Genetic parameters for variability in the birth of persistently infected cattle following likely in utero exposure to bovine viral diarrhoea virus¹

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ABSTRACT: Genetic selection is an inexpensive and complementary strategy to traditional methods of improving animal health and welfare. Nonetheless, endeavors to incorporate animal health and welfare traits in international breeding programs have been hampered by the availability of informative phenotypes. The recent eradication program for bovine viral diarrhoea (BVD) in the Republic of Ireland has provided an opportunity to quantify the potential benefits that genetic selection could offer BVD eradication programs elsewhere, as well as inform possible eradication programs for other diseases in the Republic of Ireland. Using a dataset of 188,085 Irish calves, the estimated direct and maternal heritability estimates for the birth of persistently infected calves following likely in utero exposure to BVD virus ranged from not different from zero (linear model) to 0.29 (SE = 0.075; threshold model) and from essentially zero (linear model) to 0.04 (SE = 0.033; threshold model), respectively. The corresponding genetic SD for the direct and maternal effect of the

binary trait (0, 1) ranged from 0.005 (linear model) to 0.56 (threshold model) units and ranged from 0.00008 (linear model) to 0.20 (threshold model) units, respectively. The coefficient of direct genetic variation based on the linear model was 2.56% indicating considerable genetic variation could be exploited. Based on results from the linear model in the present study, there is the potential to reduce the incidence of persistent infection in cattle by on average 0.11 percentage units per year which is cumulative and permanent. Therefore, genetic selection can contribute to reducing the incidence of persistent infection in cattle. Moreover, where populations are free from persistent infection, inclusion of the estimated genetic merit for BVD in national breeding indexes could contribute to a preservation of a BVD-free status. Results from the present study can be used to inform breeding programs of the potential genetic gains achievable. Moreover, the approaches used in the present study can be applied to other diseases when data become available.

Key words: animal breeding, bovine respiratory disease, bovine viral diarrhoea, genetics, selection, viral disease

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INTRODUCTION

Bovine viral diarrhoea (BVD) which is caused by BVD virus in the genus pestivirus, family Flaviviridae, is a contagious viral disease of cattle with global significance (Houe, 1999; Gunn et al., 2005). Production losses associated with

BVD infection cost Irish dairy and beef producers an estimated €102 million per annum (Stott et al., 2012). Therefore, it is not surprising that BVD is ranked as one of the most important endemic infectious diseases affecting the productivity and international competitiveness of the Irish livestock industry (More et al., 2010).

Infection with BVD virus in cattle manifests as either persistent or transient infection; the type of infection that develops, and the clinical signs that ensue, are dependent on the timing of infection relative to conception (Grooms, 2004; Hansen et al., 2010), the immune-competence status of the developing fetus (Smirnova et al., 2012), the virus biotype (Bachofen et al., 2010), and the virulence of the virus (Grooms, 2004). With the exception of the in utero development period, an animal infected with BVD virus at any stage of its lifetime (i.e., from birth to death) becomes transiently infected; such animals shed BVD virus for a short period before a specific antibody response develops and these animals typically develop life-long immunity to BVD virus infection (Brownlie et al., 1987; Lindberg and Houe, 2005). Many transient infections are subclinical (Brownlie et al., 1987; Barrett et al., 2011), but there is evidence that immunosuppression, arising from transient infection, can lead to secondary bacterial and/or viral illnesses such as diarrhea, respiratory disease, and reproductive disorders (Houe, 2003; Grooms, 2004). Persistently infected animals are only created when the unborn fetus is infected with BVD virus between ~30 and 120 d of gestation (Grooms, 2004; Hansen et al., 2010; Smirnova et al., 2012). Persistently infected animals shed BVD virus throughout their life and are the main source of inter-animal transmission of BVD virus (Grooms, 2004; Moennig et al., 2005). Persistently infected animals may appear without clinical signs or they may succumb to mucosal disease, characterized by ill thrift, oral lesions, lameness, and death. It is also well recognized that persistently infected animals are immunosuppressed, have greater susceptibility to other diseases, and often die before reaching maturity (Houe, 2003; Moennig et al., 2005).

BVD virus has been either successfully eliminated or the prevalence of persistently infected cattle has substantially reduced in several countries (e.g., Norway, Sweden, Denmark, Austria, Switzerland, and more recently the Republic of Ireland) and specific regions of France, Germany, The Netherlands, Italy, and United Kingdom through the implementation of BVD virus eradication schemes (Stahl and Alenius, 2012; Reardon et al., 2018); such schemes typically target the identification and culling of

persistently infected animals, followed by subsequent surveillance testing and biosecurity measures to prevent the re-introduction of BVD virus. New strains of the virus, as well as the live-trade of pregnant animals, continue to pose a significant threat for re-introduction of the disease (Houe, 1999). Such a threat materialized in the Shetland Islands which had achieved a BVD-free status, but lost this status after the purchase of a persistently infected animal (Barrett et al., 2011).

Genetic variation is known to exist in many health traits in cattle (Berry et al., 2011). However, there is no information on the extent of genetic variability in the susceptibility of cattle to BVD virus. The objective of the present study was to quantify the extent of genetic variability among Irish dairy and beef calves with regards them being born persistently infected following likely exposure to BVD virus in utero. The results in this instance will be useful in determining the feasibility of genetic selection for cattle to reduce the incidence of persistently infected progeny (both in Ireland and elsewhere) through direct selection of animals (i.e., dams and/or sires) as parents of the next generation. Moreover, breeding programs that exploit the known inherent genetic variability could help to maintain a BVD-free status where persistent infection has been eradicated. In addition, the methods applied in the present study can be used when considering forthcoming eradication programs for other diseases internationally (e.g., Infectious Bovine Rhinotracheitis or Johne's disease).

MATERIALS AND METHODS

Data

Since 2013, an industry-led compulsory national BVD eradication program has been operating in the Republic of Ireland; this program commenced after a voluntary program in 2012. As part of the eradication program, producers are required by law to obtain an ear biopsy sample from each calf (i.e., alive, aborted, or stillborn calf) ≤20 d after birth (Anon, 2018a,b). Using either an ELISA or a reverse transcription polymerase chain reaction, ear biopsy samples are tested for the presence of BVD virus in one of 14 designated laboratories. Test results are classified as positive, inconclusive, or negative based on the manufacturers' guidelines for the respective tests. Further details on the eradication program are published elsewhere (Clegg et al., 2016).

For the purpose of the present study, 11,643,625 BVD virus test results were obtained from the Irish Cattle Breeding Federation's database on 11,553,516 cattle from 89,686 Irish bovine herds from 1 January 2012 to 17 November 2017, inclusive. Tests undertaken using the ELISA method constituted over half (i.e., 56%) of the tests. Prior to trait definition, of the 3,387 animals that yielded two positive test results within 21 d of each other, the latter test result for each animal was discarded to allow for differentiation between transient and persistent infection. In addition, 1,296 inconclusive test results were not considered further. Moreover, data from one laboratory which tested <0.01% of samples (i.e., 83 samples) were also removed.

Phenotype Definition

Animals with BVD virus test result(s) were defined as either persistently infected (**PI**; $PI = 1$) or not persistently infected ($PI = 0$). Where each test result of an animal yielded a positive result, irrespective of the number of tests available for the animal, that animal was deemed persistently infected ($PI = 1$). Where each test result of an animal yielded a negative result, that animal was deemed not persistently infected ($PI = 0$). Where an animal yielded both positive and negative test results, animals were deemed not persistently infected ($PI = 0$), provided only 1 positive test result existed; otherwise, animals were not deemed as either persistently infected or not persistently infected and these animals were later removed from the dataset.

The phenotype of each animal's dam was also defined, where possible, using her own BVD virus test result(s) by the aforementioned criteria; otherwise, where a dam did not have a BVD virus test result, the phenotype of her progeny were used. A cow that produced ≥ 1 not persistently infected progeny was herself deemed not persistently infected ($PI = 0$). The phenotype of a cow that only produced persistently infected progeny was not defined and that cow's progeny were later removed from the dataset.

Exposure Definition

As nulliparous females are generally managed separately to multiparous cows on Irish farms, exposure to BVD virus in utero was defined within herd according to the management group of the animal's dam at conception. Potential exposure to BVD virus was defined for all animals except those born to a purchased dam. Animals were deemed

potentially exposed to BVD virus in utero if they were born ± 90 d of a persistently infected ($PI = 1$) contemporary in the same herd-management group.

Data Pruning

Animals born from multiple births (435,297 animals) were removed from the dataset. Animals for which test results were reported for the first time >30 d of age were discarded (1,018,021 animals) as were a further 744 calves not tested in their birth herd. Moreover, to maximize the likelihood of equal lifetime exposure to BVD virus among herd mates, animals born to purchased dams were removed (i.e., both the animal and its dam were not born in the same herd; 3,092,837 calves). A total of 186 remaining calves without a defined BVD phenotype were also discarded. In addition, 2,242 calves born to dams of unknown status or dams deemed to be persistently infected ($PI = 1$) were omitted from the dataset as it was assumed that a **PI** dam always produces a **PI** calf (Brownlie et al., 1987). Calves from primiparous dams that calved <545 d of age (i.e., 15 months; 6,892 calves) were also removed as were calves from multiparous dams that calved >666 d (i.e., 22 months; 174,240 calves) from the parity median. Furthermore, 2,025,221 calves with an unknown sire were removed as were a further 828,653 calves with an unknown maternal grand-sire. Heterosis and recombination loss coefficients for each animal and its dam were derived using methods described by VanRaden and Sanders (2003). Pedigree information for each animal was traced back to founder animals (where possible). In addition, only animals deemed potentially exposed to BVD virus (previously defined) were considered while exposure groups with <5 calves were omitted from the analyses. Following edits, 188,085 calves with a BVD status phenotype from 5,399 herds remained.

Statistical Analyses

Variance components for the binary trait of persistently infected or not persistently infected were estimated in ASReml version 4.1 using both a logit threshold model and a linear mixed model for all 188,085 calves in the one analysis (Gilmour et al., 2009). The fitted model can be written in matrix form as

$$y = X\beta + Z_{\text{sire}} + Z_{\text{mgs}} + Z_{\text{pe}} + e$$

where y is the vector of the trait observed (i.e., persistently infected or not persistently infected); β is

the vector of fixed effects; **sire** is the vector of direct additive genetic effects of the animal's sire; **mgs** is the vector of direct additive genetic effects of the animal's maternal grand-sire; **pe** is a vector of permanent environmental effects of the animal's dam; **e** is the vector of residual effects; **X** is the incidence matrix for fixed effects; and **Z** is the incidence matrix relating to the random additive genetic effects. The fixed effects included in the model were exposure group, heterosis coefficient of the animal (categorized as 0.00, 0.01 to 0.09, 0.10 to 0.19, ...0.90 to 0.99 and 1.00), heterosis coefficient of the animal's dam (categorized as 0.00, 0.01 to 0.09, 0.10 to 0.19, ...0.90 to 0.99, and 1.00), recombination loss coefficient of the animal (categorized as 0.00 to 0.09, 0.10 to 0.29, 0.30 to 0.49, and ≥ 0.50), recombination loss coefficient of the animal's dam (categorized as 0.00 to 0.09, 0.10 to 0.29, 0.30 to 0.49, and ≥ 0.50), animal gender, and the interaction between parity of the animal's dam when the animal was born (i.e., 1, 2, 3, 4, and ≥ 5) and the age (in months) of the animal's dam at calving relative to the parity median. Heritability was calculated as $(4 \times \text{additive genetic variance of the animal's sire}) / (\text{phenotypic variance})$ for the direct estimate and $(4 \times \text{additive genetic variance of the animal's maternal grand sire}) / (\text{phenotypic variance})$ for the maternal estimate.

RESULTS

Descriptive Statistics and Fixed Effects

Of the 188,085 calves used to estimate variance components, 7,780 (i.e., 4.14%) calves were deemed persistently infected; 11.82% (of the 188,085 calves) were born to a dam that had >1 progeny in the dataset. Even after edits were applied, the majority (i.e., 74%) of exposure groups included only one calf deemed persistently infected. The apparent prevalence of persistent infection was greatest in beef-breed calves compared to dairy-breed calves (Figure 1). In addition, the apparent prevalence of persistent infection was greatest in progeny born to first parity dams (i.e., 5.60%) and lowest for progeny born to fifth or greater parity dams (i.e., 2.36%; Figure 1). Relative to a first parity cow, the odds of a third, fourth, and fifth parity cow producing a persistently infected calf was 0.74 (95% CI: 0.68 to 0.81), 0.63 (95% CI: 0.57 to 0.71), and 0.39 (95% CI: 0.35 to 0.44), respectively ($P < 0.001$); there was no difference in the odds of a second parity cow producing a persistently infected calf relative to a first parity cow. No other fixed effect considered

Figure 1. Prevalence (%) and number of beef (white) and dairy (black) breed animals (in brackets) deemed persistently infected when born to first, second, third, fourth, and ≥ 5 th parity dams.

in the mixed model was associated with persistent infection ($P > 0.05$).

Variance Components

An indication of underlying genetic variability for persistent infection is captured in Figure 2 which illustrates the distribution of the mean progeny prevalence of persistent infection from sires that had at least 50 progeny deemed exposed to BVD virus in utero; those bulls sired progeny in at least five distinct herds. The average prevalence of persistent infection in the progeny of those sires when born to first, second, third, fourth, and fifth parity or greater dams was 6%, 4%, 3%, 2%, and 1%, respectively. Nonetheless, one bull sired a total of 146 calves, of which 63 were born to primiparous dams while the remaining 83 were born to multiparous dams. Of the 63 calves born to primiparous dams, 40% were deemed persistently infected. The average prevalence of persistent infection among his 83 progeny that were born to multiparous dams was still 3.5 to six times higher than the average prevalence of persistent infection of progeny born to dams of the same parity. Interestingly, based on estimated breeding values, derived by the ICBF (<http://www.icbf.com>; May 2018), for both calf mortality and cow survival, that same AI sire was ranked in the lowest (i.e., worst) 12th percentile (EBV reliability 99%) and 10th percentile (EBV reliability 88%) of all beef breeds, respectively; although not investigated in the present study, and results should thus be interpreted with caution, these results suggest that bulls which are genetically more likely to produce calves born persistently infected are also those that are most likely to produce calves that tend to die at birth or result in cows with reduced longevity.

The direct and maternal heritability estimates for the birth of persistently infected cattle following likely in utero exposure to BVD virus based on

Figure 2. Distribution of the mean prevalence of persistently infected calves, born to first (black), second (white), third (grey), fourth (striped), and ≥ 5 th (speckled) parity dams, in the progeny of sires that produced at least 50 progeny (per dam parity) in at least five herds (per dam parity) where progeny were deemed exposed to BVD virus in utero.

the threshold model were 0.29 (SE = 0.075) and 0.04 (SE = 0.033), respectively. The corresponding genetic SD for the direct and maternal effect was 0.56 and 0.20 units, respectively. The estimated direct and maternal heritability estimates using the linear model for the birth of persistently infected cattle following likely in utero exposure to BVD virus were 0.0007 (SE = 0.0012) and zero, respectively. The corresponding genetic SD for the direct and maternal effect was 0.005 and 0.00008 units, respectively. The coefficient of direct genetic variation based on the linear model was 2.56%, indicating that considerable exploitable genetic variation does exist, despite the low heritability. Irrespective of the whether the linear or threshold model was used, the absence of a maternal permanent environmental variance ($P > 0.05$) suggests no repeatability of persistent infection within dam (i.e., a dam that produces a persistently infected calf is unlikely to produce persistently infected progeny in subsequent calvings).

DISCUSSION

Breeding to Improve Animal Health and Welfare

Genetic selection for (re)production in cattle (Berry et al., 2014; Berry, 2017), and other species (Havenstein et al., 2003; Berry, 2017), is responsible for a considerable proportion of observed on-farm changes. Although there are exceptions (e.g., Nordic countries), the same genetic gain for health and welfare traits in cattle have generally not been realized. The reason for the lag in genetic gain is not, however, due to a lack of genetic differences among individuals (i.e., genetic variability) per se, but more likely a lack of routine access to

informative data (Berry et al., 2011) to accurately distinguish the genetically elite from the genetically inferior animals. To establish the potential rate of genetic gain achievable, knowledge of the extent of genetic variability is required; variance components are also necessary to inform the mixed model equations for the estimation of breeding values. The heritability statistic is also useful to determine the number of records required to achieve accurate estimates of genetic merit. Put simply, the presence of large genetic variability suggests greater genetic differences among individuals, and thus (all else being equal) faster genetic gain can be achieved. The higher the heritability, the fewer the records required to achieve that potential gain with a high degree of precision; nonetheless, low heritability traits can achieve the same degree of precision as high heritability traits, provided ample data are available (Berry et al., 2011). In any case, measures of genetic variability, genetic merit or heritability can only be generated from informative phenotypes. That said, with the increasing international pressure to improve overall animal health and welfare standards, the abundance of (disease) phenotypes that may be generated from research studies can be used to assess the potential gains achievable through breeding; results will determine the desirability and feasibility of considering such traits in national breeding programs as part of national disease eradication programs as well as maintenance of a disease-free status. Based on results from the linear model in the present study, there is the potential to reduce the incidence of persistent infection in cattle by on average 0.11 percentage units per year (based on an annual genetic gain of 0.215 SDs; Schaeffer, 2006); with just 100 half-sib progeny records, a reduction in the incidence of persistent

infection of 0.017 percentage units per year could be achieved with an accuracy of selection of 13%.

Variance Components

Although to our knowledge the present study is the first to quantify variance components for persistent infection, genetic variance and heritability estimates for bovine respiratory disease (BRD) have been documented when linear models were used (Muggli-Cockett et al., 1992; Snowden et al., 2005, 2006, 2010), although no estimates exist from threshold models. When results from the linear model were compared to those reported elsewhere (Muggli-Cockett et al., 1992; Snowden et al., 2005, 2006, 2010), both the non-significant heritability estimate and the genetic variance were lower in the present study. For example, using a mixed linear sire model, Schneider et al. (2010) reported a heritability estimate on the observed scale for BRD, classified as a binary trait (i.e., not treated or treated for respiratory reasons), ranging from 0.07 (SE = 0.04) to 0.11 (SE = 0.06) for preweaned and feedlot U.S. beef cattle; the direct genetic SD in that study ranged from 0.036 to 0.094 while neither a maternal genetic or a maternal permanent effect were considered in those genetic analyses. Based on an animal linear model, Snowden et al. (2005) reported direct heritability estimates ($P < 0.05$) ranging from 0.09 to 0.22 and maternal heritability estimates ranging from 0.00 (SE = 0.02) to 0.13 (SE = 0.07) for BRD, also classified as a binary trait (i.e., healthy or affected by BRD) in pre-weaned beef calves at the U.S. Meat Animal Research Centre; the direct genetic SD in that study ranged from 0.035 to 0.135. Snowden et al. (2005) also noted no dam permanent environmental variance, consistent with the results of the present study, while the dam genetic effect was only significant ($P < 0.05$) in a few of the beef breeds investigated.

The estimates resulting from linear models of categorical traits are incidence dependent; therefore, our results based on the linear model are likely not directly comparable with other genetic studies on BRD (Muggli-Cockett et al., 1992; Snowden et al., 2005, 2006, 2010) which reported a higher disease incidence (ranging from 8.3% to 23.9%) than the present study (4.14%). Threshold models endeavor to account for differences in trait incidence (Gianola and Foulley, 1983), thus they are expected to generate more unbiased estimates than linear models. Using both the linear model heritability estimates as well as the mean incidence of BRD reported in other studies, heritability estimates

were transformed to the underlying liability scale to mimic threshold models as described by Robertson and Lerner (1949). When the respective heritability estimates of studies (that were different from zero) were transformed to the underlying scale, the heritability estimates were 0.18 for Snowden et al. (2006) and ranged from 0.20 to 0.65 for Snowden et al. (2005), making them more in agreement with our estimate derived from the threshold model (i.e., 0.29). When the heritability estimate from the threshold model in the present study was converted to the observed scale the heritability estimate was 0.06. These results suggest that the estimates from the threshold model in the present study better reflect the variance components of viral diseases in cattle than the linear model, especially when the incidence of disease is low.

Evidence of Possible Genetic Variability in Establishment of Persistent Infection in the Fetus

The mechanism of generating persistent infections in the fetus involves a complexity of interactions between the pregnant cow, the growing fetus, and the connecting placenta (Hansen et al., 2015). Cattle have a synepitheliochorial placenta, which inhibits contact between maternal and fetal circulatory systems (Chucuri et al., 2010); as a result, the transfer of antibodies to the fetus is prevented (Tizard, 2013) yet maternal viral infections, including BVD virus, can be transferred across the placenta to the fetus (Hansen et al., 2015). For many decades, it has been hypothesized that the generation of persistent infection requires firstly for BVD virus to evade the innate immune system of the pregnant cow, secondly for BVD virus to evade the adaptive system of the pregnant cow, and finally, for BVD virus to successfully establish within the fetus without actually killing the fetus (Smirnova et al., 2012). Due to immature stage of development of the fetal immune system, it has been assumed (Grooms, 2004; Lanyon et al., 2014) that the fetus cannot recognize BVD virus as foreign; thus, the fetus may not produce an effective humoral or cellular adaptive immune response (Peterhans and Schweizer, 2010). The lack of a functioning immune system at this stage is believed to result in immune-tolerance enabling the virus to establish in the fetus resulting in persistent infection (Hansen et al., 2010).

Nevertheless, recent studies (Smirnova et al., 2012, 2014; Hansen et al., 2015) have detected both fetal innate and adaptive immune responses following inoculation of their pregnant dams with BVD virus during the first trimester of gestation.

In each of these studies (Smirnova et al., 2012, 2014; Hansen et al., 2015), fetal viremia was reduced following a fetal immune response and this suggests that although the fetus was unable to clear the virus completely, the developing fetus was competent and functioning in the first trimester of gestation, which is contrary to what was believed for many years. Clearance of BVD virus in a developing fetus may have occurred in a study by McClurkin et al. (1984) who demonstrated that following injection of two fetuses with BVD virus at 125 d of gestation, one calf seroconverted in utero (i.e., developed antibodies to BVD virus) thus becoming transiently infected while the other calf did not seroconvert (i.e., no antibodies to BVD virus were developed) but became persistently infected. Similarly, Stokstad and Løken (2002) noted that four calves born following intranasal infection of pregnant dams on days 74 to 82 of pregnancy were not persistently infected while 18 calves born to their contemporaries infected during the same period of gestation were persistently infected. Moreover, Schoder et al. (2004) reported the birth of two dizygotic twins, one of which was born persistently infected while the other was not persistently infected; their dam and the twin that was not persistently infected both tested antibody positive, indicating that they had been exposed to the virus. Each of these studies indicates possible variability in immune system development between fetuses and a possible explanation for a large genetic variance but much smaller maternal genetic variance. In addition, the chain of events that are required for the establishment and birth of a persistently infected calf (e.g., for the dam to become infected, for the virus to reach and cross the placenta, for the fetus to become infected and the fetus not to mount an immune response) may each be subject to variability among individuals, some of which (as quantified by the present study) is likely due to genetic variation under the control of both the developing fetus in utero and its dam. Following on from the present study, it could be interesting to in utero estimate breeding values for BVD of fetuses at conception and subsequently challenge genetically divergent fetuses (and their dams) with BVD virus. Should differences in the observed prevalence of persistent infection actually exist in the resulting calves born, then in depth investigation on the rationale for such differences could aid a better understanding of the mechanisms of the virus and the factors contributing to differences in susceptibility.

Limitations of the Present Study

Although the size of dataset used in the present study was large (relative to other genetic studies on viral diseases), the study is not without its limitations. For example, the mixed model used in the present study, which is used internationally for genetic analyses, assumes that after accounting for herd and other systemic environmental effects (e.g., dam parity), all individuals within a herd-group (e.g., herd parity) are managed uniformly (e.g., all animals of the same parity within a herd are subject to the same vaccination protocol). Although this assumption is generally true in Irish production systems, there are always exceptions to the norm. Such inconsistencies do not perform well in mixed model analysis as their effects are not accounted for; the resulting estimates from such analyses have large residual variation. Large residual variation was observed in the present study when the linear model was used. Much of these inaccuracies in uniformity can be overcome when the prevalence of disease is high or the number of records available is large; however, in the present study, the animal-level apparent prevalence was low (4.14% after edits). In addition, only 26% of exposure groups included in the present study had two or more persistently infected calves. When the analyses were restricted to include only animals deemed exposed by ≥ 2 animals that were defined as persistently infected, only 49% (91,877 records) of the initial dataset were available with an animal-level apparent prevalence of 4.55%; in this scenario using the linear model none of the observed variation for persistent infection could be attributed to genetic effects.

Moreover, incorrect parentage deflates heritability by p^2 , where p is the proportion of animals with correctly identified sires (Van Vleck, 1970). Therefore, the true heritability for persistent infection in the present study, after accounting for pedigree registration errors (Purfield et al., 2016), ranges from 0.0009 (linear model) to 0.39 (threshold model). In addition, the use of imperfect tests contributes to an underestimation of genetic variation and subsequent heritability (Bishop and Woolliams, 2010). According to Presi et al. (2011), sensitivity and specificity values for BVD virus ELISA tests are 98% and 99.8%, respectively; sensitivity and specificity values for BVD virus reverse transcription polymerase chain reaction tests are 97.1% and 100%, respectively (Presi et al., 2011). Coupled with the issue of imperfect tests

is that just 52% of animals deemed persistently infected in the present study had a confirmatory positive test result; the remaining animals were likely culled immediately after the initial positive test result or stillborn. Moreover, the phenotype considered in the present study considered only calves carried to full-term, in the context of the national eradication program in the Republic of Ireland. The present study did not have access to phenotypes from aborted fetuses which may also have been persistently infected. In addition, calving dates, and subsequent conception dates which were used as a proxy to determine likely exposure to BVD virus in utero could contain error. Moreover, incomplete exposure, a topic explored in detail by Bishop and Woolliams (2010, 2014), may also have biased results from the present study. In a scenario of incomplete exposure, uninfected animals may represent both animals that are resistant to a pathogen and animals that are not resistant to that same pathogen but have yet to be exposed to an infectious dose (Bishop and Woolliams, 2014). Such a scenario will bias heritability estimates downwards by ε , where ε is the proportion of the population exposed to the pathogen (Bishop and Woolliams, 2014). Twomey et al. (2016) applied the formula reported by Bishop and Woolliams (2010) to determine the impact of imperfect exposure on heritability estimates using a phenotype of liver damage caused by *F. hepatica* in Irish cows; if the exposure probability were 0.6, 0.7, 0.8, and 0.9, the true heritability of liver damage on the observed scale would be 0.10 (SE = 0.20), 0.06 (SE = 0.10), 0.04 (SE = 0.06), and 0.03 (SE = 0.05), respectively (Twomey et al., 2016). Therefore, the multiple inaccuracies in the recording of phenotypes and pedigree relationships as well as imperfect tests and exposure are likely to have contributed to a deflated heritability estimate.

While the present study did not have access to herd-level vaccination usage, variability in the birth of persistently infected calves may differ among animals in vaccinated and non-vaccinated herds. For the estimation of variance components of another immune response trait that results in respiratory disease (immune response to bovine herpesvirus) in Irish cattle, Ring et al. (2018) analyzed vaccinated herds separately from non-vaccinated herds; a negligible difference in the variance components was reported. Provided data on vaccination usage were available, further research could analyze vaccinated herds separately from non-vaccinated herds to quantify variance components for the birth of persistently infected calves.

CONCLUSIONS

The present study provides quantitative evidence that considerable genetic variability exists for the birth of persistently infected cattle following likely in utero exposure to BVD virus although no maternal genetic variance exists; genetic selection can contribute to a reduction in the incidence of persistent infection. Results from the present study can be used to inform international breeding programs of the gains achievable in reducing the incidence of persistent infection in cattle. In addition, the methods used in the present study can be applied to other diseases when data from future disease mitigation or eradication programs become available. For example, the data pruning procedures used in the present study attempted to maximize the possibility of equal lifetime exposure to the pathogen among herd-mates. Biologically plausible phenotype and exposure definitions were created to reflect both management practices and the lifecycle of the pathogen investigated; the same methods applied in the present study can be applied to other disease traits.

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