genetic correlations with the other fertility traits were not different from zero (−0.48 to 0.43). The genetic correlations between *F. hepatica*–damaged liver and fertility are in Table 3. The genetic correlations ranged from −0.41 (SE = 0.248) to 0.48 (SE = 0.217) between *F. hepatica*–damaged liver and the fertility traits.

DISCUSSION

The high animal-level prevalence of both *F. hepatica* (Sanchez-Vazquez and Lewis, 2013; Byrne et al., 2016; Twomey et al., 2016) and *O. ostertagi* (Agneessens et al., 2000; Murphy et al., 2006) in cattle is of concern globally. Although the previously reported prevalence for *N. caninum* in cattle is lower, prevalence ranges from 6 to 25% in dairy cows have been reported (Ould-Amrouche et al., 1999; Haddad et al., 2005). Prevalence levels of parasites in the present study should not be considered reflective of the true prevalence as the data were strictly edited in an attempt to ensure exposure among the analyzed animals. Nonetheless, one possible option to minimize the risk of parasite infection in dairy and beef cattle is to incorporate phenotypes for resistance to parasite diseases into breeding programs. Despite this, to our knowledge, this is the first study to document the implications of genetic selection for resistance to individual parasites on other performance traits in cattle.

Genetic Parameters for Antibody Response to Parasites

Ample genetic variation for all parasite phenotypes in the present study exists to justify consideration for inclusion in breeding programs. The coefficient of genetic variation for the antibody response to parasites (0.05 to 0.21) was similar to that observed for the milk traits (0.04 to 0.09). In comparison to the coefficient of genetic variation for the interval fertility traits (ranged from 0.03 for calving interval to 0.01 for calving to first service interval), the coefficient of genetic variation for the antibody response to parasites was large. When treated as a binary trait, the additive genetic standard deviation of antibody response to the parasites studied (2 to 10% units) was similar to the binary fertility traits in the present study (1 to 5% units), as well as other disease traits reported elsewhere such as mastitis (1.2 to 7.0% units; Berry et al., 2011b) and bovine tuberculosis (3 to 5% units; Bermingham et al., 2009). Therefore, based on the large coefficient of

Table 5. Genetic correlations (SE in parentheses) between antibody response to parasites, when treated as continuous traits, and fertility traits in the study herds

	F. hepatica	*O. ostertagi*	*N. caninum*
Age of first calving	0.08 (0.374)	0.09 (0.359)	−0.48 (0.337)
Calving interval	0.09 (0.174)	−0.11 (0.171)	0.43 (0.220)
Calving to first service interval	−0.46 (0.138)	−0.31 (0.144)	0.56 (0.175)
Number of services	0.19 (0.145)	0.01 (0.150)	0.37 (0.192)
Survival	0.36 (0.180)	−0.01 (0.184)	0.24 (0.223)
Submission rate in 24 d	0.13 (0.135)	0.15 (0.134)	−0.13 (0.172)
Calving rate in 42 d	−0.25 (0.200)	−0.06 (0.208)	0.18 (0.273)
Pregnancy rate in 42 d	0.15 (0.169)	0.10 (0.168)	−0.73 (0.182)
Pregnancy rate to first service	0.01 (0.167)	0.05 (0.165)	−0.43 (0.208)
Body condition score	−0.02 (0.066)	−0.01 (0.075)	−0.05 (0.090)

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

genetic variation, the genetic progress that has been achieved for milk production and fertility in cattle (Berry et al., 2014) could also, in theory at least, be achieved for antibody response to parasite traits, with sufficient data.

The low to moderate heritability estimates for antibody response to parasites in the present study suggests that, in the absence of parentage information or information on correlated traits, only 40 to 50 progeny are required to achieve a breeding value accuracy of 0.70 for antibody response to parasites. Although fertility traits in breeding programs worldwide require even more progeny to achieve a similar accuracy (ca. 200 progeny), the current lack of routine data on individual animal antibody responses to parasites will hinder genetic progress in breeding programs. Heritability estimates from the present study nonetheless corroborate estimates from earlier studies for the number of *O. ostertagi* larvae per gram of feces in 1,420 Dutch dairy cows (0.06; Coppieters et al., 2009) and for the antibody response to *N. caninum* in 9,723 Canadian Holsteins (0.08; Pan et al., 2004). Nevertheless, Morris et al. (2003) reported a higher heritability (0.20 to 0.39) for the antibody response to *O. ostertagi* for 370 Angus cattle in their first and second grazing seasons, albeit associated with large SE up to 0.16. A higher heritability may have been reported by Morris et al. (2003) because they only collected data from one herd, so all animals had a similar exposure.

Correlations Among Antibody Response to the Different Endo-Parasites

Results from the present study support the existence of an antagonistic relationship between the immune response to intracellular pathogens (e.g., bacteria, virus, protozoan parasites) and the immune response to extracellular pathogens (e.g., helminthic parasites), described in the Kaiko et al. (2008) review. Cattle infected or exposed to extracellular *F. hepatica* have a reduced likelihood of being positive to the tuberculin skin test, which is based on an intracellular immune response to *M. tuberculosis* (Flynn et al., 2007; Claridge et al., 2012). This is because the immune response to *F. hepatica* suppresses the immune response to the tuberculin skin test.

Helper T cells in ruminants produce TH2-type cytokines in response to trematode (*F. hepatica*) and nematode (*O. ostertagi*) parasites, also referred to as an antibody mediated immune response (AMIR; McNeilly and Nisbet, 2014; McRae et al., 2015). Alternatively, immune response to protozoan parasites (*N. caninum*) results in helper T cells producing TH1-type cytokines, also known as a cell mediated immune response (CMIR; Lunden et al., 1998; Arranz-Solís et al., 2016). Therefore, animals that are infected with *N. caninum* (i.e., have a high antibody response to *N. caninum)* are likely to have a lower antibody response to both *O. ostertagi* and *F. hepatica.*

Previous studies documented genetic differences between cattle in their ability to mount an AMIR and a CMIR (Thompson-Crispi et al., 2012; Heriazon et al., 2013). Thompson-Crispi et al. (2012) reported genetic correlations ranging from −0.45 to -0.13 (SE = 0.32 to 0.46) between AMIR and CMIR. Similarly, Heriazon et al. (2013) reported a negative correlation of -0.44 between estimated breeding values for a CMIR and an AMIR. The present study supports these studies in that cows genetically predisposed to a high antibody response to *N. caninum* (i.e., CMIR) were, on average, genetically predisposed to a lower antibody response to both *O. ostertagi* and *F. hepatica* (i.e., AMIR). As *O. ostertagi* and *F. hepatica* both cause an AMIR within the host, the positive genetic correlation observed between these two phenotypes in the present study was expected. This also corroborates a study on 370 Angus cattle (Morris et al., 2003) where strong positive genetic (ranging from 0.5 to 1.0) and phenotypic (ranging from 0.5 to 0.8) correlations were estimated among the antibody response to three different gastrointestinal nematodes, including *O. ostertagi*.

Genetic Correlations With Milk Production and Carcass Traits

Many studies have documented that antibody responses to *F. hepatica* (Charlier et al., 2007; Mezo et al., 2011), *O. ostertagi* (Charlier et al., 2009b), and *N. caninum* (González-Warleta et al., 2011), at the herd-level, are negatively associated with milk production in dairy cows. In contrast, phenotypic studies using animal-level data failed to detect any association between milk production traits and antibody response to either *O. ostertagi* (Sanchez et al., 2004; Charlier et al., 2010) or *N. caninum* (Hobson et al., 2002; Bartels et al., 2006). However, in a study of 686 Spanish dairy cows (Mezo et al., 2011), a reduction in milk yield (i.e., 2 kg/d in cows yielding on average 30 kg/d) was reported in cows with a very high antibody response to *F. hepatica* compared to cows with a negative antibody response to *F. hepatica*; nonetheless, Mezo et al.

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

(2011) failed to detect an association between antibody response and either milk fat or protein percentage. At cow level, antibody response to *N. caninum* has also been linked to compromised milk production (Thurmond and Hietala, 1997; Hernandez et al., 2001; Tiwari et al., 2007) but may be specifically associated with the abortions caused by *N. caninum* in cows (Hobson et al., 2002; Bartels et al., 2006), in that cows that have had an abortion have, on average, reduced milk yield in the subsequent lactation (Gädicke et al., 2010; El-Tarabany, 2015).

In a recent study of 1,166 dairy cows, May et al. (2017) reported that FEC for flukes (i.e., sum of *F. hepatica*, *Paramphistomum* spp., and *Calicophoron* spp.) had close to zero genetic correlations with test day milk yield, fat percentage, protein percentage as well as fat-to-protein ratio for the majority of the lactation. Although May et al. (2017) did not specifically measure a *F. hepatica* phenotype, the present study is in general agreement, in that genetic selection for *F. hepatica* traits are expected to have little or no impact on the genetic improvement of milk production traits other than through an impact on selection intensity. Yet, May et al. (2017) reported that FEC of gastrointestinal worms was negatively genetically correlated with fat percentage, protein percentage, and fat-to-protein ratio, but positively genetically correlated with both milk yield and somatic cell score, for the majority of the lactation. In other studies, close to zero genetic correlations have been documented between milk traits and FEC in goats (Morris et al., 1997; n = 4,738 records) and sheep (Afolayan et al., 2009; n = 944 records).

The lack of a genetic association between parasites and milk production was somewhat strengthened by the absence of genetic correlations between *F. hepatica*–damaged liver and carcass traits. Although a wide range of studies reported a statistically significant unfavorable association between liver damage caused by *F. hepatica* and carcass traits at the animal level (Brown and Lawrence, 2010; Sanchez-Vazquez and Lewis, 2013; Bellet et al., 2016), the documented impact has been biologically small. For instance, Sanchez-Vazquez and Lewis (2013) reported that animals with a *F. hepatica*–damaged liver had, on average, a 0.3% reduced carcass value compared to animals with no *F. hepatica*–damaged liver (n = 328,137; equivalent to £2.30 less per carcass for an average carcass value of £769). In contrast, a genetic study using FEC as the parasite phenotype documented a genetic correlation of 0.3 (SE = 0.15) with the live weight in 1,175 Australian beef heifers (Prayaga et al., 2009). In direct contrast, however, Bisset et al. (1992) reported a negative genetic correlation (−0.48; SE = 0.21) in sheep between fecal egg count (**FEC**) and weight gain in 2,611 Romney ewe lambs. Also, FEC was reported to be negatively genetically correlated with both fat depth (−0.26; SE = 0·09) and eye-muscle depth (–0.18; SE = 0.09) in 127,723 Australian merino sheep (Pollott and Greeff, 2004).

Genetic correlations with fertility traits

All parasite phenotypes in the present study had weak to moderate estimated genetic correlations with fertility traits. Although antibody response to both *F. hepatica* and *O. ostertagi* were favorably genetically correlated with fertility traits in the present study, some phenotypic studies on cows reported no association (Mezo et al., 2011; Howell et al., 2015), while others reported an unfavorable association (Sanchez et al., 2002; Charlier et al., 2007). In a study of 1,105 dairy herds, Charlier et al. (2007) reported a negative phenotypic association, at the herd-level, between antibody response to *F. hepatica* and calving interval. The fact that antibody responses to both *F. hepatica* and *O. ostertagi* were favorably genetically correlated with fertility traits in the present study supports the view that animals inclined towards a TH2-type cytokine immune response have a tendency to maintain pregnancy (Oliveira et al., 2013; Zhang et al., 2015; Yang et al., 2016).

Antibody responses to *N. caninum* had unfavorable genetic associations with fertility traits in the present study, which is similar to reported phenotypic associations (Hall et al., 2005; Canatan et al., 2014). In a study of 486 Turkish dairy cows, Canatan et al. (2014) reported cows positive for the antibody response to *N. caninum* required almost twice the number of inseminations and had, on average, a 77 d longer calving to conception interval compared to cows negative for the antibody response to the *N. caninum*. The increased odds of an abortion in *N. caninum* infected animals was 3.5 (the median value from a review of 10 studies) in dairy cows (Reichel et al., 2013). This could be caused by an antibody response to *N. caninum* differentiating into a TH1-type cytokine based immune response, which is associated with embryo loss (Innes, 2007).

The unfavorable genetic association between *F. hepatica*–damaged liver and fertility traits in the present study was expected since the liver is an important organ for energy production (i.e., production of glucose; Aschenbach et al., 2010) and for

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

preventing negative energy balance (**NEB**). Cows in NEB require the liver to control the levels of nonesterified fatty acids, thus reducing the consequences of NEB (Grummer, 2008). Therefore, cows with a *F. hepatica*–damaged liver could be more prone to the consequences of NEB. It is clearly documented that cows in NEB have reduced fertility (Roche et al., 2009; Berry et al., 2016). The observed favorable genetic association between antibody response to *F. hepatica* and the fertility traits in the present study suggests that cows with a high antibody response may be able to cope with *F. hepatica* infection and either reduce or prevent *F. hepatica*–damaged liver. This therefore implies that breeding for a higher antibody response to *F. hepatica* may be advantageous. Twomey et al. (2016) did, however, report a positive genetic correlation (0.37) between *F. hepatica*–damaged liver and positive antibody response to *F. hepatica,* although the corresponding SE was large (0.283), suggesting that current breeding goals for fertility traits could be indirectly selecting cows that are less likely to have a *F. hepatica*–damaged liver. Therefore, the introduction of *F. hepatica*–damaged liver phenotype in a national breeding goal, as Twomey et al (2016) suggested, could further benefit cow resistance to *F. hepatica*–damaged liver, as well as potentially increase genetic gain for fertility traits in cattle.

CONCLUSION

Overall, results from the present study support the view that genetic selection for the investigated endo-parasite phenotypes is possible and could be recommended in populations exposed to a high parasitic load. Current cattle breeding programs with high emphasis on fertility traits appear to be reducing liver damage caused by *F. hepatica.* Nevertheless, the introduction of *F. hepatica*–damaged liver phenotypes into national breeding programs could further reduce the prevalence of *F. hepatica*–damaged liver, with only the loss of selection intensity contributing to a reduction in the genetic gain in milk production and carcass traits. The genetic selection for antibody response to only one parasite would be unwise as the antibody response to *N. caninum* is negatively genetically correlated with the antibody response to both *F. hepatica* and *O. ostertagi*. Additionally, cows with a high antibody response to *N. caninum* are genetically prone to poorer reproductive performance; but conversely, cows with a high antibody response to both *F. hepatica* and *O. ostertagi* are genetically associated with better reproductive performance. Thus, the conflicting genetic impact of parasitism on fertility traits, as well as the lack of routine data, will hinder the introduction of antibody response to parasites into breeding programs.

Conflict of interest statement. None declared.

LITERATURE CITED

Afolayan, R.A., N.M. Fogarty, J.E. Morgan, G.M. Gaunt, L.J. Cummins, and A.R. Gilmour. 2009. Preliminary genetic correlations of milk production and milk composition with reproduction, growth, wool traits and worm resistance in crossbred ewes. Small Rumin. Res. 82:27–33. doi:10.1016/j.smallrumres.2009.01.006

Agneessens, J., E. Claerebout, P. Dorny, F.H.M. Borgsteede, and J. Vercruysse. 2000. Nematode parasitism in adult dairy cows in Belgium. Vet. Parasitol. 90:83–92. doi:10.1016/S0304-4017(00)00232-6

Arranz-Solís, D., J. Benavides, J. Regidor-Cerrillo, P. Horcajo, P. Castaño, M. del Carmen Ferreras, L. Jiménez-Pelayo, E. Collantes-Fernández, I. Ferre, A. Hemphill, et al. 2016. Systemic and local immune responses in sheep after *Neospora caninum* experimental infection at early, mid and late gestation. Vet. Res. 47:2. doi:10.1186/s13567-015-0290-0

Aschenbach, J.R., N.B. Kristensen, S.S. Donkin, H.M. Hammon, and G.B. Penner. 2010. Gluconeogenesis in dairy cows: the secret of making sweet milk from sour dough. IUBMB Life 62:869–877. doi:10.1002/iub.400

Barling, K.S., J.W. McNeill, J.A. Thompson, J.C. Paschal, F.T. McCollum 3rd, T.M. Craig, and L.G. Adams. 2000. Association of serologic status for *Neospora caninum* with postweaning weight gain and carcass measurements in beef calves. J. Am. Vet. Med. Assoc. 217:1356–1360.

Bartels, C.J.M., G. van Schaik, J.P. Veldhuisen, B.H.P. van den Borne, W. Wouda, and T. Dijkstra. 2006. Effect of *Neospora caninum*-serostatus on culling, reproductive performance and milk production in Dutch dairy herds with and without a history of *Neospora caninum*-associated abortion epidemics. Prev. Vet. Med. 77:186–198. doi:10.1016/j.prevetmed.2006.07.003

Bellet, C., M.J. Green, M. Vickers, A. Forbes, E. Berry, and J. Kaler. 2016. *Ostertagia* spp., rumen fluke and liver fluke single- and poly-infections in cattle: an abattoir study of prevalence and production impacts in England and Wales. Prev. Vet. Med. 132: 98–106. doi:10.1016/j.prevetmed.2016.08.010

Bermingham, M.L., S.J. More, M. Good, A.R. Cromie, I.M. Higgins, S. Brotherstone, and D.P. Berry. 2009. Genetics of tuberculosis in Irish Holstein-Friesian dairy herds. J. Dairy Sci. 92:3447–3456. doi:10.3168/jds.2008-1848

Berry, D.P., J. Kearney, K. Twomey, and R. Evans. 2013. Genetics of reproductive performance in seasonal calving dairy cattle production systems. Ir. J. Agric. Food Res. 52:1–16.

Berry, D.P., and R.D. Evans. 2014. Genetics of reproductive performance in seasonal calving beef cows and its association with performance traits. J. Anim. Sci. 92: 1412–1422. doi:10.2527/jas.2013-6723

Berry, D.P., R.D. Evans, and S. Mc Parland. 2011a. Evaluation of bull fertility in dairy and beef cattle using cow

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

field data. Theriogenology 75:172–181. doi:10.1016/j.theriogenology.2010.08.002

Berry, D.P., M.L. Bermingham, M. Good, and S.J. More. 2011b. Genetics of animal health and disease in cattle. Ir Vet J 64:1–10. doi:10.1186/2046-0481-64-5

Berry, D.P., N.C. Friggens, M. Lucy, and J.R. Roche. 2016. Milk production and fertility in cattle. Annu Rev Anim Biosci. 4:269–290. doi:10.1146/annurev-animal-021815-111406

Berry, D.P., E. Wall, and J.E. Pryce. 2014. Genetics and genomics of reproductive performance in dairy and beef cattle. Animal. 8:105–121. doi:10.1017/S1751731114000743

Bisset, S., A. Vlassoff, C. Morris, B. Southey, R. Baker, and A. Parker. 1992. Heritability of and genetic correlations among faecal egg counts and productivity traits in Romney sheep. New Zeal. J. Agr. Res. 35:51–58.

Bloemhoff, Y., M. Danaher, F. Andrew, E. Morgan, G. Mulcahy, C. Power, and R. Sayers. 2014. Parasite control practices on pasture-based dairy farms in the Republic of Ireland. Vet. Parasitol. 204:352–363. doi:10.1016/j.vetpar.2014.05.029

Bloemhoff, Y., A. Forbes, B. Good, E. Morgan, G. Mulcahy, C. Strube, and R. Sayers. 2015. Prevalence and seasonality of bulk milk antibodies against *Dictyocaulus viviparus* and *Ostertagia ostertagi* in Irish pasture-based dairy herds. Vet. Parasitol. 209:108–116. doi:10.1016/j.vetpar.2015.01.021

Brown, T.R., and T.E. Lawrence. 2010. Association of liver abnormalities with carcass grading performance and value. J. Anim. Sci. 88:4037–4043. doi:10.2527/jas.2010–3219

Byrne, A.W., S. McBride, A. Lahuerta-Marin, M. Guelbenzu, J. McNair, R.A. Skuce, and S.W.J. McDowell. 2016. Liver fluke (*Fasciola hepatica*) infection in cattle in Northern Ireland: a large-scale epidemiological investigation utilising surveillance data. Parasit & Vectors. 9:209. doi:10.1186/s13071-016-1489-2

Canatan, H., I. Polat, R. Bayramoglu, S. Kuplulu, M. Vural, and E. Aktug. 2014. Effects of *Neospora caninum* on reproductive performance and the efficacy of treatment with a combination of sulphadiazine-trimethoprim and toltrazuril: a longitudinal field study. Vet Med (Praha) 59:22–28.

Charlier, J., E. Claerebout, L. Duchateau, and J. Vercruysse. 2005. A survey to determine relationships between bulk tank milk antibodies against *Ostertagia ostertagi* and milk production parameters. Vet. Parasitol. 129:67–75. doi:10.1016/j.vetpar.2004.11.024

Charlier, J., L. Duchateau, E. Claerebout, D. Williams, and J. Vercruysse. 2007. Associations between anti-*Fasciola hepatica* antibody levels in bulk-tank milk samples and production parameters in dairy herds. Prev. Vet. Med. 78:57–66. doi:10.1016/j.prevetmed.2006.09.010

Charlier, J., A. De Cat, A. Forbes, and J. Vercruysse. 2009a. Measurement of antibodies to gastrointestinal nematodes and liver fluke in meat juice of beef cattle and associations with carcass parameters. Vet. Parasitol. 166:235–240. doi:10.1016/j.vetpar.2009.09.040

Charlier, J., M. Hostens, J. Jacobs, B. Ranst, L. Duchateau, and J. Vercruysse. 2012. Integrating fasciolosis control in the dry cow management: the effect of closantel treatment on milk production. PLoS ONE. 7:e43216. doi:10.1371/journal.pone.0043216

Charlier, J., J. Höglund, G. von Samson-Himmelstjerna, P. Dorny, and J. Vercruysse. 2009b. Gastrointestinal nematode infections in adult dairy cattle: Impact on production, diagnosis and control. Vet. Parasitol. 164:70–79. doi:10.1016/j.vetpar.2009.04.012

Charlier, J., J. Vercruysse, J. Smith, R. Vanderstichel, H. Stryhn, E. Claerebout, and I. Dohoo. 2010. Evaluation of anti-*Ostertagia ostertagi* antibodies in individual milk samples as decision parameter for selective anthelmintic treatment in dairy cows. Prev. Vet. Med. 93:147–152. doi:10.1016/j.prevetmed.2009.10.002

Claridge, J., P. Diggle, C.M. McCann, G. Mulcahy, R. Flynn, J. McNair, S. Strain, M. Welsh, M. Baylis, and D.J.L. Williams. 2012. *Fasciola hepatica* is associated with the failure to detect bovine tuberculosis in dairy cattle. Nat Commun. 3:853. doi:10.1038/ncomms1840

Coppieters, W., T.H.M. Mes, T. Druet, F. Farnir, N. Tamma, C. Schrooten, A.W.C.A. Cornelissen, M. Georges, and H.W. Ploeger. 2009. Mapping QTL influencing gastrointestinal nematode burden in Dutch Holstein-Friesian dairy cattle. BMC Genomics 10:96. doi:10.1186/1471-2164-10-96

Dubey, J.P., G. Schares, and L.M. Ortega-Mora. 2007. Epidemiology and control of Neosporosis and *Neospora caninum*. Clin. Microbiol. Rev. 20:323–367. doi:10.1128/CMR.00031-06

Dubey, J.P., and G. Schares. 2011. Neosporosis in animals–the last five years. Vet. Parasitol. 180:90–108. doi:10.1016/j.vetpar.2011.05.031

Edmonson, A.J., I.J. Lean, L.D. Weaver, T. Farver, and G. Webster. 1989. A body condition scoring chart for Holstein dairy cows. J. Dairy Sci. 72:68–78. doi:10.3168/jds.S0022-0302(89)79081-0

El-Tarabany, M.S. 2015. Impact of stillbirth and abortion on the subsequent fertility and productivity of Holstein, Brown Swiss and their crosses in subtropics. Trop Anim Health Prod. 47:1351–1356. doi:10.1007/s11250-015-0870-z

Englishby, T.M., G. Banos, K.L. Moore, M.P. Coffey, R.D. Evans, and D.P. Berry. 2016. Genetic analysis of carcass traits in beef cattle using random regression models. J. Anim. Sci. 94: 1354–1364. doi:10.2527/jas.2015-0246

Flynn, R.J., C. Mannion, O. Golden, O. Hacariz, and G. Mulcahy. 2007. Experimental *Fasciola hepatica* infection alters responses to tests used for diagnosis of bovine tuberculosis. Infect. Immun. 75:1373–1381. doi:10.1128/iai.01445-06

Forbes, A.B., J.Vercruysse, and J. Charlier. 2008. A survey of the exposure to *Ostertagia ostertagi* in dairy cow herds in Europe through the measurement of antibodies in milk samples from the bulk tank. Vet. Parasitol. 157:100–107. doi:10.1016/j.vetpar.2008.06.023

Gädicke, P., R. Vidal, and G. Monti. 2010. Economic effect of bovine abortion syndrome in commercial dairy herds in Southern Chile. Prev. Vet. Med. 97:9–19. doi:10.1016/j.prevetmed.2010.07.008

Gilmour, A.R., B.J. Gogel, B.R. Cuillis, and R. Thompson. 2009. ASReml User Guide Release 3.0. Hemel Hempstead: VSN International Ltd.

González-Warleta, M., J.A. Castro-Hermida, C. Carro-Corral, and M. Mezo. 2011. Anti-*Neospora caninum* antibodies in milk in relation to production losses in dairy cattle. Prev. Vet. Med. 101:58–64. doi:10.1016/j.prevetmed.2011.04.019

Grummer, R.R. 2008. Nutritional and management strategies for the prevention of fatty liver in dairy cattle. Vet. J. 176:10–20. doi:10.1016/j.tvjl.2007.12.033

Haddad, J.P.A., I.R. Dohoo, and J.A. VanLeewen. 2005. A review of *Neospora caninum* in dairy and beef cattle—a Canadian perspective. Can. Vet. J. 46:230–243.

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

Hall, C., M. Reichel, and J. Ellis. 2005. Neospora abortions in dairy cattle: diagnosis, mode of transmission and control. Vet. Parasitol. 128:231–241. doi: 10.1016/j.vetpar.2004.12.012

Heriazon, A., M. Quinton, F. Miglior, K.E. Leslie, W. Sears, and B.A. Mallard. 2013. Phenotypic and genetic parameters of antibody and delayed-type hypersensitivity responses of lactating Holstein cows. Vet. Immunol. Immunopathol. 154: 83–92. doi:10.1016/j.vetimm.2013.03.014

Hernandez, J., C. Risco, and A. Donovan. 2001. Association between exposure to *Neospora caninum* and milk production in dairy cows. J. Am. Vet. Med. Assoc. 219: 632–635. doi:10.2460/javma.2001.219.632

Hobson, J.C., T.F. Duffield, D. Kelton, K. Lissemore, S.K. Hietala, K.E. Leslie, B. McEwen, G. Cramer, and A.S. Peregrine. 2002. *Neospora caninum* serostatus and milk production of Holstein cattle. J. Am. Vet. Med. Assoc. 221:1160–1164.

Howell, A., M. Baylis, R. Smith, G. Pinchbeck, and D. Williams. 2015. Epidemiology and impact of *Fasciola hepatica* exposure in high-yielding dairy herds. Prev. Vet. Med. 121:41–48. doi:10.1016/j.prevetmed.2015.05.013

Kaiko, G.E., J.C. Horvat, K.W. Beagley, and P.M. Hansbro. 2008. Immunological decision-making: how does the immune system decide to mount a helper T-cell response? Immunology 123:326–338. doi:10.1111/j.1365-2567.2007.02719.x

Innes, E.A. 2007. The host-parasite relationship in pregnant cattle infected with *Neospora caninum*. Parasitology 134:1903–1910. doi:10.1017/S0031182007000194

Lunden, A., J. Marks, S.W. Maley, and E.A. Innes. 1998. Cellular immune responses in cattle experimentally infected with *Neospora caninum*. Parasite Immunol. 20:519–526.

May, K., K. Brügemann, T. Yin, C. Scheper, C. Strube, and S. König. 2017. Genetic line comparisons and genetic parameters for endoparasite infections and test-day milk production traits. J. Dairy Sci. doi:10.3168/jds.2017-12901

McNeilly, T.N., and A.J. Nisbet. 2014. Immune modulation by helminth parasites of ruminants: implications for vaccine development and host immune competence. Parasite 21:51. doi:10.1051/parasite/2014051

McRae, K.M., M.J. Stear, B. Good, and O.M. Keane. 2015. The host immune response to gastrointestinal nematode infection in sheep. Parasite Immunol. 37:605–613. doi:10.1111/pim.12290

Mezo, M., M. González-Warleta, J.A. Castro-Hermida, L. Muiño, and F.M. Ubeira. 2011. Association between anti-*F. hepatica* antibody levels in milk and production losses in dairy cows. Vet. Parasitol. 180:237–242. doi:10.1016/j.vetpar.2011.03.009

Morris, C., R. Green, N. Cullen, and S. Hickey. 2003. Genetic and phenotypic relationships among faecal egg count, anti-nematode antibody level and live weight in Angus cattle. Anim. Sci. 76: 167–174. doi: 10.1017/S135772980005342X

Morris, C., M. Wheeler, B. Hosking, T. Watson, A. Hurford, B. Foote, and J. Foote. 1997. Genetic parameters for milk yield and faecal nematode egg count in Saanen does. New Zeal. J. Agr. Res. 40:523–528.

Murphy, T.M., K.N. Fahy, A. McAuliffe, A.B. Forbes, T.A. Clegg, and D.J. O'Brien. 2006. A study of helminth parasites in culled cows from Ireland. Prev. Vet. Med. 76:1–10. doi:10.1016/j.prevetmed.2006.04.005

Nogalski, Z., and D. Piwczyński. 2012. Association of length of pregnancy with other reproductive traits in dairy cattle. Asian-australas. J. Anim. Sci. 25:22–27. doi:10.5713/ajas.2011.11084

Norman, H.D., J.R. Wright, M.T. Kuhn, S.M. Hubbard, J.B. Cole, and P.M. VanRaden. 2009. Genetic and environmental factors that affect gestation length in dairy cattle. J Dairy Sci. 92:2259–2269. doi:10.3168/jds.2007-0982

Oliveira, L.J., N. Mansourri-Attia, A.G. Fahey, J. Browne, N. Forde, J.F. Roche, P. Lonergan, and T. Fair. 2013. Characterization of the Th profile of the bovine endometrium during the oestrous cycle and early pregnancy. PLoS ONE. 8:e75571. doi:10.1371/journal.pone.0075571

Ould-Amrouche, A., F. Klein, C. Osdoit, H.O. Mohammed, A. Touratier, M. Sanaa, and J.-P. Mialot. 1999. Estimation of *Neospora caninum* seroprevalence in dairy cattle from Normandy, France. Vet Res. 30: 531–538. doi: hal-00902593

Pan, Y., G.B. Jansen, T.F. Duffield, S. Hietala, D. Kleton, C.Y. Lin, and A.S. Peregrine. 2004. Genetic susceptibility to *Neospora canium* infection in Holstein cattle in Ontario. J. Dairy. Sci. 87: 3967–3975. doi:10.3168/jds.S0022-0302(04)73537-7

Pabiou, T., W.F. Fikse, A.R. Cromie, M.G. Keane, A. Näsholm, and D.P. Berry. 2011. Use of digital images to predict carcass cut yields in cattle. Livest. Sci. 137: 130–140. doi:10.1016/j.livsci.2010.10.012

Pollott, G., and J. Greeff. 2004. Genetic relationships between faecal egg count and production traits in commercial Merino sheep flocks. Anim. Sci. 79:21–32. doi: 10.1017/S1357729800054497

Prayaga, K.C., N.J. Corbet, D.J. Johnston, M.L. Wolcott, G. Fordyce, and H.M. Burrow. 2009. Genetics of adaptive traits in heifers and their relationship to growth, pubertal and carcass traits in two tropical beef cattle genotypes. Vet. Med. Sci. 49:413–425. doi:https://doi.org/10.1071/EA08247

Reichel, M.P., M. Alejandra Ayanegui-Alcérreca, L.F.P. Gondim, and J.T. Ellis. 2013. What is the global economic impact of *Neospora caninum* in cattle—The billion dollar question. Int. J. Parasitol. 43:133–142. doi:10.1016/j.ijpara.2012.10.022

Roche, J.R., N.C. Friggens, J.K. Kay, M.W. Fisher, K.J. Stafford, and D.P. Berry. 2009. Invited review: body condition score and its association with dairy cow productivity, health, and welfare. J. Dairy Sci. 92:5769–5801. doi:10.3168/jds.2009-2431

Sanchez-Vazquez, M.J., and F.I. Lewis. 2013. Investigating the impact of fasciolosis on cattle carcase performance. Vet Parasitol. 193:307–311. doi:10.1016/j.vetpar.2012.11.030

Sanchez, J., A. Nodtvedt, I. Dohoo, and L. DesCôteaux. 2002. The effect of eprinomectin treatment at calving on reproduction parameters in adult dairy cows in Canada. Prev. Vet. Med. 56:165–177. doi:10.1016/s0167-5877(02)00118-6

Sanchez, J., and I. Dohoo. 2002. A bulk tank milk survey of *Ostertagia ostertagi* antibodies in dairy herds in Prince Edward Island and their relationship with herd management factors and milk yield. Can Vet J. 43:454–459.

Sanchez, J., F. Markham, I. Dohoo, J. Sheppard, G. Keefe, and K. Leslie. 2004. Milk antibodies against *Ostertagia ostertagi*: relationships with milk IgG and production parameters in lactating dairy cattle. Vet Parasitol. 120:319–330. doi:10.1016/j.vetpar.2004.01.010

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

Schweizer, G., U. Braun, P. Deplazes, and P.R. Torgerson. 2005. Estimating the financial losses due to bovine fasciolosis in Switzerland. Vet. Rec. 157:188–193. doi:10.1136/vr.157.7.188

Sekiya, M., A. Zintl, and M.L. Doherty. 2013. Bulk milk ELISA and the diagnosis of parasite infections in dairy herds: a review. Ir Vet J. 66:14. doi:10.1186/2046-0481-66-14

Thompson-Crispi, K.A., A. Sewalem, F. Miglior, and B.A. Mallard. 2012. Genetic parameters of adaptive immune response traits in Canadian Holsteins. J. Dairy Sci. 95:401–409. doi:10.3168/jds.2011-4452

Thurmond, M., and S. Hietala. 1997. Effect of *Neospora caninum* infection on milk production in first-lactation dairy cows. J. Am. Vet. Med. Assoc. 210:672–674.

Tiwari, A., J.A. VanLeeuwen, I.R. Dohoo, G.P. Keefe, J.P. Haddad, R. Tremblay, H.M. Scott, and T. Whiting. 2007. Production effects of pathogens causing bovine leukosis, bovine viral diarrhea, paratuberculosis, and neosporosis. J. Dairy Sci. 90:659–669. doi:10.3168/jds.S0022-0302(07)71548-5

Twomey, A.J., R.G. Sayers, R.I. Carroll, N. Byrne, E.O. Brien, M.L. Doherty, J.C. McClure, D.A. Graham, and D.P. Berry. 2016. Genetic parameters for both a liver damage phenotype caused by *F. hepatica* and antibody response to *F. hepatica* phenotype in dairy and beef cattle. J. Anim. Sci. 94:4109–4119. doi:10.2527/jas.2016-0621

VanRaden, P.M., and A.H. Sanders. 2003. Economic merit of crossbred and purebred US dairy cattle. J. Dairy Sci. 86:1036–1044. doi:10.3168/jds.S0022-0302(03)73687-X

Yang, L., Y. Wang, S. Wang, and L. Zhang. 2016. Changes in expression of Th1 and Th2 cytokines in bovine peripheral blood mononuclear cells during early pregnancy. Indian J. Anim. Res. 50:466–470. doi:10.18805/ijar.5538

Zhang, L., Y. Xia, F. Tang, S. Li, L. Yang, and B. Wang. 2015. The regulation of intrauterine immune cytokines and chemokines during early pregnancy in the bovine. Large Anim. Rev. 21:23–31.

Downloaded from https://academic.oup.com/jas/article-abstract/96/2/407/4828196
by Alasdair Simpson user
on 11 May 2018

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.