UNIVERSIDADE FEDERAL DO PARANÁ

SIMONE SOARES CHAVES DA SILVA

CAN GENETIC BREEDING PROGRAMS HELP REDUCE THE HOLSTEIN SUSCEPTIBILITY TO BOVINE VIRAL DIARRHEA VIRUS?

> CURITIBA 2022

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Zootecnia, Setor de Ciências Agrárias, Universidade Federal do Paraná, como requisito parcial para a obtenção do título de Mestre em Zootecnia.

Orientadora: Profa. Dra Laila Talarico Dias

Coorientador: Dr. Francisco Peñagaricano

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To my children Vivian, Nolan and Douglas Selau (in memorian)

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"There is no path to happiness, happiness is the path"

(Buddha)

RESUMO

A diarreia viral bovina (BVD) é uma doença infecciosa que acomete bovinos e está associada principalmente a perdas reprodutivas e na produção. Por essa razão, produtores de leite e técnicos ao redor do mundo passaram a dar atenção à seleção para características de saúde, pois além de causar prejuízos a esta atividade econômica, também há preocupação com o bem-estar animal. No Brasil, ainda não há trabalhos na área de genética que abordem sobre a possibilidade de se usar a seleção como uma ferramenta para auxiliar na identificação de animais resistentes à diarreia viral bovina de forma a contribuir com os programas de controle de doenças. O objetivo dessa dissertação de mestrado foi avaliar se a característica resistência ao vírus da diarreia viral bovina (BVDV) é passível de seleção em rebanhos de bovinos da raça Holandesa no estado do Paraná. No capítulo II o objetivo foi estimar o coeficiente de herdabilidade do vírus da diarreia viral bovina em bovinos da raca Holandesa e as correlações genéticas entre as habilidades preditas de transmissão (PTA) dos touros para a característica resistência ao vírus da diarreia viral bovina e características de produção, reprodução e saúde. Para tanto, foram utilizadas 6.439 informações de BVDV de animais, filhos de 5.220 vacas e 661 touros, coletadas entre de 2015 a 2021, em 7 rebanhos distribuídos no Estado do Paraná (sul do Brasil), pertencentes ao banco de dados da Associação Paranaense de Criadores de Bovinos da Raça Holandesa (APCBRH). Amostras de animais jovens, recém-nascidos a novilhas em pré-parto, bem como vacas em lactação e secas, foram testadas para a doença usando o kit de teste ELISA (IDEXX BVDV Ag/Serum Plus Test®). A característica resistência a BVDV foi tratada como binária: animais positivos = 1 (quando o resultado do teste de antígeno ELISA foi igual ou superior a 0.3) e animais saudáveis = 0 (quando o resultado do teste de antígeno ELISA foi inferior a 0.3). Os parâmetros genéticos foram estimados por meio de um modelo animal, utilizando-se amostragem de Gibbs sob um modelo limiar, apresentado a seguir: $Y = X\beta + Z_1hys + Z_2\alpha + e$ em que, Y é o vetor de observações, β é o vetor de efeitos fixos (incluindo o intercepto e, como covariável, os efeitos linear e quadrático da idade do animal), hys é o vetor de efeitos aleatórios para rebanho, ano (2015-2021) e estação (1-4) (herd-year-season) - 153 níveis, α é o vetor de efeitos aleatórios genético aditivo - 6,439 níveis, e é o vetor do efeito residual. X, Z_1 e Z_2 são as matrizes de incidência para cada efeito, respectivamente. A prevalência de infecção por BVDV foi de 0,8% e a herdabilidade para a característica resistência ao vírus da diarreia viral bovina estimada foi de 0.14 ± 0.08 . As variâncias genética e residual foram $0,15 \pm 0,09 \text{ e } 0,93 \pm 0,10$, respectivamente. As correlações genéticas estimadas entre as PTAs dos touros para BVDV e as características produtivas, reprodutivas e de saúde foram próximas de zero e não significativas. A pequena quantidade de informações de animais positivos para a doença pode justificar as correlações genéticas não significativas entre as características. Embora a resistência ao vírus da diarreia bovina apresente baixa herdabilidade, há variabilidade genética, o que significa que pode ser possível utilizá-la como ferramenta dos programas de melhoramento animal para melhorar a saúde do rebanho e complementar os protocolos de erradicação desta doença nas fazendas. Dar continuidade à coleta de informações é imprescindível, pois espera-se que com um banco de dados com volume maior de informações tanto para doenças, quanto de genealogia melhorará a acurácia das estimativas de parâmetros genéticos e dos valores genéticos estimados. Dessa forma, a seleção genética para características de saúde poderá contribuir para mitigar doencas nos rebanhos de bovinos leiteiros.

Palavras-chave: doenças infecciosas, gado leiteiro, parâmetros genéticos, seleção genética.

ABSTRACT

Bovine viral diarrhea (BVD) is an infectious disease that affects cattle and is mainly associated with reproductive and production losses. For this reason, dairy farmers and technicians around the world have started to pay attention to the selection of health traits because, in addition to causing damage to this economic activity, there is also a concern with animal welfare. In Brazil, there are still no studies in the area of genetics that address the possibility of using the selection as a tool to assist in identifying animals resistant to bovine viral diarrhea to contribute to disease control programs. The objective of this master's thesis was to evaluate whether the trait resistance to the bovine viral diarrhea virus (BVDV) is prone to selection in Holstein cattle herds in the State of Paraná. In chapter II, the objective was to estimate the heritability coefficient for resistance to bovine viral diarrhea virus in Holstein cattle and the genetic correlations between the predicted transmission abilities (PTA) of bulls for the trait resistance to bovine viral diarrhea virus and traits of production, reproduction, and health. For this, 6,439 BVDV information from animals, born to 5,220 cows and 661 bulls, collected between 2015 and 2021, in 7 herds distributed in the State of Paraná (southern Brazil), belonging to the database of Paranaense Holstein Cattle Breed Association (APCBRH). Samples from young animals, newborns to pre-calving heifers, as well as lactating and dry cows, were tested for disease using the ELISA test kit (IDEXX BVDV Ag/Serum Plus Test®). The trait resistance to BVDV was treated as binary: positive animals = 1 (when the antigen ELISA test result was equal to or greater than 0.3) and healthy animals = 0 (when the antigen ELISA test result was less than 0.3). The genetic parameters were estimated through an animal model, using Gibbs sampling under a threshold model, presented as follows: $Y = X\beta$ + $Z_1hys + Z_2\alpha + e$, where Y is a vector of observations, β is a vector of fixed effects (including the intercept and, as covariable, the linear and quadratic effect of age of animal) hys is a vector of random effects for the herd, year (2015-2021) and season (1-4) - 153 levels, α is a vector of random additive genetic effects - 6,439 levels and, e is the vector of residual effect. X, Z₁ and Z_2 are the incidence matrices for each effect, respectively. The prevalence of BVDV infection was 0.8% and the heritability for the trait resistance to bovine viral diarrhea virus estimated was 0.14±0.08. The genetic and residual variances were 0.15±0.09 and 0.93±0.10, respectively. The estimated genetic correlations between the PTA of bulls for BVDV and the productive, reproductive, and health traits were close to zero and non-significant. The small amount of information from animals positive for the disease may justify the non-significant genetic correlations between the traits. Although resistance to the bovine diarrhea virus has low heritability, there is genetic variability, which means that it may be possible to use it as a tool in animal breeding programs to improve herd health and complement protocols for the eradication of this disease on farms. Proceeding with the collection of information is essential, as it is expected that a database with a greater volume of information for both diseases and genealogy will improve the accuracy of estimates of genetic parameters and estimated genetic values. Therefore, genetic selection for health traits may contribute to mitigating diseases in dairy cattle herds.

Keywords: infectious diseases, dairy cattle, genetic parameters, genetic selection.

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LISTA OF ABREVIATIONS

AI	- Artificial insemination
BDV	- Border disease virus
BMSCC	- Bulk milk somatic cell count
BRD	- Bovine Respiratory Disease
BVD	- Bovine viral diarrhea
BVDV	- Bovine viral diarrhea virus
BVDV-PI	- Bovine viral diarrhea virus for persistently infected
CSFV	- Classical swine fever virus
СР	- Cytopathic
DIA	- Calf diarrhea
ET	- Embryo transfer
HPV-1	- Bovine herpes virus-1
IVP	- In vitro-produced
MD	- Mucosal Disease
NCP	- Non-cytopathic
PI	- Persistently infected
SNP	- Single Nucleotide polymorphism
TI	- Transient infection

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1 INTRODUCTION

Dairy farming is considered one of the main activities of Brazilian livestock. However, producers still must overcome several challenges to produce milk more efficiently (HÖTZEL *et al.*, 2014; DALCHIAVON *et al.*, 2018).

Infectious diseases represent critical economic losses in dairy production, including high costs for treatment and replacement of animals, which significantly affect reproductive efficiency and decrease milk production. Moreover, some diseases can be indicators of animal welfare and farm sustainability, as they reflect the conditions under which the animals are being raised and the efficiency of the production system (DAVIES *et al.*, 2017).

Viral infections affect dairy and beef cattle worldwide and are mainly associated with the occurrence of reproductive problems, being a limiting factor for increasing the efficiency of Brazilian cattle farming (MINEO *et al.*, 2006; ALI *et al.*, 2011).

Bovine Viral Diarrhea Virus (BVDV) is an infectious disease that affects cattle herds, but other species are also susceptible. Infections caused by BVDV are one of the main diseases that cause losses in dairy cattle. The infected animal may or not show clinical signs, making it difficult to identify the virus in the herd (FLORES *et al.*, 2005; RIDPATH, 2008). In addition to causing respiratory, digestive, and immune system impairment, BVDV is often associated with reproductive problems causing miscarriages, embryonic losses, and reproductive failures (OGUEJIOFOR *et al.*, 2019; ARNAIZ *et al.* 2021). Animals known as persistently infected (PI) continuously shed the virus in the herd, and due to the lack of clinical symptoms, are difficult to identify (CHARLESTON *et al.*, 2001; BROCK, 2003).

Although there is an attempt to control several diseases through vaccination, genetic selection has great potential to improve the health of the herd progressively and permanently. However, the lack of health traits phenotypes has been a limited factor to measure the potential of genetic selection of animals that are more resistant to diseases and its association with other traits of economic interest (RIDPATH, 2013; PARKER-GADDIS *et al.*, 2014). In this sense, farm-record information on health traits can contribute to improving breeding programs, which can be a strategy to aid eradication control programs, and identify genetic variability and its correlation to other economically important traits.

1.1 HYPOTHESIS

The resistance to bovine viral diarrhea virus (BVDV) is a health trait with genetic influence and is associated with reproduction, production, and other economically important health traits in Holstein cattle in Parana.

1.2 OBJECTIVE

1.2.1 General Objective

Estimate genetic parameters for resistance to BVDV and the genetic correlation among this characteristic and reproduction, production, and health traits in Holstein cattle.

1.2.2 Specific Objectives

To estimate the heritability coefficient for the resistance to bovine viral diarrhea virus. To perform a genetic correlation between sires' predict transmitting abilities (PTA) for bovine viral diarrhea virus and predict transmitting abilities for milk production, productive life, gestation length, heifer conception rate, mastitis, and somatic cell scores.

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2 CHAPTER 1 - LITERATURE REVIEW

Pathogens that cause infectious diseases in dairy cattle are widespread in herds around the world and cause considerable damage to the dairy system operation: health, reproduction, production and welfare (MOREIRA *et al.*, 2019). In addition, consumer awareness of farm animal well-being is progressively becoming popular (BOZZO *et al.*, 2019).

Bovine Viral Diarrhea Virus (BVDV) is an infectious disease reported in herds around the world that mainly affects dairy and beef cattle, being endemic in many countries, but other species can also be affected (PETERHANS *et al.*, 2010; ALI *et al.*, 2011). Economic losses are mainly due to poor reproductive performance, increase in abortion rates, immunosuppressive effect that leads to the development of other diseases, reduction in milk production and involuntary culling (HOUE, 2003; WATHES *et al.*, 2020).

So, genetic selection could have great potential to reduce the occurrence of diseases caused by infectious agents through the selection of animals that are more resistant to viral infections. In addition, disease control programs, and eradication measures are essential to reduce the bovine viral diarrhea virus in national herds (HU *et al.*, 2020).

2.1 BOVINE VIRUS DIARRHEA VIRUS – BVDV

The disease was first described in 1946 at Cornell University by Olafson, MacCallum and Fox, after an acute BVD (bovine viral diarrhea) outbreak in New York (GOYAL; RIDPATH, 2008). Infection with BVDV is very complex and can affect many species and wild ruminants (RIDPATH, 2008; PASSLER; WALZ, 2010).

Classified as a positive-sense RNA, with a genome length of 12.3 Kb in size and belonging to the *Flaviviridae* family of the genus *Pestivirus*, the Bovine Viral Diarrhea Virus can be divided into two groups according to its genotype: BVDV1, which, to date has about 18 subtypes, and BVDV2 with 2 different subtypes (PELLERIN *et al.*, 1994; BECHER; ORLICH; THIEL, 1998; DENG *et al.*, 2015; GIAMMARIOLI *et al.*, 2015). The species Classical swine fever virus (CSFV) and Border disease virus (BDV) also belong to this genus (TAUTZ; TEWS; MEYERS, 2015).

Moreover, a novel cattle pestivirus specie named HoBi-like virus (also known as BVDV-3), first isolated in Brazil from fetal bovine serum, has been identified in many countries (SCHIRRMEIER *et al.*, 2004; MISHRA *et al.*, 2014; BAUERMANN; RIDPATH, 2015). Due to a large number of hosts and genomic variability, the *Pestivirus* genus was recently classified by the International Committee on Taxonomy of Viruses into 11 species (SMITH *et al.*, 2017).

The BVDV1-type group presents the virus used in the production of the vaccine, while the BVDV2 group represents the isolates from persistently infected (PI) animals born from cows that were vaccinated for BVDV and from animals that died from the acute form of the disease named hemorrhagic syndrome (RIDPATH *et al.*, 1994). Although both types have the ability to cause acute infection, type 2 causes more severe symptoms than type 1 (PELLERIN *et al.*, 1994).

However, it seems that virulence is not associated to a specific type of the virus (LIEBLER-TENORIO; RIDPATH; NEILL, 2003; FULTON *et al.*, 2005). For each genotype of the virus, there can be two biotypes: cytopathic (cp) and non-cytopathic (ncp) according to the ability of the virus to cause cell death in vitro cell cultures (LEE; GILLESPIE, 1957; RIDPATH, 2003). Both biotypes are capable of causing fetal losses, and have the ability to cross the placenta and infect the fetus (CHARLESTON *et al.*, 2001). So, it is peculiar of the non-cytopathic type (ncp) of turning them into immunotolerant animals, called persistently infected (PI). It was believed that the bovine viral diarrhea virus was particular of enteric diseases, because the virus causes large lesions in the digestive tract and diarrhea, until it develops the acute and fatal form of the disease called Mucosal Disease (MD) (BAKER, 1995). However, as the studies progressed, a very significant relationship between BVDV (Bovine Viral Diarrhea Virus) with reproductive problems and an increase in abortions was observed (DUBOVI, 1994).

2.2 IMPORTANCE OF BVDV IN DAIRY CATTLE

BVDV is known to cause a considerable negative impact on health and reproductive disorder in high-producing dairy cattle. Nevertheless, losses due to infectious diseases outbreaks concerns farmers around the world.

An aspect of BVD virus is the ability to cause transient or persist infection, depending on the time of infection (HANSEN *et al.*, 2010). The persistent infection (PI) occurs when the non-cytopathic type of the virus invades the host at an early stage of gestation, two to four months (CHARLESTON *et al.*, 2001, BRACKENBURY; CARR; CHARLESTON, 2003). During this period the fetus immune system is in development and is not able to generate an immune response to the virus, becoming immune tolerant to the virus. PI animals can be born to dams that are transient infected during gestation or to PI dams (RIDPATH, 2008; PETERHANS *et al.*, 2010; RIDPATH, 2012) though its rare due to high mortality of animals before reaching breeding age. Although these animals are born healthy and seronegative to the virus, they carry and continuously spread the disease in the herd, being important sources of infection (FULTON *et al.*, 2005). Moreover, it is possible that the mutation from the non-cytopathic biotype to the cytopathic form occurs, which is quite aggressive. In PI animals, this mutation leads to the development of Mucosal Disease (MD) and, consequently, the death of the animal (PETERHANS *et al.*, 2010).

Another aspect of BVD virus is to cause transient infection (TI) and it manifests during a short period of the time, about 10-14 days after infection. The manifestations caused by the acute infection can usually vary from non-visible to mild symptoms (HOWARD, 1990). Another important factor is the role of BVD as an immunosuppressive agent and its relationship with the development of other economically important secondary infections in cattle, such as Bovine Respiratory Disease (BRD) (POTGIETER, 1997; FULTON *et al.*, 2002; CAMPBELL, 2004). Basqueira *et al.* (2017) identified BVDV in trans-tracheal lavage of heifers with bronchopneumonia, pointing out the role of the BVD virus in the manifestation of other important diseases of dairy cows. In a study carried out by Fulton *et al.* (2000) to determine the causes associated with the acute form of bovine respiratory disease point out that both BVDV1 and BVDV2 are involved in the pathology in post-weaning beef calves. The association of BVDV with bovine herpes virus-1 (HPV-1), another economic important cattle pathogen around the world, has also been documented (ERFANI *et al.*, 2019; NOAMAN; NABINEJAD, 2020).

Due to the wide variety of clinical and subclinical infections caused by the virus, such as respiratory, immunological, reproductive and venereal infections, the Bovine Viral Diarrhea virus has become one of the most important pathogens in cattle (CORAPI *et al.*, 1989; BAKER, 1989; BAKER, 1989; BAKER, 1995).

While the consequences of BVDV generate significant economic losses, the reproductive problems are of greatest concern to producers. In an experimental study conducted by Grooms *et al.* (1998), the authors observed a change in the ovarian cell types in heifers exposed to acute infection in BVDV, this finding could have a negative impact on the fertility. According to Grooms (2004), among the reproductive problems caused by BVDV, the following stand out: premature embryo death, reduction in conception rates, congenital defects, abortions and birth of debilitated animals. In the same work, the author reported that abortions can occur at any time during pregnancy in cows exposed to the virus, although the frequency in the first 3 months is higher. The author also highlighted that, when the cow is infected in the first 45 days of gestation, there is a greater occurrence of premature embryo death, significantly reducing the conception rate. In another experimental study involving pregnant heifers and

persistent infection, Hansen *et al.* (2010) observed differences in the gene expression of maternal blood cells in which the fetuses were or not PI, in addition, the infection impacted unfavorably fetus development and immune function. Besides, Pinto *et al.* (2017) related that BVDV is likely to compromise the embryo growth in an experimental in vitro-produced (IVP) bovine embryo. Therefore, the authors reported that oocytes exposed to BVDV could negatively impact embryo development and generate embryos BVDV positive in an IVP process.

In the literature there are reports that fetuses infected with the non-cytopathic biotype of the virus between 18 and 125 days of gestation became persistently infected (PI) animals (MCCLURKIN *et al.*, 1984; GROOMS, 2004). According to Moenning and Liess (1995), when contamination occurred between 100 and 150 days of gestation, congenital defects were observed, the main ones involving the central nervous and ocular systems, but other defects were also reported, such as delay in development and deformations in the bone structure.

In a study carried out by Rüfenacht *et al.* (2001), the abortion rate significantly increased during 46 and 210 days of gestation in BVDV infected Swiss dairy cows. The authors point out that programs to eradicate BVD could benefit the entire livestock industry. Although the infected fetus is able to respond immunologically to the virus in the final phase of pregnancy, between 125 and 285 days, abortions and the birth of debilitated animals have been described (GROOMS, 2004). Moreover, the presence of BVDV in semen of infected bulls, from both acutely or persistent infection have been reported (HOWARD *et al.*, 1990; GIVENS; WALDROP, 2004; ABDELKAREEM *et al.*, 2021), this could possibly decrease male fertility due to the reduction of the quality of the semen.

The disease is very contagious and transmission is most efficient by direct nose-tonose contact between the animals, however, contaminated embryos and semen can transmit the virus through artificial insemination (AI) and embryo transfer (ET) (MEYLING; JENSEN, 1988; HOUE, 1995; BIELANSKI *et al.*, 2009). Although less common, BVDV air transmission is also possible, causing a risk factor for BVDV-free herds (MARS; BRUSCHKE; OIRSCHOT, 1998; NISKANEN; LINDBERG, 2003)

The prevalence of persistently infected (PI) animals is relatively low, ranging from 0.3% to 4% on beef farms in the United States (WITTUM *et al.*, 2001; LONERAGAN *et al.*, 2005).

In Brazil, the bovine viral diarrhea virus was first reported around 1960 (FLORES *et al.*, 2005) and currently, a variety of BVDV subgenotypes are widespread throughout the country (SILVEIRA *et al.*, 2017; FLORES *et al.*, 2018). In Parana State (South of Brazil) the prevalence of PI animals was reported to be 1.78% (FREITAS *et al.*, 2021). Despite the low

prevalence of PI animals, this group disseminated large amounts of the virus, contributing to the perpetuation of BVDV in cattle (MCCLURKIN *et al.*, 1984).

In contrast, the seroprevalence for BVDV infection can be as high as 70% in Scottish dairy herds (HUMPHRY *et al.*, 2012). In Brazil, the prevalence of BVDV was reported in different States, 78.3% in Minas Gerais (HAAS *et al.*, 2020), 88.3% in Goias (DE BRITO *et al.*, 2010), 48% in Rio Grande do Sul (ALMEIDA *et al.*, 2013) and 61.98% in Parana State between the years 2000 - 2002 (FLORES *et al.*, 2005). Additionally, a recent study revealed that 82.33% of the herds involved in the research had at least one animal positive for BVDV in a Parana State province (BEDIN *et al.*, 2020). Furthermore, most seropositive animals do not present clinical manifestations or apparent infections (BAKER, 1995). Thus, the identification of these animals is not simple, making the correct diagnosis in the properties difficult.

In the dairy cattle industry, proper management of the herd's nutrition, installation, reproductive performance and health is crucial to achieving reasonable economic results and acceptable animal well-being levels. Furthermore, farmers usually evaluate the costs of any intervention needed and its benefits. As previously described, BVDV is associated with various reproductive disorder and secondary important disease and, because of its lack of evidence of symptoms, it is most neglected by producers. For example, pathogens remain a significant source of abortions in herds, negatively impacting profitability. Murray (1990) investigated infectious agents linked to abortion in 54 dairy herds in England and reported bovine viral diarrhea virus as the major cause of pregnancy loss (26,1%), followed by bacterial or fungal infections (13%), infectious bovine rhinotracheitis virus (13%), and Leptospira hardjo (12%).

In addition, the high costs of abortion are reported to cause significant economic loss around the globe. In United States, DE VRIES (2006) estimated the abortion cost of \$555 per cow in Holstein herds. A study conducted in Canada aimed at determining the economic costs of four common diseases in dairy herds: bovine viral diarrhea, enzootic bovine leucosis, Johne's Disease, and neosporosis. At the herd level, the direct production losses, and treatment costs were estimated at CAN\$2,421 for bovine viral diarrhea. In this study, direct losses for BVDV did not include milk production. However, according to the authors, considering only a reduction of 5% in milk production would have increased the costs of BVDV by 266% or CAN\$8,870.42 (WEERSINK *et al.*, 2002). Additionally, in a simulation model study for economic consequences on fertility of dairy cows, Inchaisri *et al.* (2010) estimated losses due to infertility from €34 to €231 cow/year, mainly caused by lower milk production and a rise in interval calving. In New Zealand, Heuer, Healy and Zerbini (2007) estimated a loss caused by infection with BVDV of NZ\$44.5 million per year for the dairy industry. The information available in the literature confirms that BVDV can lead to important economic losses and, therefore, this disease should not be ignored.

The genetic selection of animals resistant to Bovine Viral Diarrhea can be a strategy to improve herd health and reproductive performance, minimize infectious diseases and decrease, mainly, calf mortality. These factors can positively impact animal welfare, increase farm profitability and provide progressive and permanent genetic gains for the herd. Another important factor is that, in general, health-related traits have low heritability, as they are polygenic and highly influenced by the environment.

2.3 GENETIC PARAMETERS FOR BVDV IN DAIRY CATTLE

Selection in the dairy industry has emphasized production traits over the years. However, greater milk production is usually negatively associated with health traits and thus increases susceptibility to disease (RAUW *et al.*, 1998). The development of health traits has been implemented by the dairy system as a way of finding a balance between herd health, production, and animal welfare. Therefore, Zoetis (Kalamazoo, MI) implemented in their SNP panels six health traits known as wellness traits, which included: mastitis, lameness, metritis, retained placenta, displaced abomasum and ketosis (VUKASINOVIC *et al.*, 2017). Given the importance of health events, most recently the company included two other cow health traits: milk fever and respiratory disease. To date, Zoetis Genetics, has also been made commercially available, in addition to the new eight cow wellness traits, three calf wellness traits (diarrhea, calf livability, and respiratory disease) (ZOETIS, 2020; 2022). The negative impact on animal welfare and farm profitability, mainly due to the high costs of calf replacement, as a result of early involuntary culling, calf diseases, and poor performance, validate the inclusion of calf health traits (ZHANG *et al.*, 2022).

Although the consequences of Bovine Viral Diarrhea on infertility and animal health are known, there are still few studies that have estimated genetic parameters for the trait resistance to Bovine Viral Diarrhea. Additionally, traits that are highly influenced by the environment and difficult to measure, such as health, generally have low heritability. Table 01 shows the estimated heritability for important health traits that affect dairy farms reported in the literature.

Author (year)	Trait	Country	Breed	No. animals	$h^2 \pm SE$
Berry (2014)	BVDV	Ireland	Dairy and beef	86,786	0.16 <u>±</u> 0.02
McClure <i>et al.</i> (2014)	BoHV-1	Ireland	Dairy and beef	5,589	0.06 <u>+</u> 0.03
	Antibodies gE gB				0.28 <u>±</u> 0.05
McClure <i>et al.</i> (2014)	Fasciola hepatica	Ireland	Dairy and beef	5,530	0.15 ±0.06
Ring et al. (2019)	BVDV-PI	Ireland	Dairy and beef	188,085	0.29±0.08
Haagen <i>et al.</i> (2021)	BRD	United States	Holstein	10,527	0.10
Zhang <i>et al.</i> (2022)	DIA	China	Holstein	184,563	$0.10 \pm 0.01;$ 0.10 ± 0.01 Logit and probit model, respectively

TABLE 1. Heritability estimates for the traits susceptibility to BVDV, Bovine herpesvirus type 1, liver-fluke, calf respiratory disease and calf diarrhea.

BVDV= Bovine viral diarrhea virus, BoHV-1 = Bovine herpesvirus type 1, *Fasciola hepatica* = liver-fluke, BVDV-PI = bovine viral diarrhea virus for persistently infected (PI) animals exposed to BVD virus in utero, BRD = calf respiratory disease (until 365 days of age), DIA = calf diarrhea (until 120 d after birth), SE = standard error, SD = standard deviation

In Table 1 it is possible to notice that the existence of genetic variation on those health traits allow the inclusion of these phenotypes in genetic breeding programs, in order to reduce the occurrence of these diseases, as well as to complement the control and eradication measures adopted on the farms.

As previously described, animals infected with the Bovine Viral Diarrhea virus become immunosuppressive and predispose the individual to other diseases. The association between Bovine Respiratory Diseases and BVDV has been widely studied (POTGIETER, 1997; FULTON, 2009). In a study carried out by Fulton *et al.* (2000) to determine the causes associated with the acute form of bovine respiratory disease point out that both BVDV1 and BVDV2 are involved in the pathology in post-weaning beef calves. The authors concluded that the severity of respiratory diseases in the presence of BVDV was justified by the

immunosuppressive effect it has, resulting in decreased function of lung macrophages and blood leukocytes.

In respect of commercial livestock, Brazil is considered a significant country in the world scenario. However, the lack of studies regarding health traits is due to the limited amount of solid phenotypic data. This could have an important impact on the dairy industry over the years as, to improve disease resistance through breeding, the phenotypic recorded data is crucial. Further, this impairs either genetic breeding programs, as it depends on the availability, or disease control/eradication program, which relies on evidence to make better decisions (BERRY *et al.*, 2011; PARKER-GADDIS *et al.*, 2014). Moreover, in Brazil, recording health data is not mandatory, and the inadequacy of regular and standardized testing for BVDV in addition to the complexity in identifying the disease, as many animals may had been sick due to BVDV but were assumed to be another disease, can impact the amount of information. Further, in commercial farms, annotation of health data occurrences is not so simple as farm management is complex and therefore recording practices may be uncertainty. Therefore, genetic evaluation for the trait resistance to BVDV in dairy cattle has been difficult to estimate.

Although the lack of consistent health data has been an issue in many countries, the association between BVDV and others important economic traits has been reported. According to Yavru *et al.* (2013), the detection of BVDV in the blood of seropositive cows may be associated with a 28 to 71% reduction in the first service conception rate, according to the absence or presence of abnormal cervical mucous discharge (CMD), respectively. Moreover, Arnaiz *et al.* (2013) reported an important increase in calving to conception intervals after a BVDV outbreak, impacting negatively the fertility performance. Aragaw *et al.* (2021) recently estimated the association of BVDV and reproductive disorder of dairy cows in Ethiopia. The authors reported that cows with prolonged cases of mastitis and calving intervals were 1.7 and 2.2 more probably to be BVDV seropositive, which affects milk production. In addition, the negative effects of the disease also reflect the decrease in the reproductive efficiency of animals.

Appropriate planning and implementation of control strategy and eradication programs can contribute to mitigating the disease at the national level (MOENNING; HOUE; LINDBERG, 2005). Control programs aim at keeping a low prevalence of the disease whereas the purpose of eradication programs hope for the non-appearance of the disease for a certain period of time (HOUE; LINDBERG; MOENNING, 2006). Nonetheless, the initiative to introduce control and eradication programs on dairy farms can bring benefits with regard to the bovine viral diarrhea virus (HUMPHRY *et al.*, 2012). In some countries, BVDV control programs have already been successfully implemented, as a consequence, the disease is controlled or even eradicated. The Nordic countries were the first to successfully implement BVDV control and eradication programs. In 1992, Norway established the eradication scheme and, by 2004, the country was considered BVDV-free (LOKEN; NYBERG, 2013). In Austria, a voluntary program was conducted during the years 1998-2004 before it became compulsory in August 2004 (MARSCHIK *et al.*, 2018). In 2013 Ireland initiated a mandatory eradication program after just a year of voluntary national BVD eradication program and, by 2020 the program reduced from 0.66% prevalence of PI animals to 0.03% (GRAHAM *et al.*, 2021). The country is looking to be BVDV free by 2023, after 10 years the mandatory program began (O'DONNELL, 2022). In Scotland, the control program began on a voluntary basis in 2010, and since 2013, farmers are required to have their herds screened for BVDV annually (SCOTTISH GOVERNMENT, 2019). Further, BVD negative herds can save every year to the Scottish livestock industry between £2,000 to £14,000, depending on herd structure (HAW, 2019).

Additionally, a meta-analyze study revealed that countries where BVDV control and eradication protocols were implemented, had 1.5 times lower BVDV prevalence compared to countries that did not implement any measure. Interestingly, the same study reported that in Europe, where many countries implemented the first control programs, the prevalence of PI and antibody-positive animals reduced over the year. Moreover, Norway, Finland, and Sweden have eradicated the disease (SCHARNBÖCK *et al.*, 2018).

In Brazil, there is no specific BVDV control and eradication program at the national level. In Parana State (South of Brazil), a voluntary control scheme was implemented by the farmers' association (APCBRH) in 2015. Continuous education of farmers and technicians is an important step in order to bring awareness about this complex pathogen, which contribute to control and eradication schemes progress (LINDBERG; ALENIUS, 1999).

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3 CHAPTER II - GENETIC PARAMETERS FOR RESISTANCE TO BOVINE VIRAL DIARRHEA VIRUS IN HOLTEIN CATTLE

GENETIC PARAMETERS FOR THE TRAIT RESISTANCE TO BOVINE VIRAL DIARRHEA VIRUS IN HOLTEIN CATTLE

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ABSTRACT

Bovine viral diarrhea disease (BVDV) is an important infectious disease that affects herds worldwide, and is mainly associated with reproductive problems. Moreover, the infection is also linked to cause immunosuppression, respiratory and enteric disease, which makes the BVDV one of the main pathogens to cause economic losses in dairy farms. The objective of this study was to estimate the heritability coefficient of bovine viral diarrhea virus in Holstein cattle and the genetic correlations between the predicted transmission abilities (PTA) of bulls for resistance to bovine viral diarrhea virus with milk production, productive life, gestation length, heifer conception rate, mastitis, and somatic cell scores traits. Dataset of 6,439 animals (born of 661 sires and 5,220 cows) belonging to 7 commercial Holstein dairy farms located in the southern region of the State of Parana, South of Brazil, were analyzed. The genetic parameters were estimated through an animal model, using Gibbs sampling under a threshold model, presented as follows: $Y = X\beta + Z_1hys + Z_2\alpha + e$, where Y is a vector of observations, β is a vector of fixed effects (including the intercept and, as covariable, the linear and quadratic effect of age of animal) hys is a vector of random effects for the herd, year and season - 153 levels, α is a vector of random additive genetic effects - 6,439 levels and, e is the vector of residual effect. X, Z_1 and Z_2 are the incidence matrices for each effect, respectively. The prevalence of BVDV infection in this study was 0.8%. The heritability estimated was 0.14±0.08, suggesting that some genetic variability exists. The estimated genetic correlations between the PTA of bulls for BVDV and the productive, reproductive, and health traits were close to zero and non-significant. The small amount of information from animals positive for the disease may be a reason for a non-significant genetic correlation between the traits. Because this is the first study to evaluate the genetics of the trait resistance to BVDV, further researches regarding this trait are necessary in order to validate the results. Understanding the genetics of the host and the genetic correlation between BVDV and other traits that affect animal performance can help animal breeding programs to identify bulls and cows more resistant to diseases. Therefore, genetic selection can be a tool to be used in combination with complement eradication protocols carried out on farms to improve herd health and animal welfare.

Keywords Dairy cattle, genetic selection, infection disease, welfare traits

3.1 INTRODUCTION

Bovine viral diarrhea virus (BVDV) is an infectious disease reported in herds around the world that mainly affects dairy and beef cattle, being endemic in many countries (PETERHANS *et al.*, 2010; ALI *et al.*, 2011). Classified as RNA, it belongs to the *Flaviviridae* family of the *Pestivirus* genus, the bovine viral diarrhea virus can be divided into two groups according to its genotype: BVDV1 and BVDV2 (PELLERIN *et al.*, 1994). The BVDV1-type group presents the virus used in the production of the vaccine, while the BVDV2 group represents the isolates from persistently infected (PI) animals born from cows that were vaccinated for BVDV and from animals that died from the acute form of the disease called hemorrhagic syndrome (RIDPATH *et al.*, 1994).

BVDV infection is rather complex, and in livestock animals, it can have a significant negative economic and welfare impact. Due to the wide variety of clinical and subclinical symptoms caused by the virus, such as respiratory, immunological, reproductive and venereal problems, the bovine viral diarrhea virus has become one of the most important pathogens in cattle. In severe cases it can lead to the death of the animal due to acute enteric infection, known as mucosa disease (MD) (CORAPI *et al.*, 1989; BAKER, 1995).

Although the consequences of BVDV can lead to significant economic issues, it is the losses caused by reproductive problems that generate the greatest concern to the producers. According to Grooms (2004), premature death of the embryo, reduction in conception rates, congenital defects, abortions, and birth of debilitated animals are among the reproductive problems caused by BVDV. Economic costs due to BVDV infection can be as high as USD687.80 per animal depending on the country (RITCHER *et al.*, 2017). However, economic losses can include reduced milk production, other diseases related to production such as mastitis, retained placenta, as well as longer calving intervals, death from acute infection and delay in growth (NISKANEN *et al.*, 1995; HOUE, 2003; SCHMITT–VAN DE LEEMPUT *et al.*, 2020).

Another important factor is the role of BVDV as an immunosuppressive agent and its relationship with the development of other economically important infections, such as Bovine Respiratory Disease (BRD) (FULTON *et al.*, 2000; CAMPBELL, 2004). Although the effects of BVDV on infertility and health of animals are well known, there are only few studies that show the genetic point of view about the disease. The lack of health data is an issue encountered in many countries, as most disease recording is not mandatory, so no solid and constant

information on economic important dairy health traits is maintained (PARKER-GADDIS *et al.*, 2014). Nonetheless, there is growing evidence that genetic variability for disease resistance traits exists, as the development of health traits has been implemented by the dairy system, as a way to reduce infectious diseases, improve animal welfare, and increase herd profitability (NEUENSCHWANDER *et al.*, 2012; PARKER-GADDIS *et al.*, 2014).

Genetic approaches have great potential to improve the health of the herd progressively and permanently and can be used as a complementary tool in combination with control and eradication protocols carried out on farms to improve herd health and animal welfare (BERRY *et al.*, 2011). The identification of genetic variance components and parameters can promote a better understanding of the genetics of the host inherent to this complex disease, which could contribute to the development of new strategies to select by breeding animals that are more disease resistant. So, the aim of this study was to estimate the heritability coefficient for susceptibility to BVDV and the genetic correlation between sire predicted transmitting abilities (PTA) for bovine viral diarrhea virus and predicted transmitting abilities for milk production, productive life, gestation length, heifer conception rate, mastitis, and somatic cell scores in Holstein dairy cattle in Parana State.

3.2 MATERIAL AND METHODS

3.2.1 Phenotypic Data

Records of 18,464 disease incidence in animals tested between September 2015 and June 2021, belonging to 8 commercial Holstein dairy farms located in the southern region of the State of Parana, South of Brazil, were analyzed. The data set was provided by the Paranaense Holstein Cattle Breed Association (APCBRH), located in Curitiba, Paraná. Young animals, from newborns to pre-calving heifers, as well as lactating and dry cows, were tested for the disease using an ELISA test kit (IDEXX BVDV Ag/Serum Plus Test®). Serum, plasma, blood, or ear biopsy samples were used to test for the presence of BVDV at the APCBRH laboratory diagnostic, according to the manufacture's instructions. The trait susceptibility to BVDV was treated as binary: animals positive = 1 when ELISA antigen test result was equal to or greater than 0.3, and healthy animals = 0, when ELISA antigen test result was lower than 0.3.

Dataset was edited and the animals were removed according to the following criteria of exclusion:

- bulk milk ELISA test result (180);
- animals that were not possible to identify (70);

- both sire and dam pedigree information were not available (10,083);
- animals that were tested more than once, in this case, only the first date of the test was kept (1372);
- contemporary group (herd-year-season) with less than 3 animals (49);
- duplicated information (271).

After the edition, the dataset consisted of 6,439 animals (born of 661 sires and 5,220 cows), 7 herds and 23,961 in the pedigree matrix.

3.2.2 Statistical Models

For environment analysis was considered a general linear model (GLM) procedure conducted through the statistical program R, as follows:

$$Y_{ij} = \mu + HYS_i + ID_j + ID_j^2 + e_{ij}$$

Where:

 Y_{ii} = is the categorial score for BVDV (0 healthy or 1 disease) from HYS_i ,

 μ = is the overall mean,

 HYS_i = is the random effect of H (herd, 7), Y (year, 2015 – 2021) and S (1 – 4),

 $ID_j ID_j^2$ = is the linear and quadratic effect, respectively, of animals' age,

 e_{ii} = is the random residual effect.

Preliminary analyses were conducted for the trait using a GLM procedure through the statistical program R (R Core Team, 2021) and there was a statistically significant difference between the linear and quadratic variable of age, as well as the environmental random effect of herd, year and season for the trait resistance to BVDV.

For the health trait resistance to bovine viral diarrhea virus, the linear predictor **Y** can be calculated as follows:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}_1\mathbf{h}\mathbf{y}\mathbf{s} + \mathbf{Z}_2\boldsymbol{\alpha} + \mathbf{e}$$

Where: **Y** is a vector of observations (0 or 1), $\boldsymbol{\beta}$ is a vector of fixed effects in the model, **hys** is a vector of random herd-year-season effects (153 levels), $\boldsymbol{\alpha}$ is a vector of random additive genetic effects (6,439 levels), and **e** is the vector of residual effect. The vector $\boldsymbol{\beta}$ includes the intercept and, as covariable, the linear and quadratic effect of the animals' age (as a class variable grouped every 30 days - 119 levels). The matrices **X**, **Z**₁ and **Z**₂ are the incidence matrices relating phenotypic records to fixed, herd-year-season and animal effects respectively.

A threshold animal model was implemented to estimate variance components, heritability, and sires breeding value was predicted through THRGIBBS1F90 / BLUPF90 family of programs (TSURUTA, MISZTAL, 2006). A total of 500,000 chain iterations were concluded after discarding the first 50,000 as burn-in, saving every 25 samples. POSTGIBBSF90 program was used to conclude the analyses and the convergence was performed through the R package boa (SMITH, 2007). Sire predicted transmitting ability (PTA) for bovine viral diarrhea virus (BVDV) was calculated.

For the genetic correlation, estimated by Pearson correlation, it was considered two production traits: milk production (MP) and productive life (PL), two health traits: mastitis (MAS) and somatic cell scores (SCS), and two reproduction traits: gestation length (GL) and heifer conception rate (HCR). From the 661 sires presented in the pedigree file, 565 could be identified in the Council on Dairy Cattle Breeding (CDCB, 2022) database, so the predicted transmitting abilities (PTA) information for MP, PL, GL, HCR, MAS, and SCS were obtained at the CDCB website, and were used in the analysis.

For edition, preliminary analysis and genetic correlation analyses, it was used the statistical program R (R Core Team, 2021).

3.3 RESULTS

Table 2 shows the herd prevalence of the bovine viral diarrhea virus in 7 commercial Holstein dairy farms located in the state of Parana, south of Brazil.

Herd	Number	Age	e at evalua	tion	Positive	Prevalence %
		(in days)				
		min.	mean	max.		
1	655	1	8	21	0	0
2	269	1	27	304	1	0.37
3	874	1	56	2616	3	0.34
4	1,939	1	275	2606	2	0.1
5	198	1	85	2526	0	0
6	935	1	218	3018	12	1.28
7	1,569	1	633	3570	33	2.1
TOTAL	6,439	1	186	3570	51	0.8

TABLE 2. HERD PREVALENCE FOR THE DISEASE BOVINE VIRAL DIARRHEA VIRUS IN HOLSTEIN DAIRY CATTLE IN PARANA STATE, SOUTH OF BRAZIL

The prevalence of the disease was calculated as the number of positive cases divided by the total number of animals. The heritability estimated in this study for resistance to BVDV was of low magnitude, 0.14 ± 0.08 (standard deviation). The genetic and residual variance estimated was 0.15 ± 0.09 and 0.93 ± 0.10 , respectively.

The genetic correlation between sire's predicted transmitting abilities (PTA) for bovine viral diarrhea virus and predicted transmitting abilities for milk production, productive life, gestation length, heifer conception rate, mastitis, and somatic cell scores are listed in Table 3

Trait	BVDV	MP	PL	GL	HCR	SCS
MP	-0.01	-	-	-	-	-
PL	-0.07	0.45***	-	-	-	-
GL	0.02	-0.35***	-0.30***	-	-	-
HCR	0.05	-0.01	0.33***	0.05	-	-
SCS	0.06	-0.13*	-0.55***	0.10**	-0.21***	-
MAS	-0.06	0.05	0.59***	-0.09*	0.22***	-0.73***

TABLE 3. GENETIC CORRELATIONS OF PTA FOR BVDV WITH PTA FOR PRODUCTION, REPRODUCTION AND HEALTH TRAITS

BVDV = bovine viral diarrhea virus; MP = milk production; PL = productive life; GL = gestation length; HCR = heifer conception rate; SCS = somatic cell scores; MAS = mastitis resistance P value < : 0.05*; 0.01**; 0.001***

The genetic correlations of predicted transmitting abilities for BVDV and production, reproduction and health traits were close to zero and non-significant. No significant genetic correlation was also found between milk production and mastitis and heifer conception rate. Milk production genetic correlation was high and positive with productive life and moderate and low negatively associated with gestation length, and somatic cell scores, respectively. Productive life was negative moderate and high genetic correlated with gestation length and somatic cell scores, respectively, and high positively correlated with mastitis and moderate with heifer conception rate. The reproduction gestation length trait showed a low positive genetic correlation with somatic cell score and a low negative association with mastitis, whereas the heifer conception rate was negatively correlated with somatic cell scores and positively correlated with somatic cell scores and positively significant correlated with heifer conception rate. A very high and negative genetic correlation between health traits somatic cell scores and mastitis result was observed.

3.4 DISCUSSION

Although the number of information used in this study was substantial, the number of BVDV-positive animals was considered small, which is a limitation implying the results. The lack of phenotypic data regarding health traits is an issue faced worldwide as most diseases notification is not mandatory (PARKER-GADDIS *et al.*, 2014). Furthermore, farmers that belong to the voluntary program are likely to cull the calves just after the positive test result. In this case, no solid information about those animals is maintained, making it hard to identify positive cases. Additionally, calves that were not carried to full-term were not included in the phenotype, which diminishes the prevalence of the disease. Altogether, the estimation of genetic variance for resistance to BVDV is challenging due to the lack of records of this phenotype, and not due to the lack of genetic variability.

To our knowledge, this is the first study to estimate the heritability for the trait resistance to BVDV and perform genetic correlations between predicted transmitting abilities for bovine viral diarrhea virus and production, reproduction, and health traits in Brazilian Holstein dairy cattle. In the literature, there are only two studies that estimated the genetic parameters for resistance to bovine viral diarrhea virus until now (BERRY, 2014; RING *et al.* 2019). The heritability estimated in this study was of low magnitude, (0.14 \pm 0.08). This result is similar to the heritability of 0.16 \pm 0.08 reported by Berry (2014) for 86,786 Irish beef and dairy calves. Using a threshold model, Ring *et al.* (2019) estimated the heritability of 0.29 \pm 0.07

for 188,085 Irish beef and dairy calves persistently infected (PI) animals exposed to the BVD virus while in-utero, demonstrating that the information about existing genetic variability for this trait can be used to reduce persistent infection in cattle herds through genetic selection. The authors concluded that resistance to BVDV was influenced by genetic factors and could respond to selection.

Overall, health traits have been reported to have low heritability in many studies, so the low to moderate heritability estimated in the literature for resistance to BVDV is, so far, consistent with the results reported (GONZALES-PEÑA et al. 2019; GONZALES-PEÑA et al. 2020; JOHNSTON et al. 2020; ZHANG et al. 2022). For example, genetic variance and parameters estimates for health event calf scours (DIAR) and calf respiratory disease (RESP) have been documented. Using a threshold animal model, Gonzales-Peña et al. (2019) estimated heritabilities of 0.045 for diarrhea and 0.042 for calf respiratory disease for Holstein cattle, and for the Jersey population, the heritabilities estimated were 0.06 and 0.08 for RESP and DIAR, respectively (GONZALES-PEÑA et al., 2020). Higher heritability for diarrhea, 0.20 and 0.09 for pneumonia in Irish commercial dairy calves were reported by Johnston et al. (2020). Using different approaches, Zhang et al. (2022) estimated diarrhea and pneumonia heritabilities ranging from 0.09 - 0.10 and 0.07 - 0.09 for probit, and logit models, respectively. Overall, health traits are considered complex, having an important environmental impact and are usually controlled by many genes (TIEZZI et al., 2015). Although the heritability estimates for the health traits were demonstrated to be low, some genetic variability exists. Therefore, genetic selection for disease resistance is feasible. The inclusion of health traits evaluation in dairy cattle programs should be considered, suggest the authors (BERRY et al., 2011).

Moreover, the constant advancement of genomics techniques allowed the development of genomic predictions for health traits in United States commercial dairy herds (ZOETIS, 2022). In this sense, breeding for wellness traits will, over the years, generate a positive impact on herd health performance. As previously described, animals infected with the Bovine Viral Diarrhea virus become immunosuppressive and predispose the individual to other diseases. Furthermore, the genomic association between bovine respiratory diseases and BVDV has been widely studied (POTGIETER, 1997; FULTON *et al.*, 2009). Neibergs *et al.* (2011) identified genomic regions on chromosomes 2 and 26 of *Bos taurus* linked to Bovine Respiratory Disease that are associated with persistent Bovine Viral Diarrhea (PI) infection in beef cattle. Genes and regulatory regions identified on these chromosomes are involved in the resistance or susceptibility of animals persistently infected with BVDV. In a genome-wide association study (GWAS) considering 21.743 ear notch samples from commercial beef units in Kansas (EUA), Casas *et al.* (2014) identified an important region on chromosome 14 linked to the persistent type of BVDV and 15 other important markers moderately associated with the disease distributed on chromosomes 1, 2, 6, 8, 10, 15 and 18. The authors suggested that genes associated with these regions are involved in several regulatory pathways that promote the animal's resistance to surviving persistent infections and also in modulating the immune system. Thus, genomic analyses respecting to the trait resistance to BVDV can also be a promising tool to be used as a complement to control schemes.

The genetic correlations of PTA for BVDV and milk production, productive life, gestation length, heifer conception rate, somatic cell scores, and mastitis were close to zero and non-significant. The small amount of positive information on the health data may be a reason for the inconsistencies in the result of a non-significant genetic correlation between the traits.

In Ethiopia, Aragaw *et al.* (2021) have also encountered difficulties in demonstrating a significant association between BVDV and reproductive events. The authors concluded that limited information retrieval due to the absence of reproduction data, along with the possibility of occurrence of other important reproductive problems in the herds may be a reason for this result.

Genetic breeding programs depend on phenotypic records and traditional genetic evaluation demands a large amount of phenotypic health data information, including individual animals and their ancestry, to achieve better genetic merit accuracy (BERRY *et al.*, 2011). In Brazil, control measures for BVDV are being implemented but notification of BVDV cases is not mandatory, so adhesion to the control program is voluntary and still low. Therefore, it is still challenging to have farmers recording this sort of information.

In France, a study conducted with Holstein cattle showed a significant BVDV-status associated with increased bulk milk somatic cell count (BMSCC) (BEAUDEAU *et al.*, 2005). Tiwari *et al.* (2007) described an important decrease in milk (305-d), fat, and protein production in Canadian dairy cows of BVDV-seropositive herds when compared to cows that belonged to negative BVDV herds, demonstrating the negative impact of BVDV in production. As reported by Yavru *et al.* (2013), the detection of BVDV in the blood of seropositive Holstein cows that were inseminated with BVDV contaminated semen may be associated with a 28 to 71% reduction in the first service conception rate. Arnaiz *et al.* (2013) reported an important increase in calving to conception intervals after a BVDV outbreak, impacting negatively the fertility performance. Another study conducted by Epperson *et al.* (2020) involving 370 beef cows and 528 beef heifers in nine different herds revealed that BVDV outbreaks during insemination

season reduced the first service AI conception rates when compared to herds infection free. In addition, the same study showed a decrease in pregnancy rates in BVDV infected herds versus no infection herds. Recently, Aragaw *et al.* (2021) described that dairy cows with mastitis were 2.2 times more potential to be seropositive for BVDV when compared to no cases of mastitis. The study of Aragaw *et al.* (2021) also revealed a significant association between BVDV and anestrus, repeat breeding and calving interval. The negative effects of the disease also reflect the decrease in the reproductive efficiency of animals.

Bovine viral diarrhea is an important cattle infectious disease due to the wide range of clinical and subclinical outcome infections it causes. It is also associated with immune dysfunction predisposing the cow to other important diseases such as bovine respiratory disease, mastitis and retained placenta. BVDV also implicates in reduced milk production and reproductive efficiency. In severe cases it can lead to the death of the animal due to acute enteric infection, known as mucosa disease (MD). Furthermore, infected dams can produce PI calves that will shed the virus constantly in the herd. Even though the disease is well established in the literature, researches involving host genetic factors is still scarce (RING *et al.*, 2018).

Although much is known about the impact of BVDV on dairy cow performance, the mechanisms involving the genetics of the host in respect of the trait resistance to BVDV still need to be revealed. The variance components estimated in this analysis suggest that some genetic variability exists. It is possible to infer that even with a low contribution in phenotypic variance, the use of genetic information may be one of the factors to be monitored within BVDV control programs in order to reduce the incidence of persistent infection in dairy herds.

3.5 CONCLUSION

The presence of some genetic variance allows the conclusion that the use of genetic selection for health traits could be a tool to be included in long-term eradication/control of disease schemes.

In dairy farms management, we suggest recording data for disease traits such as BVDV as well as its pedigree information. The implementation of control and biosecurity measures, along with the planning of an eradication program can be a strategy to minimize health problems in dairy herds.

Author Contributions

Declaration of Competing Interest

The authors declare that the research was conducted without any commercial or financial relationships.

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4 FINAL CONSIDERATIONS

There has been genetic variation in a wide range of health traits among cattle, suggesting that breeding for disease resistance could aid dairy farmers as a complementary tool to control infectious diseases. The genetic selection of animals more resistant to disease animals have the potential to bring permanent and cumulative gains to the herd, in addition to being economically feasible. Nonetheless, for breeding programs to promote greater accuracy of the genetic merit of animals, phenotypic information about the trait is needed. The formation of a consistent database regarding health traits is a challenge faced by many countries, including Brazil. The development of an appropriate software system for farmers' management could improve the recording of health information. Moreover, it could aid the development of disease control/eradication programs. However, the current need for constantly testing animals is costly, being one of the reasons why producers do not continue testing for the disease regularly, which is a challenge for control schemes. Nevertheless, the rapid identification and elimination of PI animals, testing regularly for the disease, and vigilance of cattle movement is crucial for control programs' success. In addition, to help farmers to mitigate health issues, constant education about the disease, vaccination protocols, and biosecurity measures are strongly recommended.

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ANEXO 1 – LIVESTOCK SCIENCE GUIDE



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DESCRIPTION

Livestock Science promotes the sound development of the **livestock sector** by publishing original, peer-reviewed research and review articles covering all aspects of the broad field of animal production. The journal welcomes submissions on the avant-garde areas of **animal genetics**, **breeding**, **growth**, **reproduction**, **nutrition**, **physiology**, and **behaviour** in addition to **genetic resources**, **welfare**, **ethics**, **health**, **management** and **production** systems. The high-quality content of this journal reflects the truly international nature of this broad area of research. Submissions focusing on diagnosis, disease treatments and epidemiology are not welcomed and works entirely based on either laboratory work or laboratory animals are only rarely considered. Papers presenting reviews and meta-analyses must ensure that they provide new insights to our readers. When the novelty of the research presented (including meta-analyses) is due to the methods used, authors are encouraged to classify their works as either Short Communications.

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AUDIENCE

Animal Scientists, Animal Breeders.

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