Genetic variability in the humoral immune response to bovine herpesvirus-1 infection in dairy cattle and genetic correlations with performance traits

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ABSTRACT

Bovine herpesvirus-1 (BoHV-1) is a viral pathogen of global significance that is known to instigate several diseases in cattle, the most notable of which include infectious bovine rhinotracheitis and bovine respiratory disease. The genetic variability in the humoral immune response to BoHV-1 has, to our knowledge, not ever been quantified. Therefore, the objectives of the present study were to estimate the genetic parameters for the humoral immune response to BoHV-1 in Irish female dairy cattle, as well as to investigate the genetic relationship between the humoral immune response to BoHV-1 with milk production performance, fertility performance, and animal mortality. Information on antibody response to BoHV-1 was available to the present study from 2 BoHV-1 sero-prevalence research studies conducted between the years 2010 to 2015, inclusive; after edits, BoHV-1 antibody test results were available on a total of 7,501 female cattle from 58 dairy herds. National records of milk production (i.e., 305-d milk yield, fat yield, protein yield, and somatic cell score; n = 1,211,905 milk-recorded cows), fertility performance (i.e., calving performance, pregnancy diagnosis, and insemination data; n = 2,365,657 cows) together with animal mortality data (i.e., birth, farm movement, death, slaughter, and export events; n = 12,853,257 animals) were also available. Animal linear mixed models were used to quantify variance components for BoHV-1 as well as to estimate genetic correlations among traits. The estimated genetic parameters for the humoral immune response to BoHV-1 in the present study (i.e., heritability range: 0.09 to 0.16) were similar to estimates previously reported for clinical signs of bovine respiratory disease in dairy and beef cattle (i.e., heritability range: 0.05 to 0.11). Results from the present study suggest that breeding for resistance to BoHV-1 infection could reduce the incidence of respiratory disease in cattle while having little or no effect on genetic selection for milk yield or milk constituents (i.e., genetic correlations ranged from −0.13 to 0.17). Moreover, even though standard errors were large, results also suggest that breeding for resistance to BoHV-1 infection may indirectly improve fertility performance while also reducing the incidence of mortality in older animals (i.e., animals >182 d of age). Results can be used to inform breeding programs of potential genetic gains achievable for resistance to BoHV-1 infection in cattle.

Key words: bovine herpesvirus-1, infectious bovine rhinotracheitis, bovine respiratory disease, animal health

INTRODUCTION

Infectious bovine rhinotracheitis (**IBR**) is a contagious viral respiratory disease of cattle caused by infection with bovine herpesvirus-1 (**BoHV-1**). Listed as a notifiable disease by the World Organization for Animal Health, IBR is of global importance and may even be considered a disease of trade, especially within the European Union (**EU**). Several countries and regions have achieved an IBR-free status according to Article 10 of EU Council Directive 64/432/EEC, whereas others have approved eradication programs according to Article 9 of the same Directive. In both cases, Commission 2007/584/EC grants them additional guarantees with respect to trade with other member states of the EU. Furthermore, Council Directive 2003/43/EC prohibits the entry of bulls with BoHV-1 antibodies to bovine semen collecting centers in member states or third countries where semen is collected for intra-community trade or import to the EU. Cowley et al. (2011) reported that 74.9% of Irish dairy and beef herds were sero-positive for BoHV-1. Although no national IBR control or eradication program currently exists in Ireland, Animal Health Ireland (www.animalhealthireland

.ie) is currently developing the technical and business case for such a program.

Clinical signs of IBR in cattle include reduced appetite (Muylkens et al., 2007), elevated body temperature (Thompson et al., 1965; Muylkens et al., 2007), conjunctivitis and inflammation of the nares and trachea (Thompson et al., 1965), reduced milk production (Hage et al., 1998), compromised reproductive performance (Graham, 2013), and death (AFBI and DAFM, 2016). Bovine herpesvirus-1 infected animals are also predisposed to secondary infections (Yates, 1982). The severity of clinical signs arising from BoHV-1 infection vary depending upon the immune status of the animal (Muylkens et al., 2007) and the virulence of the BoHV-1 strain (Kaashoek et al., 1996). Infection with BoHV-1 for the very first time (i.e., primary infection) typically results in clinical signs and the shedding of BoHV-1 (Engels and Ackermann, 1996). Following primary infection, animals become latently infected, no longer exhibiting clinical signs, synthesizing or shedding BoHV-1 (Engels and Ackermann, 1996), but continuing to harbor the virus in their nervous system (Muylkens et al., 2007). These latently infected animals have the potential to reactivate and re-excrete BoHV-1 (Geraghty et al., 2012), generating new primary infections during periods of stress, corticosteroid treatment, or when re-exposed to circulating BoHV-1. Latently infected animals are lifelong carriers of BoHV-1 and potential transmitters of the virus between herds. Transmission of BoHV-1 can also occur by airborne spread, use of semen from infected bulls, or through the use of contaminated equipment or clothing.

To our knowledge, no study has attempted to quantify the genetic variability in the humoral immune response to BoHV-1 in dairy cattle or its association with performance. However, evidence of genetic variability in the prevalence of clinical signs to other viral diseases in cattle does exist. Muggli-Cockett et al. (1992) identified breed differences among 9 purebred and 3 composite beef breeds in clinical signs of bovine respiratory disease (**BRD**) with Braunvieh and Pinzgauer breeds exhibiting a greater prevalence of BRD than the other purebred and composite breeds. Heringstad et al. (2008) also reported a heritability estimate for BRD of 0.05 in a population of Norwegian Red calves, although in that study BRD was unlikely to have been caused by BoHV-1 because the Norwegian cattle population is deemed free of IBR (Heringstad et al., 2008).

The objective of the present study was to quantify the genetic variation present among Irish dairy cattle females in their humoral immune response to BoHV-1 and the genetic association of humoral immune response to BoHV-1 with milk and fertility performance

traits as well as animal mortality. Results can be used to determine the feasibility of genetic selection in cattle for enhanced resistance to BoHV-1 through either selection for resistant breeding animals or exclusion of susceptible animals from breeding stock. Furthermore, results can be used to determine if current breeding goals for performance traits may be influencing the humoral immune response to BoHV-1.

MATERIALS AND METHODS

Data

The BoHV-1 data originated from 2 Irish sero-prevalence studies undertaken by the Animal and Grassland Research and Innovation Centre, Teagasc, Moorepark, Fermoy, Co. Cork, Ireland, between the years 2010 and 2015, inclusive. National records of milk production performance and fertility performance were also available from the Irish Cattle Breeding Federation (**ICBF**) database for the years 2010 to 2015, inclusive. Furthermore, national animal mortality records were available from the ICBF database for animals that were born between the years 2001 and 2015, inclusive.

BoHV-1 Data

One BoHV-1 data set originated from a sero-prevalence study of BoHV-1 conducted between October 2010 and February 2013, which consisted of 6,534 female cattle from 24 dairy herds. Herds that participated in the study were Teagasc research farms or participants in the Dairy Management Information System, a system that collates producer-recorded stock, farm inputs, production, and reproduction information (Crosse, 1991). The average number of cows per herd over the study period was 193, ranging from 71 to 758 cows. Holstein, Jersey, Norwegian Red, and Friesian were the main breeds, accounting for 96% of animals. Blood samples were collected from each animal at least once during the 4-yr period and tested for the presence of BoHV-1 antibodies. Each herd's vaccination history for each year was also collected. The only information available pertaining to herd-level vaccination status was whether the herd was either not vaccinating or vaccinating with a marker vaccine; information on the frequency of vaccination or the type of vaccination used (i.e., live or inactivated vaccine) was not available. Herd-level vaccination status was used to interpret the test kit used for detecting animal-level BoHV-1 antibodies. Currently, 2 types of test kits are available to detect BoHV-1 antibodies (i.e., gB and gE test kits). Marker vaccines, non-marker vaccines, and field virus

each cause the production of antibodies to the glycoprotein B of BoHV-1 virus; therefore, gB antibody tests detect BoHV-1 antibodies derived from marker vaccines, non-marker vaccines, or field virus. On the other hand, only non-marker vaccines and field virus cause the production of antibodies to glycoprotein E of BoHV-1 virus; marker vaccines do not contain glycoprotein E and thus they do not cause the production of antibodies to the glycoprotein E of BoHV-1 virus; therefore, gE antibody tests detect BoHV-1 antibodies derived only from non-marker vaccines or field virus (World Organisation for Animal Health, 2010). As the only type of vaccine licensed in the Republic of Ireland is the marker vaccine (S.I. No. 528 of 2002), animals with BoHV-1 antibodies in vaccinated herds (n = 13 herds) were detected using a gE test kit; animals with BoHV-1 antibodies in nonvaccinated herds (n = 11 herds) were detected using a gB test kit. All antibody testing was performed on individual blood samples at Enfer Diagnostics (Newhall, Naas, Co. Kildare, Ireland) using an IDEXX ELISA test kit (www.idexx .com), appropriate for the vaccination status of each herd. Fifty-two percent of all samples were analyzed using the gE test kit. Sample-to-positive (S/P) ratio was used to classify test results as positive, negative, or inconclusive; the cut-off thresholds used to classify tests results as positive, negative, or inconclusive were in accordance with the manufacturer's guidelines for each respective test. For vaccinated animals, a positive antibody response was identified by an S/P ratio ≤0.60, whereas a negative antibody response was identified by an S/P ratio ≥0.70; an inconclusive antibody response was identified by an S/P ratio that was intermediate to a positive antibody response and a negative antibody response. For nonvaccinated animals, a positive antibody response was identified by an S/P ratio ≥0.55, whereas a negative antibody response was identified by an S/P ratio ≤0.50; an inconclusive antibody response was identified by an S/P ratio that was intermediate to a positive antibody response and a negative antibody response. Inconclusive test results (n = 16) were removed from the data set. When gE and gB test kit results were combined, the overall apparent prevalence of BoHV-1 antibody positive animals in the data set was 26%.

The second data set originated from a separate field trial carried out on 10,669 cows from 67 dairy herds during the 2015 calendar year. The aim of this trial was to collect accurate phenotypic health and performance data from a large sample of the national dairy cow population. Each participating herd was a member of HerdPlus, a breeding information service provided by ICBF, and had a history of accurate and timely performance recording. For logistical reasons, the participating herds were located within a 1-h drive from Moorepark Research Centre. The average herd size was 157 cows, ranging from 39 to 527 cows. Holstein, Jersey, and Friesian were the main breeds, accounting for 97% of the cows. Throughout the trial, producers recorded all cow-related diseases and treatments on the ICBF database. Each herd's vaccination history for that year was collected as part of a survey and later verified. The only information available pertaining to herd-level vaccination status was whether the herd was either not vaccinating or vaccinating with a marker vaccine; information on the frequency of vaccination and the type of vaccination used (i.e., live or inactivated vaccine) was not available. Blood samples were collected from each cow in the autumn of 2015 and analyzed for the presence of BoHV-1 antibodies. The BoHV-1 antibody testing, appropriate for the vaccination status of each herd (i.e., 55 herds were vaccinating, whereas 12 herds were not vaccinating), was carried out on individual blood samples using either an IDVet gE ELISA (www .id-vet.com) or a Qiagen gB ELISA (www.qiagen.com) test kit at FarmLab Diagnostics (Emlagh, Elphin, Co. Roscommon, Ireland). Eighty-six percent of tests were undertaken using the gE test kit. Sample-to-positive ratio was used to classify test results as positive or negative; the cut-off thresholds used to classify tests results as positive, negative, or inconclusive were in accordance with the manufacturer's guidelines for each respective test. For vaccinated animals, a positive antibody response was identified by an S/P ratio ≤0.40, whereas a negative antibody response was identified by an S/P ratio ≥0.50; an inconclusive antibody response was identified by an S/P ratio that was intermediate to a positive antibody response and a negative antibody response. For nonvaccinated animals, a positive antibody response was identified by an S/P ratio ≥0.55, whereas a negative antibody response was identified by an S/P ratio ≤0.45; an inconclusive antibody response was identified by an S/P ratio that was intermediate to a positive antibody response and a negative antibody response. Inconclusive test results (n = 101) were removed from the data set. When gE and gB test kit results were combined, the overall apparent prevalence of cows that had a positive antibody response to BoHV-1 in the data set was 23%.

After combining both data sets, 19,353 BoHV-1 antibody test results were available on 16,242 female cattle from 81 dairy herds. As well as considering dichotomized BoHV-1 traits (i.e., positive or negative), continuous BoHV-1 traits were also considered further (i.e., S/P ratio for animals considered positive or negative based on the binary trait). To facilitate a combined

analysis of tests carried out using gE test kits from different manufacturers (i.e., IDEXX or IDVet, where the dependent variable was the continuous trait), test results were standardized to a common variance and a mean of zero [i.e., (test value − mean test value of the respective test kit manufacturer) ÷ standard deviation of test values for the respective test kit manufacturer]. Similarly, test results from samples carried out using gB test kits from different manufacturers (i.e., IDEXX or Qiagen) were also standardized; test results carried out using differing test kits (i.e., gE or gB) were not standardized to a common variance or a mean of zero.

BoHV-1 Edits

Test results for animals sired by a beef breed (n = 166) and nulliparous animals that were either less than 182 d of age (n = 1) or more than 908 d of age (n = 158) on the date of blood sample collection were discarded. As a comprehensive history of herd vaccination status was not available for older cows, BoHV-1 test results from ≥6th parity cows (n = 1,788) were also removed. Furthermore, test results from cows that calved less than 545 d of age (n = 4) were removed as were test results from cows that calved more than 545 d from the parity median (n = 68) or cows that did not calve within 545 d of the date of blood sample collection (n = 219). To maximize the likelihood of equal lifetime exposure to BoHV-1, only animals born in the herd that they were blood sampled in were retained; 15,019 test results from 12,823 animals in 81 herds remained. Moreover, only the most recent test result for animals deemed exposed to BoHV-1 (described herein) was considered further; a total of 7,501 animals from 58 herds remained.

BoHV-1 Exposure Definitions

In Irish dairy herds, nulliparous females (i.e., females ≤30 mo without a calving event) are typically managed separately from cows (i.e., females with ≥1 calving event); as a result, exposure to BoHV-1 was defined in each herd-management group separately. Exposure to BoHV-1 was defined in 2 ways: the first, a relaxed definition, considered a herd's vaccination status, and the second definition, a strict definition, did not consider a herd's vaccination status.

Relaxed Definition. An animal in a nonvaccinated herd-management group was deemed exposed where that animal was tested for BoHV-1 antibodies in the same year as at least one animal that returned a positive BoHV-1 test result, irrespective of that animal's age. An animal in a vaccinated herd-management group was

deemed exposed where that animal was either older or born in the same year as at least one animal that returned a positive BoHV-1 test result, provided both animals were tested for BoHV-1 antibodies in the same year.

Strict Definition. An animal that was both born and tested for BoHV-1 antibodies in the same year as at least one animal that returned a positive BoHV-1 test result was deemed exposed; this definition applied to both animals in vaccinated and nonvaccinated herds.

Milk Production Performance Data

Milk production performance data were available for the years 2010 and 2015, inclusive for 2,647,818 lactations from 1,211,905 milk-recorded cows in 10,421 dairy herds; milk performance traits included 305-d milk yield, fat yield, protein yield, and SCC divided by 1,000 for cows in their first to fifth parity, inclusive. Fat concentration, protein concentration, and fat-to-protein ratio were calculated from the available data. Somatic cell score was derived from the natural logarithm of SCC after dividing by 1,000. Lactations with any milk performance trait missing or deviating >3 standard deviation units from the parity mean (n = 108,990 lactations) were discarded as were lactations from cows that produced twins (n = 41,552 lactations) or lactations that began fewer than 300 d following a cow's most recent calving (n = 17,585 lactations). In addition, lactations from cows that calved <545 d of age (n = 1,523 lactations) or >545 d from the parity median (n = 67,092 lactations) were discarded. Moreover, lactations from cows that did not reside in their birth herd were also removed; 286,374 lactations from 152,230 cows in 7,327 herds were removed. A total of 2,124,836 lactations from 1,017,009 cows in 9,028 herds remained.

Fertility Performance Data

Calving performance (n = 5,699,148), pregnancy diagnoses (n = 1,254,358), together with natural service and AI data (n = 4,257,607), were available for 2,365,657 cows in 18,069 dairy herds for the years 2010 to 2015, inclusive. Where possible, 11 fertility performance traits were derived for each cow-parity separately for cows in their first to fifth parity, inclusive. Prior to trait definition, where 2 services occurred within 5 d of each other, the initial service was discarded. Fertility performance records from cows that calved <545 d of age (n = 1,586 records) or >545 d from the parity median (n = 266,567 records) were discarded. In addition, cow parities that resulted in twin progeny (n

= 79,244) were removed as were fertility performance records from cows that did not reside in their birth herd (n = 775,174 records).

Fertility Performance Trait Definition

Fertility performance traits considered in the present study were described in detail by Berry et al. (2013). The traits considered were age at first calving (**AFC**), calved during the initial 42 d of a herd's calving season (**CALV42**), calving interval (**CIV**), calving to first service interval (**CFS**), submission rate in the initial 21 d of a herd's breeding season (**SR21**), number of services (**NSV**), calving to conception interval (**CCI**), first service to conception interval (**FSC**), pregnant to first service (**PRFS**), pregnant during the initial 21 d of a herd's breeding season (**PR42**), and survival (**SURV**). The 11 fertility traits are described in the present study under 4 broad sections that include (1) calving, (2) breeding, (3) conception, and (4) survival.

Calving. Age at first calving was defined as the age, in days, when a female first calved; cows that calved for the first time >1,240 d of age (n = 4,993 cows) were not considered for AFC. As Irish herds typically endeavor to achieve compact calving systems, calving seasons were defined separately for each herd to capture the distinct periods in a herd where many cows calve in close proximity to each other. A herd's calving season was defined for nulliparous and pluriparous animals separately using methods described by Berry et al. (2013). The onset of a calving season was triggered by a calving event that was followed by at least 4 subsequent calvings occurring within 14 d of the initial calving. The calving season concluded when a calving event was not followed by a subsequent calving in the following 21 d. Only calving seasons with at least 5 nulliparous animals or at least 20 multiparous cows were considered where the calving period was 35 to 200 d in length. The trait CALV42 was defined as whether a cow calved (CALV42 = 1) or did not calve (CALV42 = 0) within the initial 42 d of a herd's calving season; a cow that did not calve within a calving season was not considered for CALV42. Calving interval was defined as the number of days between consecutive calving events; where a cow was serviced within 150 d of calving, CIV records between 300 and 800 d, inclusive, were considered, and otherwise CIV records ranging from 300 to 600 d were considered.

Breeding. Calving to first service interval was calculated as the number of days between a cow's calving and her first service event (either AI or natural service); only CFS records between 10 and 250 d, inclusive, were retained. To achieve compact calving systems, producers must operate a compact breeding system. Thus, breeding seasons were defined using a similar methodology to calving seasons; breeding seasons were defined for primiparous and multiparous animals combined. A breeding season began when 5 cows were serviced within 14 d of an initial service. A breeding season terminated when a service was not followed by a subsequent service in the following 21 d. Only breeding seasons between 35 and 140 d in length were considered where there were more than 20 cows per breeding season. Submission rate in the initial 21 d of a herd's breeding season was defined as whether a cow was serviced for the first time (SR21 = 1) or was not serviced for the first time (SR21 = 0) in the initial 21 d of a herd's breeding season, irrespective of her calving date; a cow that was serviced for the first time either before or after a breeding season was not considered for SR21. Number of services was defined as the total number of services a cow received per parity; where a cow received more than 10 services, NSV was fixed to 10. To eliminate herds that typically record only a cow's final service, all fertility performance records were discarded from herd-years that documented only one service for >80% of cows; 855,793 fertility records from 8,665 herds were removed.

Conception. The day a cow conceived was assumed as her final service date where the number of days between her final service and her subsequent calving was between 268 and 298 d, inclusive. Where a subsequent calving date was not available, a cow was assumed to conceive on her final service date provided a viable pregnancy was detected at scanning and a service did not follow that scan.

Where a conception date was available, CCI was defined as the number of days between calving and conception; only CCI records ranging from 10 to 350 d, inclusive, were considered. First service to conception interval was defined as the number of days between a cow's first service and conception; only FSC intervals up to 350 d were retained. Cows considered to have conceived on the day they were first serviced were assumed pregnant to first service (PRFS = 1); otherwise, cows that subsequently calved more than 313 d after their first service together with cows scanned without a viable pregnancy after their first service were assumed not pregnant to first service (PRFS = 0). Irrespective of calving date, a cow was assumed pregnant if she conceived in the initial 42 d of a predefined breeding season (PR42 = 1); a cow serviced in the initial 42 d of a breeding season that did not subsequently calve within 313 d of that service together with any cow scanned without a viable pregnancy >42 d after the start of a breeding season was assumed not pregnant within 42 d of the breeding season (PR42 = 0).

Survival. A cow was assumed to have survived parity i if she reached parity $i + 1$ (SURV = 1); a cow that did not reach parity $i + 1$ was assumed not to have survived parity i (SURV = 0), provided the cow either died or was slaughtered within 400 d of calving or the difference between the cow's most recent test-day milk record was more than 140 d from the herd's most recent test-day milk record. Cows that did not meet the aforementioned criteria were not considered for SURV.

Mortality Data

Since the implementation of Statutory Instrument No. 655/2003, cattle producers in the Republic of Ireland are legally required to inform the Department of Agriculture, Food and the Marine of each animal birth, calving, farm movement, death, slaughter and export events. These data were extracted from the ICBF database for all animals born between January 1, 2001, and December 31, 2015. Only singletons born to dams aged between 545 and 3,650 d at calving were considered, as were cow parities that resulted in singletons; the data set consisted of 12,853,257 animals in 121,588 dairy herds. Animals that did not reside in their birth herd (n = 180,436 animals) were not considered further. Primiparous lactations from cows that calved <545 d of age (n = 2,665 cows) or >1,240 d of age (n = 30,754 cows) were discarded as were pluriparous cow lactations from cows that calved >545 d from the parity median (n = 113,052 lactations from 17,336 cows).

Mortality Trait Definition

Four nulliparous mortality traits were defined in the present study based on animal age and, where possible, a cow mortality trait was defined for each cow-parity separately for cows in their first to fifth parity, inclusive; the definition of mortality traits have been described in detail by Ring et al. (2018). Briefly, a nulliparous animal's first year of life was segregated into 4 age groups, namely 0 to 2 d of age, 3 to 30 d of age, 31 to 182 d of age, and 183 to 365 d of age. An animal that died during an age group was defined as dead (i.e., 1) in that respective age group, whereas an animal that survived the entire duration of an age group was defined as alive (i.e., 0) in that age group; animals recorded as alive on December 31, 2015, that had not yet reached the final day of an age group were not considered in the respective age group. For cow mortality traits, a cow that reached parity $i + 1$ was assumed not to have died in parity i (i.e., 0), whereas a cow that died immediately before reaching parity $i + 1$ was assumed to have died in that parity (i.e., 1). For computational reasons, nulliparous mortality traits were only considered further

for animals born between 2007 and 2015, inclusive (n = 48,840,094 records remained from 8,641,002 animals), whereas only cow mortality traits were retained for animals that calved between 2007 and 2015, inclusive (n = 4,303,543 records remained from 2,368,514 cows). In addition, only herds with at least one registered death in a mortality category were considered for that respective category.

Pedigree

Pedigree information for each animal was traced back at least 4 generations, where possible, and founder animals were assigned a genetic group. Animals sired by a beef breed or an unknown sire were not considered further. Additionally, nulliparous mortality traits were not considered further for animals with an unknown maternal grand-sire. Heterosis and recombination loss coefficients for each animal were calculated as $1 - \sum_{i=1}^{n} \text{sire}_i \cdot \text{dam}_i$ and $1 - \sum_{i=1}^{n} \frac{\text{sire}_i^2 + \text{dam}_i^2}{2}$, respectively, where sire_i and dam_i were the proportion of breed i in the sire and dam, respectively (VanRaden and Sanders, 2003). Heterosis coefficients were further segregated into 1 of 12 categories (i.e., 0.00, 0.01 to 0.09, 0.10 to 0.19, 0.20 to 0.29, 0.30 to 0.39, 0.40 to 0.49, 0.50 to 0.59, 0.60 to 0.69, 0.70 to 0.79, 0.80 to 0.89, 0.90 to 0.99, and 1.00) and recombination loss coefficients were segregated into 1 of 4 categories (i.e., 0.00 to 0.09, 0.10 to 0.29, 0.30 to 0.49, and ≥0.50).

Contemporary Groups

To represent spring-calving herds, which are both the predominant enterprise type in Ireland (Berry et al., 2013) and are representative of the herds that had a BoHV-1 phenotype, only herds that calved at least 85% of their cows between January and May, inclusive, were considered further. In spring-calving herds, animals that are either born or calve in close proximity to each other are typically managed uniformly; as a result, contemporary groups were defined in the present study for each herd separately and for each trait separately using methods described by Berry et al. (2013). Briefly, an algorithm was applied to the data to cluster animals together within a herd that were either born or calved within 10 d of each other; where 10 animals were not initially clustered together, the group was amalgamated with an adjacent group. This process was reiterated until the contemporary group contained a minimum of 10 animals, provided the interval between the initial and final event (i.e., calving or birth) did not exceed 100 d. Nulliparous animals were assigned a

Table 1. Number of animals (n), mean prevalence (%), genetic SD (σ_g), and heritability estimates (h^2; SE in parentheses) for antibody response to bovine herpesvirus-1 (BoHV-1) where animals were deemed exposed to BoHV-1 based on the relaxed and strict exposure definitions

BoHV-1 trait	Relaxed exposure definition				Strict exposure definition			
	n	%	σ_g	h^2	n	%	σ_g	h^2
Vaccinated								
Binary	4,600	31	0.11	0.12 (0.031)	3,842	38	0.12	0.13 (0.036)
Continuous	4,600	—	0.29	0.14 (0.034)	3,842	—	0.32	0.16 (0.039)
Nonvaccinated								
Binary	2,568	41	0.10	0.14 (0.046)	2,027	52	0.10	0.12 (0.051)
Continuous	2,568	—	0.22	0.15 (0.048)	2,027	—	0.22	0.12 (0.052)

contemporary group based on their birthdate. With the exception of CALV42 and AFC in primiparous cows, pluriparous cows were assigned a contemporary group based on their calving date; primiparous cows were assigned a contemporary group for CALV42 and AFC based on their birthdate. Contemporary groups with <5 animals were discarded.

A random sample of contemporary groups were chosen within each milk production performance, fertility performance, and mortality trait separately where at least 85% of animals in a contemporary group were sired by an animal that also sired at least one animal in the BoHV-1 data set. This edit was imposed for computational reasons to reduce the number of records per trait to (where possible) approximately 100,000. The total number of records available per trait in the final data set is in Table 1 and Supplemental Table S1 (https://doi.org/10.3168/jds.2018-14481). The number of records that had both a BoHV-1 test result and either a milk performance trait, fertility performance trait, or a mortality record are in Supplemental Table S1 (https://doi.org/10.3168/jds.2018-14481).

Statistical Analyses

Variance components for BoHV-1 were estimated in 2 separate analyses; the first considered animals exposed to BoHV-1 based on the relaxed definition whereas the second considered animals exposed to BoHV-1 based on the strict definition. Both analyses considered BoHV-1 as either a binary trait or separately as a continuous trait, and variance components for nonvaccinated (i.e., gB test kit) and vaccinated (i.e., gE test kit) animals were estimated separately using univariate animal linear mixed models in ASReml (Gilmour et al., 2009). Vaccinated and nonvaccinated animals were also analyzed together where BoHV-1 was considered only as a binary trait. Genetic correlations for BoHV-1 measured in both vaccinated and nonvaccinated animals were estimated using bivariate animal linear mixed models in ASReml (Gilmour et al., 2009).

Irrespective of whether the analysis from the relaxed exposure definition or strict exposure definition was considered, the resulting variance components for BoHV-1 were similar in both univariate analyses. As a result, only animals deemed exposed to BoHV-1 based on the relaxed definition were considered for all bivariate analyses with milk performance traits, fertility performance traits, and animal mortality traits. Genetic correlations between BoHV-1 and milk performance traits, between BoHV-1 and fertility performance traits, as well as between BoHV-1 and cow mortality traits, were estimated using bivariate repeatability animal linear mixed models in ASReml (Gilmour et al., 2009); bivariate analyses between BoHV-1 and the nulliparous mortality traits were analyzed using animal linear mixed models (i.e., no repeatability effect). The fitted models were

$$\text{BoHV-1} = \text{CG} + \text{het} + \text{rec} + \text{test age|parity} + \text{test date|test kit} + a + e,$$

$$\text{Perf}_a = \text{CG} + \text{het} + \text{rec} + \text{calve age|parity} + a + \text{PE} + e,$$

$$\text{Perf}_b = \text{CG} + \text{het} + \text{rec} + a + e,$$

$$\text{Perf}_c = \text{CG} + \text{het} + \text{rec} + \text{CFS|CFS} + \text{calve age|parity} + a + \text{PE} + e,$$

$$\text{Mort}_{\text{null}} = \text{CG} + \text{het} + \text{rec} + \text{het}_{\text{dam}} + \text{rec}_{\text{dam}} + \text{sex} + \text{calve age|parity}_{\text{dam}} + d + a + e,$$

$$\text{Mort}_{\text{cow}} = \text{CG} + \text{het} + \text{rec} + \text{sex}_{\text{progeny}} + \text{calve age|parity} + a + \text{PE} + e,$$

where BoHV-1 = BoHV-1 test result (i.e., binary and continuous traits); Perf_a = milk performance traits of milk kilograms, fat kilograms, protein kilograms, fat percent, protein percent, fat to protein ratio, and SCS

as well as fertility performance traits of CALV42, CIV, CFS, SR21, NSV, CCI, FSC, PR42, and SURV; $Perf_b$ = fertility trait of AFC; $Perf_c$ = fertility trait of PRFS; $Mort_{null}$ = nulliparous mortality traits; $Mort_{cow}$ = cow mortality traits; CG = fixed effect of contemporary group; het = fixed effect of animal's heterosis coefficient; het_{dam} = fixed effect of animal's dam heterosis coefficient; rec = fixed effect of animal's recombination loss coefficient; rec_{dam} = fixed effect of animal's dam recombination loss coefficient; CFS|CFS = fixed quadratic effect of the fertility trait CFS; sex = fixed effect of animal's sex; $sex_{progeny}$ = fixed effect of sex of animal's progeny; test age|parity = fixed effect of the interaction between an animal's age in months relative to the parity median at sample collection by the animal's parity (i.e., 0, 1, 2, 3, 4, 5); test date|test kit = fixed effect of the interaction between an animal's sample date and the test kit used (i.e., gE or gB kit); calve age|parity = fixed effect of the interaction between an animal's parity (i.e., 0, 1, 2, 3, 4, 5) and age in months relative to the parity median at calving; calve age|parity$_{dam}$ = fixed effect of the interaction between the parity of an animal's dam (i.e., 0, 1, 2, 3, 4, 5) and the dam's age (in mo) relative to the parity median when the animal was born; a = random additive genetic effect of the animal, where a $\sim N(\mathbf{0}, \mathbf{A}\sigma^2_a)$ with σ^2_a representing the additive genetic variance of the animal and $\mathbf{A}$ the additive genetic relationship matrix among animals; PE = random effect of the animal's permanent environment, where PE $\sim N(\mathbf{0}, \mathbf{I}\sigma^2_{PE})$ with σ^2_{PE} representing the permanent environmental variance and $\mathbf{I}$ the identity matrix; d = random additive genetic effect of the animal's dam, where d $\sim N(\mathbf{0}, \mathbf{A}\sigma^2_d)$ with σ^2_d representing the additive genetic variance for the maternal component; e = random residual effect, where e $\sim N(\mathbf{0}, \mathbf{I}\sigma^2_e)$ with σ^2_e representing the residual variance.

RESULTS AND DISCUSSION

Descriptive Statistics and Fixed Effects for BoHV-1

Prior to the applied edits, the mean apparent prevalence of positive antibody response to BoHV-1 was higher for nonvaccinated animals (30%) than for vaccinated animals (22%), with 86% of herds having at least one animal that had a positive antibody response to BoHV-1; the mean apparent prevalence of positive antibody response to BoHV-1 following edits are in Table 1. As cow parity increased, so did the mean apparent prevalence of positive antibody response to BoHV-1 in both vaccinated and nonvaccinated herds (Figure 1). Therefore, it was not surprising that both the main effects of parity number and age relative to the parity median at BoHV-1 test-date together with

their interaction were associated ($P < 0.001$) with antibody response to BoHV-1 (i.e., both the binary and continuous BoHV-1 traits) in the present study. Considering both vaccinated and nonvaccinated animals together as a binary trait, relative to a first parity cow, the likelihood of a second, third, fourth, and fifth parity cow yielding a positive antibody response to BoHV-1 was 1.05 (95% CI: 1.02 to 1.07), 1.16 (95% CI: 1.14 to 1.19), 1.22 (95% CI: 1.19 to 1.25), and 1.31 (95% CI: 1.27 to 1.35), respectively. Although the association between antibody response to BoHV-1 and parity number differed by animal age relative to the parity median ($P < 0.001$), the general trend by parity and by age was the same (i.e., animals tended to be more likely to yield a positive antibody response to BoHV-1 when they were older and as parity number increased). Neither the heterosis coefficient nor the recombination loss coefficient was associated ($P > 0.05$) with antibody response to BoHV-1. Both the overall apparent BoHV-1 prevalence, when considering vaccinated animals and nonvaccinated animals together, and the higher apparent BoHV-1 prevalence for nonvaccinated animals relative to vaccinated animals in the present study, are consistent with previous BoHV-1 prevalence estimates in cows (O'Grady et al., 2008; Cowley et al., 2011; Sayers et al., 2015). For example, earlier Irish studies have reported that between 73 to 80% of beef (O'Grady et al., 2008) and dairy (Cowley et al., 2011; Sayers et al., 2015) herds comprise at least one animal that yields a positive antibody response to BoHV-1.
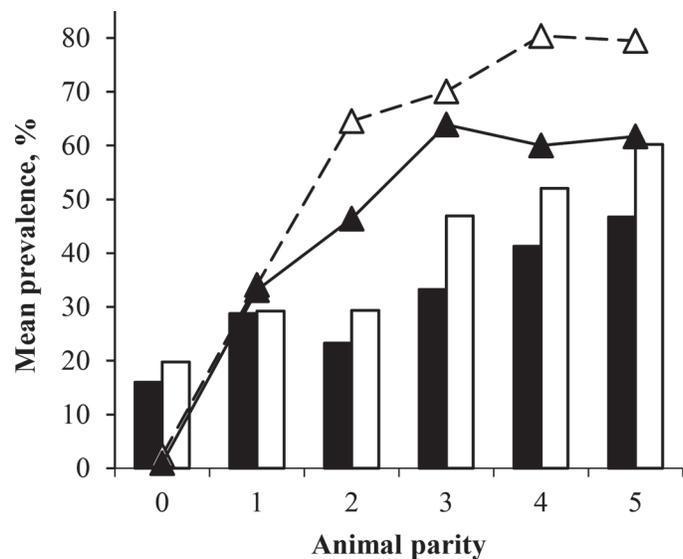
Figure 1. Mean apparent prevalence of bovine herpesvirus-1 (BoHV-1) antibody positive test results per parity in vaccinated (bars) and nonvaccinated (lines) animals that were deemed exposed to BoHV-1 based on the relaxed (filled) and strict (no fill) exposure definitions.
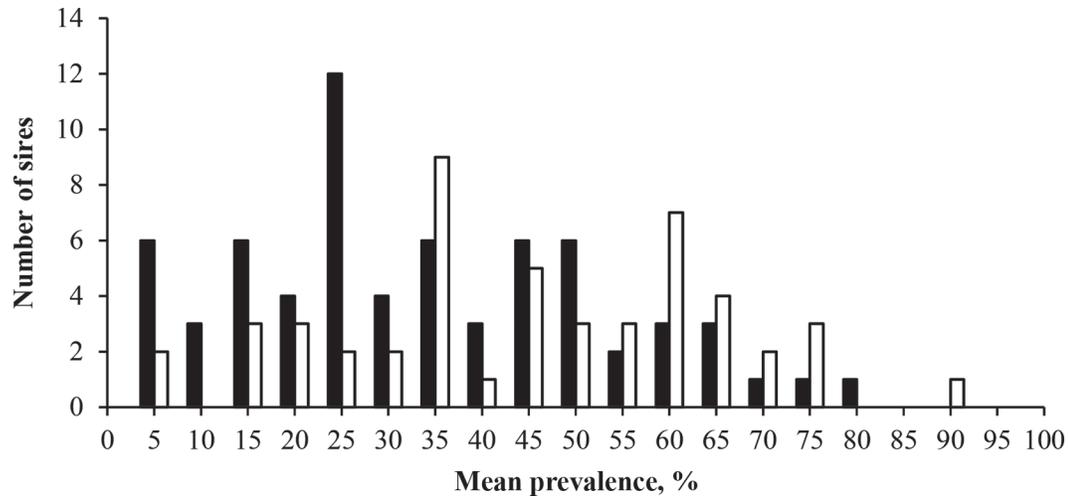
Figure 2. Distribution of mean prevalence of bovine herpesvirus-1 (BoHV-1) antibody positive test results in the daughters of sires that produced at least 25 daughters in at least 5 contemporary groups where daughters were deemed exposed to BoHV-1 based on the relaxed (filled) and strict (no fill) exposure definitions.

A possible indicator of underlying genetic variability for antibody response to BoHV-1 is captured in Figure 2, which illustrates the distribution of the mean daughter prevalence of BoHV-1 from sires that had at least 25 daughters, deemed exposed to BoHV-1, in at least 5 contemporary groups in the present study. One sire produced 46 daughters deemed exposed to BoHV-1 (mean parity = 3.40) in 20 herds, of which 74% of his daughters yielded a positive antibody response to BoHV-1. Another sire produced 37 daughters (mean parity = 3.50), also deemed exposed to BoHV-1, in 4 herds where only 16% of his daughters yielded a positive antibody response to BoHV-1. Although, to our knowledge, others have not reported variation in the mean prevalence of viral diseases among the progeny of individual sires, variability in the prevalence of both viral and bacterial diseases has been documented elsewhere between breeds (Muggli-Cockett et al., 1992; Snowder et al., 2005; Richardson et al., 2014). For example, Richardson et al. (2014) estimated breeding values in Irish cattle for susceptibility to bovine tuberculosis; they concluded that Simmental, Charolais, and Belgian Blue breeds were considerably more likely to succumb to bovine tuberculosis than the Holstein-Friesian or Aberdeen Angus breeds.

Variance Components

Irrespective of whether a binary or a continuous BoHV-1 dependent variable was considered, the estimated variance components for antibody response to BoHV-1 were similar for the relaxed and strict exposure definitions (Table 1); the estimated direct heritability estimates for antibody response to BoHV-1 ranged from 0.12 (SE = 0.031) to 0.16 (SE = 0.039). The corresponding genetic standard deviation for the binary BoHV-1 traits ranged from 0.10 to 0.12 units. Where vaccinated and nonvaccinated BoHV-1 test results were considered in the same analysis, only as a binary trait, heritability estimates for antibody response to BoHV-1 for the relaxed and strict definitions were 0.09 (SE = 0.023) and 0.12 (SE = 0.028), respectively.

Although the present study did not have information pertaining to the type of vaccination used per herd (i.e., live or inactivated vaccine), differences in the genetic variability to BoHV-1 may exist among animals that received a live vaccine compared with an inactivated vaccine. Estimation of the genetic parameters for BoHV-1 for each vaccination type separately could provide a more useful insight into breeding for resistance to BoHV-1. To our knowledge, no heritability estimates for antibody response to BoHV-1 are available in the literature, nonetheless variance components estimated in the present study are similar to estimates for clinical signs of BRD in US and Norwegian cattle populations. For instance, Snowder et al. (2006) reported a direct heritability estimate of 0.08 for BRD in feedlot beef calves (n = 18,122) in the US Meat Animal Research Center over the years 1987 to 2001. Heringstad et al. (2008) also documented a heritability estimate for BRD, which they noted was unlikely to be caused by IBR infection, of 0.05 in Norwegian Red calves (n = 250,212). More recently, Schneider et al. (2010) reported a heritability estimate for BRD of 0.11 in preweaned US calves (n = 1,519) and 0.07 in a population of US feedlot cattle (n = 3,277); the standard errors of the

estimates were, however, large (0.04 to 0.06) relative to the heritability estimate itself. Nevertheless, the present study is the first to elucidate that genetic selection of animals for antibody response to BoHV-1 is possible. In addition, the extent of genetic gain following selection for antibody response to BoHV-1 has the potential to be similar for both vaccinated and nonvaccinated animals (i.e., the genetic standard deviation of the binary BoHV-1 trait was similar for vaccinated animals and nonvaccinated animals; Table 1), and the number of records required to achieve high reliability (estimated breeding values) are also similar for both BoHV-1 traits. In a single-trait selection index, the incidence of animals yielding a positive antibody response to BoHV-1 following exposure to the pathogen could be reduced by 1.6% per year (with an index reliability of 70% assuming a genetic standard deviation gain of 0.09 units) in a well-designed breeding program; this rate of genetic gain could be achieved with 100 progeny records per sire that have been exposed to BoHV-1. Nonetheless, this rate of genetic gain does not consider differences in disease dynamics such as genetic variation in host infectivity (i.e., some individuals may have a stronger ability to transmit infection than others; Anacleto et al., 2015), possible differences in the pathogenicity of viral strains (Kaashoek et al., 1996), or the potential lack of availability of data from animals that have been exposed to BoHV-1 where the number of herds that choose to vaccinate for BoHV-1 increases. Woolhouse et al. (2005) estimated that just 20% of cattle herds are responsible for transmitting 80% of infectious diseases, which indicates that the rate of disease infectivity is not equal among individuals. The phenomenon of "super-spreaders" has important implications for breeding programs; genetic selection against "super-spreaders" has the potential to minimize the generation of new BoHV-1 infections. Recent statistical models that account for the dynamic nature of infections (Anacleto et al., 2015) could be used to estimate genetic parameters for infectivity of BoHV-1, provided data were available pertaining to (1) animal contact rate, (2) duration of the infectious period, and (3) the ability of the host to transmit infection (Lipschutz-Powell et al., 2014). Further research on the genetic variability of BoHV-1 could focus on possible genetic variability in infectivity of BoHV-1 among cattle. Differences in the expression of clinical signs, the quantity of virus shed, and the timing of virus shedding relative to inoculation have also been reported in calves experimentally infected with varying strains of BoHV-1 (Kaashoek et al., 1996; Spilki et al., 2004). Results from Kaashoek et al. (1996) and Spilki et al. (2004) indicate that genetic variation in the humoral immune response to BoHV-1 may differ between BoHV-1 strains; the present study, however, did not have information pertaining to viral strain.

Concerns have been expressed by some (e.g., Stear et al., 2001) that breeding for immune response or disease resistance (e.g., selection of animals for a negative antibody response to BoHV-1) may lead to reduced immune competence. Nevertheless, following BoHV-1 infection, animals can never clear the virus and they have the ability to repeatedly re-synthesize and re-excrete BoHV-1 (Muylkens et al., 2007); thus, antibody-positive animals must be considered BoHV-1 infected (World Organisation for Animal Health, 2010).

Possible Mechanisms for Genetic Variation

Successful BoHV-1 infection in cattle depends upon attachment, binding, and penetration of the virus into the cells of cattle (Muylkens et al., 2007), followed by replication and viral export. Potential defense mechanisms of cattle against BoHV-1 infection, which may be (partly) under genetic control, include avoidance of (animate and inanimate) infected objects (Medzhitov et al., 2012), natural barriers of the skin including hair and mucous membranes (Ackermann et al., 2010; Biswas et al., 2013), coughing and sneezing (Levings and Roth, 2013), variation in the length of the tracheobronchial tree (Ackermann et al., 2010), and antimicrobial properties of the innate immune system (Barber, 2001; Levings and Roth, 2013). Avoidance of BoHV-1 may function by the animal detecting BoHV-1 in the environment, which results in the animal changing its own behavior (Hart, 1990; Medzhitov et al., 2012); such a phenomenon has been documented in rodents (Ehman and Scott, 2001). For example, Ehman and Scott (2001) reported that female mice were capable of discriminating between males that were infected with macroparasites from noninfected males; moreover, the female mice tended to preference the uninfected males as mating partners. It may be possible that, much like the mice (Ehman and Scott, 2001), cattle may be able to detect BoHV-1 shedders, thus resulting in a change of behavior to avoid BoHV-1 infection. If the animal does not alter its behavior sufficiently to avoid BoHV-1, external barriers of the animal can play a role in reducing infection. For instance, the general route of entry for BoHV-1 is via the upper respiratory tract (Muylkens et al., 2007); nostril hairs in the respiratory tract of cattle can provide a physical barrier to the inhalation of pathogens (Ackermann et al., 2010) and the combination of mucus and cilia functions (known as mucociliary clearance) can assist with the removal of inhaled particles (Ackermann et al., 2010). In humans, suboptimal mucociliary clearance has been documented

in patients that suffer from chronic rhinosinusitis but not in control patients (Hamilos and Baroody, 2007). In addition, genetic variation in genes that contribute to the regulation of mucociliary clearance has been associated with chronic rhinosinusitis in humans (Purkey et al., 2014); it may be possible that genetic variation also exists in cattle for mucociliary clearance. Furthermore, Beecher et al. (2014) documented variability among 3 dairy genotypes in the body mass components of slaughtered cows; they noted that on a per unit of BW basis, Holstein-Friesian cows had, on average, a lighter heart, lungs, pancreas, reticulorumen, and omasum than Jersey cows ($P < 0.05$). These findings support the notion that differences among animals may exist in the length of the tracheobronchial tree. A longer tracheobronchial tree, but in particular a longer trachea, may reduce the likelihood of pulmonary infection by increasing the distance required for pathogens to travel from the point of entry through the upper respiratory tract (Ackermann et al., 2010); the increased transit time and surface area may facilitate a greater period of exposure to the innate immune system, helping to destroy the pathogens or at least minimize their effects.

Correlations Between BoHV-1 for Vaccinated and Nonvaccinated Animals

For both exposure definitions used in the present study (i.e., the relaxed and strict exposure definitions), the genetic correlations between BoHV-1 in vaccinated and nonvaccinated animals were weak (i.e., ranging from −0.15 to 0.33) and not different from zero ($P > 0.05$), irrespective of whether the dependent variable was a binary or a continuous trait. The genetic correlations between vaccinated and nonvaccinated animals for antibody response to BoHV-1 as a binary trait were −0.15 (SE = 0.308) and 0.10 (SE = 0.270) based on the relaxed and strict definitions, respectively; where BoHV-1 was considered as a continuous trait, the genetic correlations between vaccinated and nonvaccinated animals were 0.07 (SE = 0.322) and 0.33 (SE = 0.274) for the relaxed and strict definitions, respectively. Although the standard errors were large, results from the present study suggest that the humoral immune response to BoHV-1 may differ depending upon vaccination status.

In a review of the literature on IBR, Muylkens et al. (2007) explains that when a nonvaccinated animal is exposed and infected with BoHV-1 for the very first time, that animal responds with nonspecific inflammatory and cellular reactions. After several days, the animal develops humoral and cell-mediated immune responses that inhibit the transmission of BoHV-1 to other animals (Engels and Ackermann, 1996). The purpose of vaccination is to generate immune "memory" cells that will activate immediately upon an initial encounter with the BoHV-1 antigen, without the animal ever having been exposed to wild-type BoHV-1. That "memory" enables the vaccinated animal to mount a more rapid and robust immune response (than the unvaccinated animal) should the animal ever become naturally infected with BoHV-1 (Sjaastad et al., 2010). Theoretically, if the animal can generate a faster immune response, the animal should have some ability to prevent infection. As a result, vaccinated animals should be able to accelerate through some of the critical immune response steps when exposed to wild-type BoHV-1 for the first time compared with the response of nonvaccinated animals. Therefore, it may be plausible that a hypothetical nonvaccinated animal is genetically less likely to produce a positive antibody response to BoHV-1 because it has the ability to produce a very large quantity of natural killer cells (i.e., kills virus-infected cells) or interferon type 1 (i.e., inhibits virus replication) at a rapid pace. In contrast, a different nonvaccinated animal may be genetically more likely to produce a positive antibody response to BoHV-1 when exposed to the pathogen because it is slower at producing natural killer cells or interferon type 1. That said, if both these animals were vaccinated before initial exposure to wild-type BoHV-1, their genetic ability to withstand infection may alternate. For example, the "memory" cells of the first animal may have a poorer recognition ability than the second animal, meaning that the first animal would be genetically more likely to produce a positive antibody response to BoHV-1 than the second animal.

Results from the present study suggest that the regions of the bovine genome that influence susceptibility to BoHV-1 may differ according to vaccination status (i.e., near-zero genetic correlations were estimated between BoHV-1 for vaccinated and nonvaccinated animals). Nonetheless, results from the present study (discussed herein) also indicate similar genetic correlations between performance traits with BoHV-1 in both vaccinated and nonvaccinated animals. That does not, however, suggest that identical regions of the genome govern differences in humoral immune response to BoHV-1 in both vaccinated and nonvaccinated animals. This is because performance traits, such as milk and fertility, are complex traits that are controlled by a large number of genes, each with a very small effect (Garrick and Fernando, 2015). Further research on the genomic regions associated with humoral immune response to BoHV-1 in both vaccinated and nonvaccinated animals could provide more insight into this.

BoHV-1 and Milk Performance

To our knowledge, no estimates exist on the genetic inter-relationships between milk performance traits and the humoral immune response to viral diseases in cattle. The present study suggests that genetic selection for milk yield or milk constituents likely has little or no effect on whether the animal yields a positive or negative antibody response to BoHV-1, and vice versa. Irrespective of whether vaccinated or nonvaccinated animals were considered, the genetic correlations between 305-d milk performance traits and antibody response to BoHV-1, considered as either a binary or a continuous trait, were weak and not different from zero ($P > 0.05$). The genetic correlations between BoHV-1 and all the milk performance traits ranged from −0.13 (SE = 0.099) to 0.17 (SE = 0.096). No difference existed between the genetic correlations of BoHV-1 with milk performance traits, irrespective of the BoHV-1 trait investigated, and thus only results for the combined BoHV-1 trait are presented (i.e., vaccinated and nonvaccinated animals considered as a binary trait) in Table 2. The genetic correlations between the milk production traits and antibody response to BoHV-1 estimated in the present study support the near-zero genetic correlations documented elsewhere between clinical signs of BRD and other performance traits in cattle. For example, excluding bone yield, Snowder et al. (2007), using data from feedlot beef cattle, estimated genetic correlations between BRD with growth, carcass, and meat palatability traits ranging from −0.16 to 0.20, albeit with large standard errors (0.07 to 0.17); this indicates that genetic selection for growth, carcass, or meat palatability traits is likely to have no effect on genetic predisposition to BRD.

Phenotypic correlations in the present study between BoHV-1 and 305-d milk performance traits ranged from −0.04 (SE = 0.017) to 0.05 (SE = 0.023). Phenotypic studies elsewhere in dairy cattle (Hage et al., 1998; van Schaik et al., 1999) on performance losses arising from BoHV-1 documented a reduction in dairy cow milk yield of 0.92 to 9.52 L per infected cow during the period immediately following infection, for a short period. Based on bulk-tank milk samples, Sayers (2017) documented a reduction in 305-d milk yield in Irish herds that yielded a positive antibody response to BoHV-1; nevertheless, Sayers (2017) noted that the reduction in herd milk yield was likely a consequence of the creation of new BoHV-1 infections within the herd rather than a persistent loss of milk production among cows infected with BoHV-1 over a longer period. In the Netherlands, Hage et al. (1998) estimated a reduction in milk yield of 9.5 L/d in cows that were newly infected with BoHV-1 over a 14-d period following an induced BoHV-1 outbreak. During the infectious period, Hage et al. (1998) observed no increase in clinical mastitis prevalence, no change in mean fat or protein concentration and no increase in SCC. Results from these studies (Hage et al., 1998; van Schaik et al., 1999; Sayers, 2017) suggest that while a reduction in milk yield is often observed in cows that become infected with BoHV-1, the duration of the affected period and the associated reduction in milk performance is short-lived.

BoHV-1 and Fertility Performance

Even though the standard errors were generally large, a consistent trend was observed that animals genetically predisposed to yielding a positive antibody response to BoHV-1 were more likely to have suboptimal fertility; the conclusion was irrespective of the BoHV-1 trait considered and as a result only correlations between the combined BoHV-1 trait and fertility performance traits are presented (Table 3). To our knowledge, no associations are documented between animal genetic predisposition to IBR infection (or other respiratory infections) and fertility performance in cattle; on the other hand, the documented phenotypic associations between IBR infection and fertility performance are generally unfavorable (Graham, 2013). In Croatia, for example, Biuk-Rudan et al. (1999) noted that 69% of Holstein-Friesian cows which tested positive for IBR

Table 2. Mean, genetic SD (σ_g), direct h^2 estimates (SE in parentheses), as well as the genetic correlations (r_g; SE in parentheses) among 305-d milk performance traits with antibody response to bovine herpesvirus-1 where vaccinated and nonvaccinated animals were considered as the same (binary) trait

Trait	Mean	σ_g	h^2	r_g
Milk, kg	6,154	451.24	0.33 (0.011)	0.06 (0.073)
Fat, kg	255	17.01	0.29 (0.011)	0.04 (0.074)
Protein, kg	220	13.14	0.27 (0.011)	0.04 (0.077)
Fat, %	4.18	0.32	0.62 (0.010)	−0.01 (0.056)
Protein, %	3.58	0.16	0.66 (0.009)	0.01 (0.056)
Fat:protein ratio	1.17	0.07	0.44 (0.010)	−0.01 (0.064)
$\text{Log}_e(\text{SCC}/1{,}000)$	4.43	0.22	0.10 (0.008)	−0.12 (0.099)

Table 3. Mean (or median where appropriate), genetic SD (σ_g), direct h^2 estimates (SE in parentheses), as well as the genetic correlations (r_g; SE in parentheses) between fertility performance traits with antibody response to bovine herpesvirus-1 where vaccinated and nonvaccinated animals were considered as the same (binary) trait

Trait	Mean	σ_g	h^2	r_g
Age at first calving,[1] d	737	7.23	0.011 (0.003)	0.05 (0.193)
Calved within 42 d of calving season, proportion	0.76	0.03	0.011 (0.003)	−0.24 (0.169)
Calving interval,[1] d	369	5.07	0.011 (0.003)	0.26 (0.182)
Calving to first service interval, d	76	2.57	0.034 (0.005)	−0.29 (0.134)
Submission rate ≤21 d of start of breeding season, proportion	0.77	0.06	0.024 (0.004)	−0.06 (0.142)
No. of services	1.54	0.09	0.014 (0.003)	0.22 (0.147)
CCI,[1] d	86	2.17	0.008 (0.002)	0.12 (0.173)
First service to conception interval, d	13	1.83	0.004 (0.002)	0.39 (0.205)
Pregnant to first service, proportion	0.54	0.05	0.009 (0.004)	−0.20 (0.168)
Pregnant within 42 d of breeding season, proportion	0.74	0.05	0.015 (0.003)	−0.10 (0.160)
Survival, proportion	0.84	0.04	0.015 (0.003)	−0.06 (0.155)

[1]Calving to conception interval, median presented instead of mean.

had reproductive disorders (e.g., repeat breeding and cystic ovaries), whereas only 31% of their contemporaries that tested negative for IBR had reproductive disorders. In a separate study, Raaperi et al. (2012) reported that cows residing in Estonian herds with a BoHV-1 prevalence ranging from 1 to 49% had a 7.3 times greater odds of aborting (95% CI: 2.0 to 26.9) during gestation and a 5.2 times greater odds of requiring more inseminations per pregnancy (95% CI: 1.5 to 18.4) than cows residing in herds with a 0% BoHV-1 prevalence. The phenotypic associations between IBR and fertility estimated in previous studies support findings in the present study for a tendency of animals genetically more likely to have inferior fertility also to be genetically more likely to yield a positive antibody response to BoHV-1.

BoHV-1 and Mortality

Even though the genetic correlations between antibody response to BoHV-1 and mortality in the present study were not different from zero ($P > 0.05$), results from the present study suggest that animals whose progeny were genetically predisposed to yielding a positive antibody response to BoHV-1 also had progeny that were more likely to die >6 mo of age (Table 4). Consistent with the genetic correlations between BoHV-1 and the performance traits of milk and fertility, differences in the genetic correlations among the 5 BoHV-1 traits did not exist; therefore, only results for the combined BoHV-1 trait are presented (i.e., vaccinated and nonvaccinated animals considered as a binary trait) in Table 4.

Respiratory infection (including infection with BoHV-1) is the most commonly diagnosed cause of mortality, accounting for 21% of deaths, in both young and mature cattle submitted for postmortem examination to Irish veterinary laboratories (AFBI and DAFM, 2016). Therefore, it is not surprising that the present study identified an unfavorable genetic relationship between antibody response to BoHV-1 and mortality. In previous studies, Snowder et al. (2005, 2006) reported breed differences in the incidence of beef calf mortality following diagnosis with BRD infection. For example, Snowder et al. (2005) noted that Simmental (i.e., 18%), MARC III (i.e., a composite beef breed; 17%), and Red Poll (i.e., 16%) breeds had the highest mortality rate of calves diagnosed with BRD (n = 4,199), whereas the lowest mortality rate was in Limousin (i.e., 7%) and Braunvieh (i.e., 9%) breeds. Interestingly, the variability in calf mortality among breeds was not a function of the breed proportion diagnosed with BRD, as

Table 4. Mean, genetic SD (σ_g), direct heritability estimates (h^2_{direct}; SE in parentheses), maternal heritability estimates ($h^2_{maternal}$; SE in parentheses), as well as the genetic correlations (r_g; SE in parentheses) among animal mortality traits and antibody response to bovine herpesvirus-1 where vaccinated and nonvaccinated animals were considered as the same (binary) trait

Trait	Mean	σ_g	h^2_{direct}	$h^2_{maternal}$	r_g
Death 0 to 2 d of age, %	2.58	0.010	0.0038 (0.0016)	0.0071 (0.0019)	0.08 (0.251)
Death 3 to 30 d of age, %	2.44	0.012	0.0060 (0.0019)	0.0010 (0.0010)	−0.13 (0.213)
Death 31 to 182 d of age, %	2.54	0.007	0.0022 (0.0012)	0.0005 (0.0008)	−0.06 (0.282)
Death 183 to 365 d of age, %	0.85	0.003	0.0008 (0.0009)	0.0000 (0.0000)	0.53 (0.374)
Death during cow lactation, %	2.35	0.015	0.0092 (0.0035)	NE[1]	0.34 (0.200)

[1]NE = not estimated.

the Braunvieh breed had the highest incidence of BRD (i.e., 19%) yet their mortality rate was lower than the average mortality rate of all breeds (i.e., 13%).

It has been reported that, in general, death does not occur as a direct consequence of infection with BoHV-1 itself per se, but that death often occurs following secondary infections that arise due to BoHV-1 infection (Yates, 1982). It may be possible that animals genetically predisposed to yielding a positive antibody response to BoHV-1 are also animals that tend to have suboptimal immune function, making them predisposed to infection with several pathogens, which subsequently increases their likelihood of dying. Heritability estimates (that range from 0.16 to 0.41) have been reported for immune response traits in Canadian dairy cows (Thompson-Crispi et al., 2012). Results from the present study support previous findings that genetic selection for a negative antibody response to BoHV-1 may help in reducing the incidence of animal mortality.

CONCLUSIONS

Breeding for animals that are resistant to BoHV-1 infection (i.e., a negative antibody response) could provide producers with an additional method to reduce the incidence of IBR or even potentially realize the additional EU intra-community trade guarantees available to countries that are either free from IBR or have an approved eradication program. Results from the present study substantiate that ample genetic variation exists for antibody response to BoHV-1; therefore, considerable genetic gains could be made. Moreover, results from the present study imply that selection for animals that are resistant to BoHV-1 infection would not have ramifications for genetic selection for milk production traits (other than an effect on selection intensity), whereas it may be beneficial in improving animal fertility and possibly even reducing the incidence of animal mortality.

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