Economic and production effects of bovine viral diarrhoea

Insights from dairy systems with and without control

Xiaomei Yue

Propositions

1. Bovine viral diarrhoea is the "elephant in the room" in countries without a systematic control programme.
   (this thesis)

2. Economic benefits of bovine viral diarrhoea virus control programmes are declining.
   (this thesis)

3. Effective disease control requires a sense of urgency among all actors.

4. The impact factor of a journal does not correspond with the quality of the scientific work published in it.

5. Compliance with the same coronavirus control measures varies widely among people of different nationalities.

6. The parental responsibility should be independent of grandparents.

Propositions belonging to the thesis, entitled

Economic and production effects of bovine viral diarrhoea: Insights from dairy systems with and without control

Xiaomei Yue
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CHAPTER 1

General Introduction

1.1 Background

1.1.1 Bovine viral diarrhoea virus

Bovine viral diarrhoea (**BVD**) is a viral cattle disease that presents in most cattle-raising countries worldwide. BVD is listed by the World Organisation for Animal Health as a notifiable disease (Houe, 1995; Richter et al., 2019; OIE, 2021). The causal agent, bovine viral diarrhoea virus (**BVDV**), is classified in two main genotypes namely BVDV-I and BVDV-II, of which BVDV-I is the predominant genotype globally, while BVDV-II is reported to be limited to a few countries and regions (e.g., North America, Germany, Belgium, France, the Netherlands and Japan; Ridpath et al., 1994; Couvreur et al., 2002; Fulton et al., 2005; Lindberg et al., 2006; Zhu et al., 2009; Aduriz et al., 2015). Since the 1960s BVDV prevalence surveys have been conducted in dairy herds in many countries and regions. Antibody prevalence at animal level averaged 48.38% in Europe, while in North America, East Asia, Australia, and North Africa, it was 53.35%, 40.88%, 52.60%, and 53.97%, respectively (Scharnböck et al., 2018).

As an important endemic infection, BVDV can be transmitted vertically and horizontally. Vertical transmission is a consequence of dam being infected in the early stage of gestation (approximately in the first trimester), resulting in a calf which is born persistently infected (**PI**) (Houe, 1995; Brownlie et al., 1998). These PI cows, with a prevalence of less than 2%, are the main reservoir of BVDV (Scharnböck et al., 2018). They excrete massive doses of virus in urine, faeces, milk and semen throughout their lifespan (Khodakaram-Tafti and Farjanikish, 2017). Susceptible cows that have been exposed to BVDV become transiently infected (**TI**), shed virus (much less than PI cows shed) and develop immunity within approximate 2 weeks (Baker, 1990; Mars et al., 1999; Sarrazin et al., 2014). Horizontal transmission can occur both via PI and TI cows, while PI cows are more efficient transmitters than TI cows considering the amount of virus shed and the period of infection (Khodakaram-Tafti and Farjanikish, 2017).

Infection of BVDV has a negative effect on the production and economic performance of dairy herds. From a production perspective, BVDV infections are associated with poor herd performance, leading to reduced milk yield, prolonged time to first calving, longer calving interval, premature culling and higher calf mortality rate (Valle et al., 2001; Gates et al., 2013; Burgstaller et al., 2016b). Consequently, BVD is one of the costliest enzootics for farmers and society (Ezanno et al., 2020). The direct losses due to BVDV infection were reviewed and varied from 0.4 to 612 euro[1] per cow per year, with 178 euro per cow per year as the average direct losses (Richter et al., 2017). This huge range is related to variation in observed BVDV biological variables and heterogeneous study designs (Richter et al., 2017). At the farm level, economic losses due to a introduction of one PI cow are estimated at 3,000 euros per herd (40 cows) per year in the Netherlands (Gunn et al., 2005). At the regional or national level, the previously estimated losses varies from 4.4 million euros per million cattle in Switzerland to 12 million euros per million cattle in Styria, Austria (Obritzhauser, 2000; Buchwalder, 2006; Richter et al., 2017).

Many countries and regions developed BVDV control or eradication programmes. Control programmes aim to obtain and maintain the BVDV prevalence in a relatively low level, while the ultimate purpose of eradication programmes is to obtain the (certified) free status of BVDV (Directorate-General for Health and Food Safety; Andrews and Langmuir, 1963; Houe et al., 2006; Pinior et al., 2017). Scandinavian countries (Denmark, Finland, Norway and Sweden) launched eradication programmes in the early 1990s and entered the final stage of eradication ten years later (Bitsch et al., 1994; Waage et al., 1994; Moennig et al., 2007). Inspired by the success of Scandinavian countries, many other European countries/regions designed BVDV control/eradication programmes. Some countries/regions implemented mandatory programmes (e.g., Sweden, Germany, Ireland, Scotland, the Netherlands, Belgium, etc.), while some are in the process of voluntary control (e.g., England, Wales, Italy, France and Galicia; Metcalfe, 2019; van Roon et al., 2020; Moennig and Yarnall, 2021). Nevertheless, there are still many countries that have not yet developed BVDV control programmes (Scharnböck et al., 2018).

1.1.2 Decision making in BVD

Different countries are at different stages of BVDV control, therefore information required for decision making in these countries is different. This thesis provides practical information to support decision-makers in countries with and without a systematic BVDV control programme. A systematic BVDV control programme is identified by three central elements: biosecurity, elimination of PI animals and surveillance, as opposed to control attempts without clear objectives and monitoring to assess progress (Lindberg et al., 2006).

China is one of the countries that has not implemented a systematic BVDV control programme. Since first reported in 1980, a number of studies provided insight in the prevalence

[1] Presented as US dollars in the original publication and converted to Euros here, using the exchange rate of 1.00 EUR = 1.13 USD on 20 January 2022.

of BVDV in Chinese dairy herds. The reported BVDV prevalence ranges greatly from 2.6% (Kang et al., 2013) to 98.53% (Deng et al., 2015), while the pooled BVDV prevalence was reviewed as 53% by Ran et al. (2019). The prevalence of BVDV varies among provinces and regions, with the highest prevalence found North China[2]. North China, together with the Northeast[3] and Northwest[4], are the "Three Norths" in China, contributing 82% of China's total raw milk production (Figure 1.1, China Dairy, 2020). The number of dairy cows in the Three North accounts for 72% of the national total (Figure 1.1, China Dairy Yearbook, 2018; China Dairy, 2020). Further, since the "Opinions on Promoting the Revitalization of the Milk Industry and Ensuring the Quality and Safety of Dairy Products" was issued by the General Office of the State Council in 2018, the number of large-scale dairy herds has rapidly increased in China, especially in North China (Wang et al., 2021).

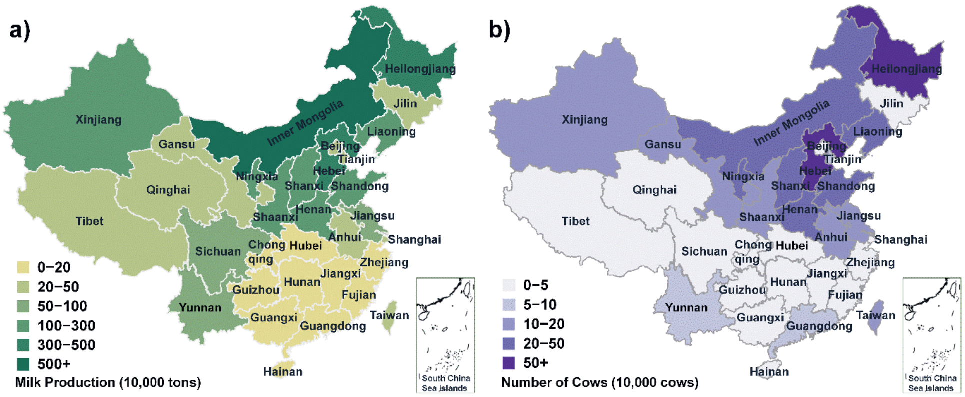

Figure 1.1 Distribution of raw milk production (a) and number of dairy cows in China (b).

China is in the primary stage of BVDV control. There are some attempts on implementing regional BVDV control programmes. For instance, thirty large-scale dairy farms (herd size >500) in Beijing participated in a BVDV control programme modified based on the Scandinavian countries' experience. This programme included identification and culling of PI cows, isolation of TI cows, virus testing for new-born calves, and virus testing and isolation of newly introduced animals. During this programme, PI animals were identified in 76.7% of the herds participating in the programme, demonstrating the urgency and necessity of BVDV control in China (Zhang et al., 2012).

[2] North China, including Beijing, Tianjin, Hebei Province, Shanxi Province and Inner Mongolia Autonomous Region.
[3] Northeast China, including Liaoning, Jilin, Heilongjiang Province.
[4] Northwest China, including Shaanxi, Gansu, Qinghai, Ningxia Hui Autonomous Region and Xinjiang Uygur Autonomous Region.

For countries without a systematic BVDV control programme, such as China, the first decisions regarding BVDV control include whether to investigate the BVDV infection situation, whether to develop a (systematic) BVDV control programme. If the decision is made to develop a BVDV control programme, decisions need to be made regarding the objectives of the programme as well as the optimal control scenario to be performed in the systematic BVDV control programme. The decision to investigate the BVDV infection situation depends on the decision-makers' perception of the severity of BVDV infection, which in turn depends on their basic knowledge of BVDV infection: clinical manifestations, identification of sick cattle, etc. The decision to develop a (systematic) BVDV control programme may depend on decision-makers' perceived severity of BVDV infection, perceived benefits of controlling BVDV and their conviction that BVDV can successfully be controlled and/or eradicated (Champion and Skinner, 2008). Information to support this set of decision needs to include the current prevalence of BVDV, negative production and economic effects of BVDV infection, the elements of a systematic BVDV control programme, and the expected efficacy of a systematic BVDV control programme. Knowledge of (successful) experiences of other countries with BVDV control/eradication programmes, cost-effectiveness of systematic BVDV control programmes will support these decisions. Furthermore, in order to design an effective systematic BVDV control programme, information on technically feasible and economically sound BVDV control programmes, progressive BVDV control goals is needed (Perry et al., 2001).

The Netherlands, as one of the countries that has implemented a systematic BVDV control programme, launched a voluntary BVDV control programme (BVDV-free programme) in 1997. The aim of the that voluntary BVDV-free programme was to control BVDV at the herd level by detecting and removing PI animals and monitoring the subsequent BVDV-free status (van Duijn et al., 2019; van Roon et al., 2020). Throughout the years, the BVDV-free programme has been adjusted and optimized and consists of three phases (Figure 1.2): test and cull phase (I), monitoring phase (II), and removal phase (III). In phase I all cattle in the herd need to be tested for virus and the identified PI animals (if any) need to be removed. Subsequently, all new-born calves are tested for virus for 10 consecutive months. If no new-born calves are tested positive, the herd obtains the BVDV-free certificate and enters the monitoring phase (phase II). Two options are available in the monitoring phase, in which option 1 is to test 5 random calves in the age of 8-12 months biannually for BVDV antibodies (i.e., spot test), option 2 as an alternative is to test antigen in all new-born calves that are being reared in the herd (van Duijn et al., 2019). When, during this monitoring phase it occurs that BVDV had been introduced, the herd loses its BVDV-free certificate and enters the removal phase for PI animals (phase III). In addition, it is mandatory for herds participating in the BVDV-free programme to test for BVDV on animals purchased from not-free herds for BVDV.

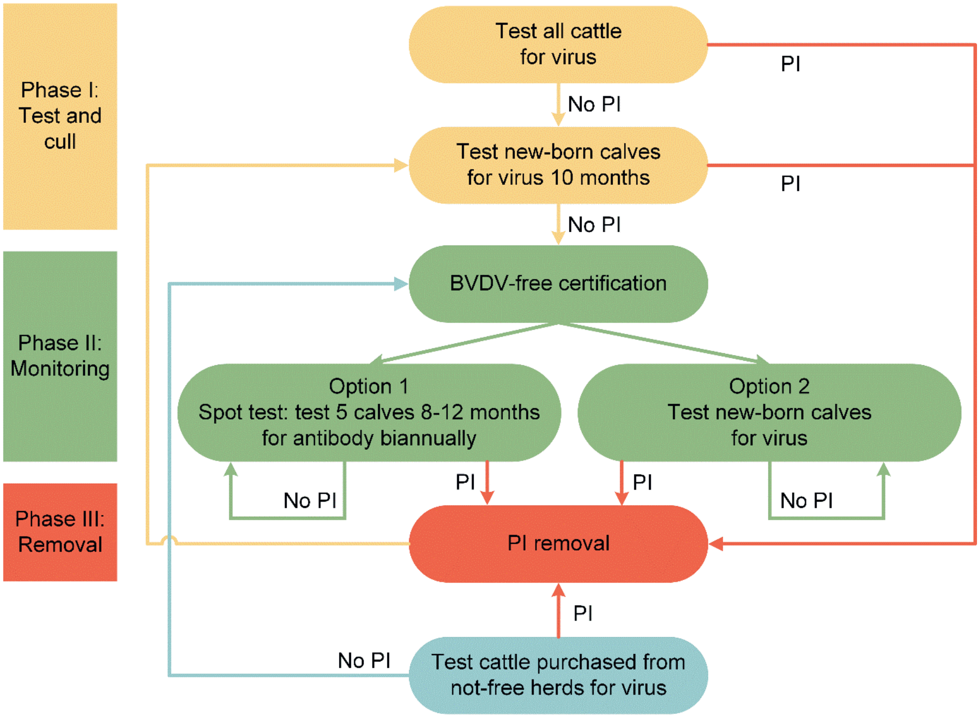

Figure 1.2 Flow chart of the bovine viral diarrhoea virus (BVDV)-free programme in the Netherlands, based on the work of van Duijn et al. (2019) and van Roon et al. (2020), PI=persistently infected animal.

After more than twenty years, the BVDV control in the Netherlands has entered the eradication phase and is coming to the tail end. The success of BVDV control in the Dutch dairy herds can be illustrated by the reduction in number of herds with virus circulation and the increase in number of herds with BVDV-free or unsuspicious status. In 1995, before initiation of the control programme, 84% of the Dutch dairy herds were antibody positive in bulk milk (van Duijn et al., 2019); in 2015–2016, the percentage of dairy herds with recent BVDV circulation was 8.7% (Royal GD, 2018). To make the final step towards eradication of BVDV, since 2018, a mandatary national eradication programme has been in place for dairy farms (ZuivelNL, 2018). As of the third quarter of 2021, 85% of dairy herds had a BVDV-free or BVDV-unsuspected status (Royal GD, 2021a). Economically, Santman-Berends et al. (2017) concluded that it is beneficial to implement control scenarios for BVDV in the dairy industry that involve testing and removing of PI cattle.

For countries with a systematic BVDV control programme, such as the Netherlands, decisions regarding BVDV control include how to monitor BVDV cost-effectively, how to prevent and solve re/new introductions and how to achieve the goal of eradication of BVDV. Information that can support these decisions includes not only those mentioned above in countries without a systematic programme, but also the efficacy and economic effectiveness of the current programme and other available surveillance and control strategies as well as farmers' perspective on the various control programme options.

1.2 Problem statement

1.2.1 Support decisions in countries with a systematic BVDV control programme

For decision-makers in countries with a systematic BVDV control programme, the ultimate goal is to eradicate BVDV and maintain this BVDV-free status. To achieve this goal economically and efficiently, evaluations on the effects of the control programme on the production and economic performance of the involved dairy herds are necessary. BVDV control/eradication programmes were economically justified in some countries (i.e., Norway, Ireland, France, and Switzerland) based on simulation models (Dufour et al., 1999; Valle et al., 2005; Häsler et al., 2012; Stott et al., 2012; Pinior et al., 2017). In the Netherlands, the economic effects of different BVDV control scenarios were estimated normatively by Santman-Berends et al. (2015). To our knowledge, no empirical studies exist on the economic consequences of BVDV controls in the Netherlands, for instance based on accounting data. The economic rationality of the BVDV-free programme has been evaluated based only on normative analyses, and empirical analyses can provide more insight into the efficiency of these programmes.

Re/new introduction of BVDV is one of the most important concerns is a BVDV control/eradication programme. Existing research has identified risk factors for re/new introduction in BVDV control programmes (Veldhuis et al., 2018; Pinior et al., 2019; van Duijn et al., 2021). However, the effects of new introduction of BVDV on herd performance (e.g., milk yield, udder health, reproduction, culling, calf mortality) in a BVDV control programme has not been determined yet. To support decisions on control measures, information on the effects of new introductions on herd performance is needed to ultimately assess the (cost-)effectiveness of the current control measures.

1.2.2 Support decisions in countries without a systematic BVDV control programme

For decision-makers in countries without a systematic BVDV control programme, one of the key barriers to effective control of BVDV is considered to be insufficient resources and information regarding BVDV.

For instance, Chinese decision-makers need more adequate information on BVDV infections. Studies over the past four decades have provided important information on the BVDV prevalence in Chinese dairy herds (Xin et al., 2009; Zhen, 2017). However, most studies do not address within-herd prevalence. This knowledge is especially lacking for large-scale dairy herds. With the increase of large-scale dairy herds in China, more large-scale dairy herds will face the problem of BVDV infection. This calls for investigation into the prevalence of BVDV in large-scale dairy herds to provide decision-makers with the most recent BVDV infection status.

For decision support in Chinese dairy herds, the effects of BVDV infection on production and economic performance still needs to be determined. Previous research has established the impact of BVDV infection based on the situation in European countries (Houe, 2003; Pinior et al., 2017; Richter et al., 2017). Given that the layout, herd size, management practices, climate, feed, grazing, etc. in Chinese dairy farms are different from those in western countries, existing estimates may not be applicable to Chinese dairy herds. Estimates of the effects of BVDV infection will provide decision-makers in China a clearer overview of the detriment of BVDV and facilitate the development of a (systematic) BVDV control programme.

1.3 Objective of this thesis

The overall objective of this thesis was to determine the effects of BVDV infection on the production and economic performance of dairy herds in order to support decision making in countries with and without a systematic BVDV control programme. The Netherlands and China were studied as countries with and without a systematic BVDV control programme, respectively. This objective was divided into five sub-objectives:

i. Investigate the economic and production effects of BVDV-free certification in Dutch dairy herds.
ii. Determine the effects of a new BVDV introduction on milk yield in BVDV-free herds participating in the Dutch BVDV-free programme.

iii. Determine the effects of a new BVDV introduction on herd performance (i.e., somatic cell count, calving interval, culling risk, and calf mortality rate) in BVDV-free herds participating in the Dutch BVDV-free programme.

iv. Investigate the within-herd seroprevalence of BVDV in large dairy herds in North China.

v. Simulate the dynamics of BVDV infection and the associated production and economic losses in a large-scale Chinese dairy herd using a bio-economic simulation model.

1.4 Outline of the thesis

The overall structure of this thesis takes the form of seven chapters, including this general introduction (Chapter 1), followed by five research chapters (Chapter 2-6) each addressing one sub-objective, and ends with a general discussion (Chapter 7). Figure 1.3 provides a schematic overview of the structure of the thesis along with link between the chapters.

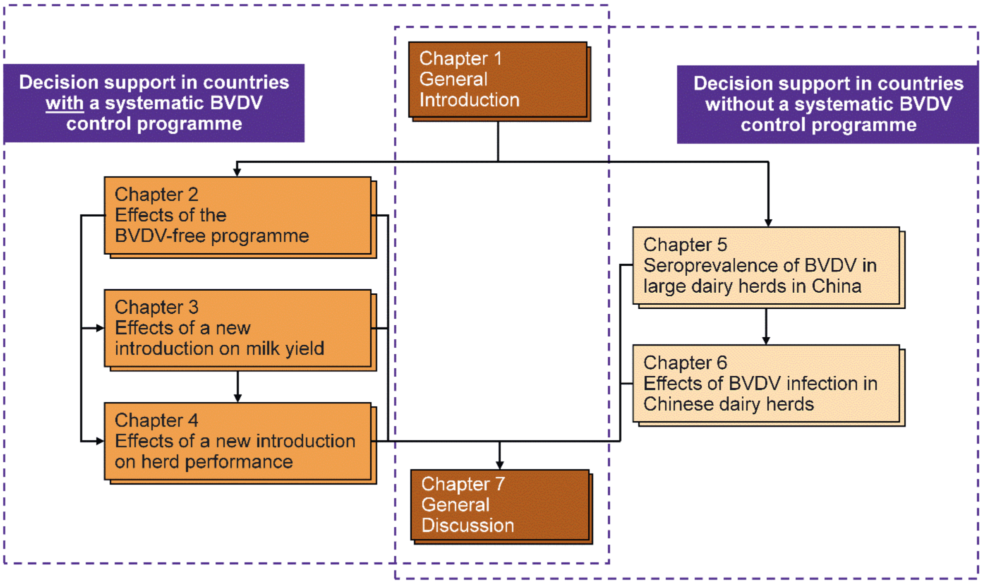

Figure 1.3 Schematic overview of the thesis and link between the chapters.

Chapter 2 describes a case-control study investigating the economic (gross margin) and production effects (somatic cell count, calving interval, and milk yield) of BVDV-free certification using propensity score matching (PSM) and difference-in-difference (DID) approach. Accounting data and herd performance data were used to provide insight in the effects of the BVDV-free programme.

Chapter 3 and Chapter 4 determine the effects of a new BVDV introduction on dairy herds involved in the BVDV-free programme. Effects of new BVDV introduction on the average daily milk yield (Chapter 3) and herd performance including somatic cell count, calving interval, culling risk, and calf mortality rate (Chapter 4) were studied. For this purpose, production data of a large number of Dutch dairy herds were combined with surveillance data. Mixed models were developed based on longitudinal data on herd characteristics, BVDV infection status, and herd performance.

Chapter 5 investigates the seroprevalence of BVDV in three large-scale dairy herds in North China based on data collected from the field.

Chapter 6 simulates the dynamics of BVDV infection and the associated production and economic losses in a large-scale Chinese dairy herd. A dynamic stochastic bio-economic simulation model was extended to estimate the direct and indirect economic losses from the introduction of BVDV.

Chapter 7 discusses the main findings of this thesis, assesses the data and methods, outlines the implication, and draw the main conclusions of this thesis.

2

CHAPTER 2

Estimating the Effect of a Bovine Viral Diarrhoea Virus Control Programme: An Empirical Study on the Performance of Dutch Dairy Herds

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Abstract

More and more European countries have implemented a bovine viral diarrhoea virus (**BVDV**) control programme. The economic effects of such programmes have been evaluated in simulations, but empirical studies are lacking. We investigated the economic (gross margin) and production effects (milk yield, somatic cell count, and calving interval) of BVDV-free certification based on longitudinal annual accounting and herd performance data from Dutch dairy herds between 2014 and 2019. This study was designed as a case-control study: case herds were defined as herds where the BVDV status changed from unknown to BVDV-free during the study period, while control herds were BVDV-free during the entire study period. Potential bias between the covariates of the two herd groups was reduced by matching case and control herds using the propensity score matching method. To compare the differences between case and control herds before and after BVDV-free certification, we used the time-varying Difference-in-Differences estimation (**DID**) methodology. The results indicate that there was no significant change in milk yield, somatic cell count, calving interval, and gross margin upon BVDV-free certification. There are several possible explanations for the non-significant effects observed in our study, such as the unknown status for case herds, not knowing the true BVDV infection situation in case herds and not knowing if control measures were implemented in case hers prior to participating in the BVDV-free programme. In our study, the effects of BVDV-free certification might have been underestimated, given that the Dutch BVDV control programme became mandatory during the study period, and some of the case herds might have never experienced any BVDV infection.

Keywords: dairy, bovine viral diarrhoea virus, control programme, propensity score matching, difference-in-different, economic

2.1 Introduction

Bovine viral diarrhoea (**BVD**) is a contagious cattle disease, reported in 88 countries worldwide (Richter et al., 2017; Pinior et al., 2019). Infections with bovine viral diarrhoea virus (**BVDV**) cause reproductive disorders (e.g. infertility, early embryonic deaths, abortion, prolonged calving interval) and reduce productivity (e.g. reduced milk yield, increased premature culling and mortality among calves and cows), resulting in poor herd and economic performance (Grooms, 2006; Stott et al., 2010; Damman et al., 2015). Direct monetary losses due to BVDV range from 0.45 to 604.13 euros per animal (Richter et al., 2017).

Four Scandinavian countries (Norway, Sweden, Finland, and Denmark) launched national BVDV eradication programmes in the early 1990s, and entered the final stage of eradication ten years later (Moennig et al., 2007; Thomann et al., 2017). This successful experience inspired other European countries (e.g., Switzerland, Germany, Ireland, UK, and France) to implement voluntary or compulsory BVDV control programmes (Joly et al., 2005; Graham et al., 2015; Heffernan et al., 2016; Kaiser et al., 2016; Wernike et al., 2017). In the Netherlands, a voluntary BVDV control programme, the so-called "BVDV-free" programme, was launched in 1997 (Mars and Van Maanen, 2005). After twenty years, the BVDV-free programme had reached out to 49% of the Dutch dairy farms (van Duijn et al., 2019). To further eradicate BVDV, the national mandatory BVDV control programme started from April 1, 2018 (ZuivelNL, 2018). As of the first quarter of 2021, already 84% of Dutch dairy farms had a BVDV-free or BVDV-unsuspected status, up from 65% in the first quarter of 2018 (Royal GD, 2018, 2021b).

There is a growing body of literature that estimates the effects of the implementation of BVDV control measures on production (e.g., milk yield, somatic cell count (**SCC**), calving interval) of dairy farms. Existing empirical studies have found that the positive effects of BVDV eradication on production are limited. For instance, Tschopp et al. (2017) found no significant difference in milk yield before and after BVDV eradication in Swiss dairy farms, but reported a slight decrease in bulk milk SCC after the herds were declared free of BVDV infection. Contrary, Berends et al. (Berends et al., 2008) found no significant changes in bulk milk SCC after the Dutch dairy herds were certified as BVDV-free. Similarly, no significant difference in calving interval was observed between BVDV-free herds and herds with at least one persistently infected (**PI**) animal in Austria (Burgstaller et al., 2016a). Berends et al. (Berends et al., 2008) was the most recent Dutch study that empirically evaluated the effects of becoming BVDV free. How these may have changed following the introduction of the (mandatory) Dutch BVDV control programmes remains unexplored.

A recent review summarized the economic consequences of BVDV prevention and mitigation activities in twelve countries worldwide (Pinior et al., 2017). Control programmes were economically justified in only four countries (i.e., Norway, Ireland, France, and Switzerland), based on simulation models (Dufour et al., 1999; Valle et al., 2005; Hasler et al., 2012a; Stott et al., 2012). In the Netherlands, Santman-Berends et al. (Santman-Berends et al., 2015) simulated the economic effects of different BVDV control scenarios. Besides these published simulation studies, to our knowledge, no empirical studies exist that are based on accounting data. Therefore, the economic effects of the Dutch BVDV-free programme are still unknown.

The objective of our study was to empirically investigate the economic (gross margin) and production effects (SCC, calving interval, and milk yield) of BVDV-free certification. The analysis will be based on recent longitudinal annual accounting and herd performance data.

2.2 Materials and methods

2.2.1 Data Collection

Longitudinal herd-level data on herd characteristics, herd performance, accounting and BVDV status were provided by Dirksen Management Support (DMS, Beusichem, the Netherlands). The data represented 1,828 yearly observations of 456 anonymized Dutch dairy herds cooperating with DMS over the years 2011 to 2019. Herd characteristics included land use and herd size. Herd performance consisted of data on total milk production, milk fat and protein percentage, calving interval, non-return rate, age of culled cows, number of culled cows, number of inseminations, etc. The annual accounting data involved total revenues (consisting of milk revenues and calf and cattle revenues), fixed and variable costs (e.g., feed costs, fertilizer costs, animal health costs), and gross margin (i.e., total revenues minus total variable costs). For each year, the BVD status of the herd was categorized as either BVDV-free, not-free, or unknown. BVDV-free means that the herd has participated in the BVDV control programme and obtained BVDV-free certification, while not-free means that the herd has participated in the control programme but has not yet obtained the BVDV-free certification. Unknown means that the herd does not participate in the BVDV-free programme, making the actual BVDV infection status unknown.

2.2.2 Data Editing

Three new variables were generated: farm intensity (no. of milking cows/hectare/year), milk yield (kg/cow/year), and gross margin (euros/kg milk/year). The data were cleaned as follows.

Firstly, 482 observations with missing data on BVDV status or with meaningless values (e.g., SCC=0, calving interval=0) were removed. Secondly, only herds with data for at least two consecutive years were included, and therefore 68 observations were excluded from the data set. Thirdly, some extreme values (i.e., farm intensity >5 cows/hectare, herd size >400 cows, land use >200 hectares) were detected by visual inspection and 21 observations were excluded. Fourthly, as there were only five observations in 2011 and 2012, these were excluded as well.

After these cleaning steps, the data set included 1,252 observations from a total of 270 herds. Only 27 of these 270 herds changed from 'BVDV not free' to 'BVDV free'. Therefore, we focused our study on herds where the BVDV status changed from 'unknown' to 'BVDV free' (51 herds), and we excluded the 'BVDV not-free' herds. A sub-data set was created per year, resulting in five sub-data sets (i.e., from 2015 to 2019). Each sub-data set included data of the year where the herds BVDV status changed from unknown to free (i.e., case herds), data of the preceding year (BVDV status unknown) and data of the following year (BVDV status free). Consequently, the five sub-data sets included three observations per case herd. The respective observations for the same 3 years from herds that were BVDV-free during the entire study period (i.e., control herds) were added to the five sub-data sets. Because 2020 data was not available, the 2019 sub-data set only included observations of two years (2018 and 2019). There were no case herds for the year 2014, and therefore no sub-data set was created for this year, and the data of 2013 were not used. The five sub-data sets from 2015 to 2019 contained 310, 323, 322, 270, and 180 observations from 104, 108, 108, 92, and 90 dairy herds, respectively. Data editing was conducted in R version 4.0.5 (R Core Team, 2018).

2.2.3 Case and control herds matching

This study was designed as a case-control study to compare the production and economic parameters of case and control herds before and after BVDV certification. The studied case and control herds were not randomly assigned, which may lead to large differences between the observed covariates between the two groups, leading to biased estimates of the effects (D'Agostino Jr, 1998). To reduce this potential bias, case and control herds were matched using the propensity score matching (**PSM**) method (Rosenbaum and Rubin, 1983; Caliendo and Kopeinig, 2008; Rose and Van Der Laan, 2009). Specifically, herd size, farm intensity, and milk yield in the year that the case herds were certified as BVDV-free were selected as continuous covariates to match the case and control herds for the calving interval and gross margin analyses. In the matching procedure for the milk yield and SCC analyses, herd size and farm intensity were used to match case and control herds. The PSM procedure was performed with the psmatch2 module (Leuven and Sianesi, 2003) in STATA version 15 (StataCorp, 2017). The propensity scores were estimated through a logit regression of the BVDV-free certification on the selected covariates (Rosenbaum and Rubin, 1983). Different matching algorithms for matching on the propensity score (nearest neighbour matching without replacement, 1:1, 1:2, 1:3, 1:4 nearest neighbour matching with 0.01 calliper width, kernel matching) were examined to determine the most suitable matching method for each sub-data set. The matching performance of different algorithms was assessed by comparing the number of matched groups and the standardized percentage bias (generally less than 5%) after matching with the post-estimation command pstest (Rosenbaum and Rubin, 1985; Haviland et al., 2007; Austin, 2014). The selected PSM matching algorithms for each sub-data set is listed in Table 2.1. Two matching algorithms were selected: 1:2 nearest neighbour matching with 0.01 calliper width (control herds were matched with replacement), and Kernel matching. The balancing of the covariates in all sub-data sets before and after matching are presented in the Supplementary materials Table 2.S1 and 2.S2. Compared with the unmatched results, the standardized percentage bias of all covariates was reduced after matching. This proves the effectiveness of PSM in reducing the confounding effects between the case and control herds and prepares for further statistical analysis.

Table 2.1. Selected matching algorithms for five sub-data sets of the analysis for calving interval, gross margin milk yield, and somatic cell count

Sub-data set	Selected matching method for analysis of calving interval, and gross margin	Selected matching method for analysis of milk yield and somatic cell count
2015	1:2 nearest neighbour matching with 0.01 calliper width	Kernel matching
2016	1:2 nearest neighbour matching with 0.01 calliper width	Kernel matching
2017	Kernel matching	Kernel matching
2018	1:2 nearest neighbour matching with 0.01 calliper width	Kernel matching
2019	Kernel matching	1:2 nearest neighbour matching with 0.01 calliper width

The matched sub-data sets were merged into two final data sets: a data set for analysing calving interval and gross margin (i.e., data set 1); and a data set for analysing milk yield and SCC (i.e., data set 2). Table 2.2 shows the number of case and control herds in each (sub)data set. Forty-one case herds (116 observations) and 101 control herds (373 observations) were included in data set 1. Data set 2 was slightly larger, with a total of 627 observations from 43 case herds and 109 control herds.

Table 2.2. Summary of the matched sub-data sets using the property score matching method and the merged final data sets

Analysed parameters	Data set	No. of case herds[1] (No. of obs.)	No. of control herds[2] (No. of obs.)	Total no. of studied herds (Total no. of obs.)
Calving interval, gross margin	2015	7 (21)	12 (36)	21 (57)
	2016	12 (36)	21 (63)	33 (99)
	2017	12 (36)	86 (258)	98 (294)
	2018	6 (15)	12 (36)	18 (51)
	2019	4 (8)	44 (88)	48 (96)
	Data set 1[3]	41 (116)	101 (373)	142 (489)
Milk yield, somatic cell count	2015	7 (21)	66 (198)	73 (219)
	2016	14 (42)	76 (228)	90 (270)
	2017	12 (36)	80 (240)	92 (276)
	2018	6 (15)	63 (189)	69 (204)
	2019	4 (8)	8 (16)	12 (24)
	Data set 2[3]	43 (122)	109 (505)	152 (627)

[1] Case herds = herds of which the BVDV status changed from unknown to BVDV-free during the study period.
[2] Control herds = herds that were BVDV-free during the entire study period.
[3] The final data set is panel data, so duplicate records in different sub-data set were removed.

2.2.4 Data analysis

To estimate the effect of BVDV-free certification, economic and production performance was compared between case and control herds before and after BVDV-free certification using Difference-in-Differences (**DID**) estimation methodology, which is commonly used to evaluate the causal effects of an intervention (Ashenfelter and Card, 1985; Beck et al., 2010; Callaway and Sant'Anna, 2020). Figure 2.1 illustrates the DID estimation methodology for this study. The constant difference in outcome (i.e., milk yield, SCC, calving interval, and gross margin) between the case and control herds after BVDV-free certification was computed, as well as the difference in outcome between the two groups before the BVDV-free certification. Subsequently, the effect of BVDV-free certification was estimated by subtracting the constant difference from the difference between the two groups before certification.

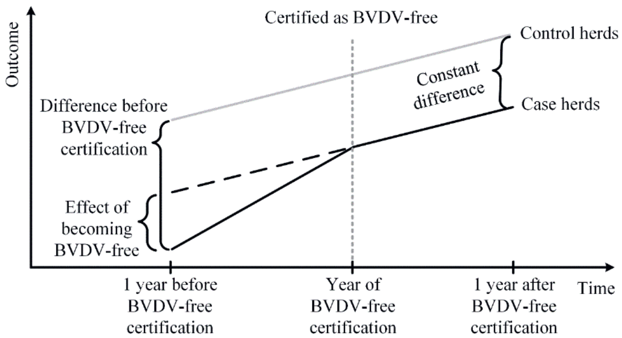

Figure 2.1. Schematic diagram of using the Difference-in-Differences estimation methodology to analyse the effect of BVDV-free certification on Dutch dairy farms.

The time-varying DID estimation methodology, applied to the situation where a programme is implemented in multiple time periods, was used in this study (Callaway and Sant'Anna, 2020). The regression set-up is as follows (Beck et al., 2010):

$$ln(Y)_{it} = \alpha + \beta D_{it} + \delta X_{it} + \mu_i + \rho_t + \varepsilon_{it}, i = 1, \dots, n; t = 2014, \dots, 2019 \quad [2.1]$$

where Y_{it} represents indicators of calving interval, milk yield, SCC, and gross margin of herd i in year t. The four analyzed parameters have been natural log-transformed because they failed the normal distribution test. The variable of interest is D_{it}, a dummy variable that equals 1 for unknown BVDV status and equals 0 when the status is BVDV free. The coefficient β indicates the effect of BVDV-free certification on the outcome parameters. X_{it} refers to the time-varying herd-level control variables, including continuous variables on herd size and milk yield and the categorical variable farm intensity. Farm intensity consists of three categories: small ($n \leq 1.6$ cows/ha/year, reference category), medium ($1.6 < n \leq 2.6$ cows/ha/year), and large ($2.6 < n \leq 5$ cows/ha/year). The categories of farm intensity were defined by the histogram and heterogeneity trend over intervals. Particularly, the independent variable milk yield was excluded from the SCC and milk yield regression analyses, since this control variable could be expected to act as intervener (Lindberg and Emanuelson, 1997). μ_i, ρ_t are vectors of herd and year dummy variables that account for herd and year fixed effects, and ε_{it} is the error term. The DID estimation methodology was performed with the xtreg command (StataCorp., 2021) in STATA version 15 (StataCorp, 2017).

2.3 Results

2.3.1 Descriptive statistics

Table 2.3 provides the descriptive statistics (data set 1 and 2) of the performance of Dutch dairy herds in relation to BVDV status between 2014 and 2019. In data set 1, the average calving interval was 402 (Standard deviation (**SD**)=18) days in case herds, and 406 (SD=21) days in control herds. The gross margin was 0.293 (SD=0.056) euros/kg milk in case herds, and 0.279 (SD=0.054) euros/kg milk in control herds. In data set 2, the milk yield of case herds was 8,800 (SD=816) kg/cow/year, while that of the control herds was 8,900 (SD=889) kg/cow/year. The SCC was 156,000 (SD=46,000) cells/mL in case herds and 163,000 (SD=51,000) cells/mL in control herds.

Table 2.3. The descriptive statistics of the performance in the studied Dutch dairy herds from 2014 to 2019

Variables	Data set 1 (for the analysis of calving interval and gross margin)						Data set 2 (for the analysis of milk yield and SCC)					
	Case herds[1] (No. of herds = 41, No. of obs. = 116)		Control herds[2] (No. of herds = 101, No. of obs. = 373)		Overall (No. of herds = 142, No. of obs. = 489)		Case herds[1] (No. of herds = 43, No. of obs. = 122)		Control herds[2] (No. of herds = 109, No. of obs. = 505)		Overall (No. of herds =152, No. of obs. = 627)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Herd size, n cows	110	38	118	46	116	45	110	38	112	41	112	41
Land use, ha	56	19	58	22	57	22	57.2	21	55.9	21	56.1	21
Farm intensity, n cows/ha/year	2.01	0.37	2.09	0.45	2.07	0.44	1.98	0.39	2.04	0.42	2.03	0.41
Milk yield, kg/cow/year	8,870	768	8,920	869	8,910	846	8,800	816	8,900	889	8,880	876
Fat, %	4.42	0.18	4.4	0.17	4.41	0.17	4.42	0.18	4.38	0.16	4.39	0.17
Protein, %	3.55	0.1	3.53	0.09	3.54	0.09	3.55	0.10	3.52	0.08	3.53	0.09
SCC, 1,000 cells/mL	158	45	165	52	163	51	156	46	163	51	161	50
Calving interval, days	402	18	406	21	405	21	401	18	407	22	406	21
Non-return rate, %	62	13	58	13	59	13	62	13	58	12	59	12
No. of inseminations, n	2.07	0.46	2.21	0.48	2.18	0.48	2.05	0.45	2.18	0.42	2.16	0.43
Milk return, euro/kg milk/year	0.369	0.05	0.366	0.041	0.367	0.043	0.367	0.050	0.366	0.042	0.366	0.044
Gross margin, euro/kg milk/year	0.293	0.056	0.279	0.054	0.282	0.055	0.293	0.057	0.279	0.053	0.282	0.054

[1] Case herds = herds for which the BVDV status changed from unknown to BVDV-free during the study period.
[2] Control herds = herds that were BVDV-free during the entire study period.

2.3.2 Estimated effects of BVDV-free certification

Table 2.4 presents the results of the time-varying DID estimation methodology to study the effects of BVDV-free certification on milk yield, SCC, calving interval, and gross margin of Dutch dairy herds between 2014 and 2019. Overall, the results did not demonstrate any difference between the herds with BVDV-free and unknown status, and therefore no effects of BVDV-free certification on economic and production performance were observed.

Table 2.4. Summarized results of the Difference-in-Differences analysis for the effects on calving interval (days), gross margin (euros/kg milk/year), milk yield (kg/cow/year) and somatic cell count (1,000 cells/mL) of Dutch dairy herds bovine viral diarrhoea virus (BVDV)-free certification between 2014 and 2019

Effects	Categories	Calving interval		Gross margin		Milk yield		Somatic cell count	
		Exponent of estimated coefficient	*p*-value	Exponent of estimated coefficient	*p*-value	Exponent of estimated coefficient	*p*-value	Exponent of estimated coefficient	*p*-value
Intercept		384	0.00	0.43	0.00	8,820	0.00	186	0.00
BVDV certification status	BVDV-free	Referent							
	Unknown[1]	0.996	0.51	1.007	0.72	0.994	0.42	0.999	0.96
Herd size, n cows		1.000	0.09	0.999	0.18	1.000	0.59	1.000	0.86
Farm intensity, n cows/ha/year	Small[2]	Referent							
	Medium[2]	0.998	0.78	1.016	0.46	0.987	0.25	0.924	0.00
	Large[2]	0.990	0.19	0.998	0.93	0.982	0.18	0.887	0.00
Milk yield, kg/cow/year		1.000	0.61	1.000	0.12	-	-	-	-
Year	2014	Referent							
	2015	0.999	0.93	0.759	0.00	1.013	0.08	0.924	0.00
	2016	0.989	0.14	0.689	0.00	1.021	0.02	0.961	0.15
	2017	0.991	0.23	0.979	0.46	1.055	0.00	0.904	0.00
	2018	0.986	0.04	0.933	0.01	1.060	0.00	0.867	0.00
	2019	0.987	0.16	0.924	0.01	1.064	0.00	0.861	0.00

[1] The unknown status refers to a herd that did not participate in the BVDV-free programme, for which the actual BVDV infection status was unknown.
[2] The farm intensity variable consists of three categories: small (n ≤ 1.6 cows/ha/year), medium (1.6 < n ≤ 2.6 cows/ha/year), and large (2.6 < n ≤ 5 cows/ha/year).

2.4 Discussion

In this case-control study, the economic (gross margin) and production effects (SCC, calving interval, and milk yield) of BVDV-free certification were investigated using PSM and DID approach. This study is based on longitudinal annual herd performance and accounting data of 152 Dutch dairy herds from 2014 to 2019. The results indicated that the four analysed parameters did not significantly change when herds changed from unknown status to BVDV-free. In other words, for herds whose status changed from 'unknown' to 'BVDV-free', no changes were observed in milk yield, SCC, calving interval, and gross margin compared to herds that were BVDV-free during the entire study period.

The current study was designed as a case-control study. In order to estimate the effects of BVDV-free certification on the premise of eliminating potential confounding effects between case and control herds, the PSM-DID approach was used. The DID estimation methodology provides unbiased effect estimates if there is a parallel trend in the analysed parameters between the case and control herds in the absence of the control programme (Wing et al., 2018). Propensity score matching is commonly used to achieve this parallel trend assumption of DID (Stuart et al., 2014). In this study, different PSM algorithms were conducted in different sub-data sets to determine the most suitable matching method for each sub-data set. The two selected matching methods, 1:2 nearest neighbour matching with 0.01 calliper width and Kernel matching, while ensuring matching performance, matched as many case and control herds as possible. The smaller standardized percentage bias after matching confirms the efficacy of the matching process. However, only approximately half of the observations were retained after the matching process: 489/1.252 observations were included in the SCC, calving interval, and gross margin analysis, while 627/1252 were included in the milk yield analysis. Future studies should include more observations and herds to further investigate the effects of the BVDV-free programme.

To the best of our knowledge, our study is the first to use herd characteristics, herd performance, accounting, and BVDV status data to analyse the effects of the Dutch BVDV-free programme. Nevertheless, further empirical studies are suggested considering the nature of the available data in this study. As a retrospective case-control study, the study herds were not randomly selected, which could have introduced selection bias. All dairy herds included in this study cooperated with DMS, and there are farmers' seminars every year to discuss how to improve the farm performance (expert opinion obtained from interview). Therefore, the dairy farmers in this study can be characterized as farmers with an above-average interest in optimizing farm management, who are committed to improving economic performance. In addition, during the study period from 2014 to 2019, the studied herds performed better than the average Dutch dairy herds, with a larger herd size (116 cows, Table 2.2) and milk yield than the national average (116 vs 98 cows, and 8,910 vs 8,733 kg/cow/year, Table 2.2 and CRV, 2021). Therefore, further research including more herds with a higher variety in characteristics (e.g., herd size, cattle breed, region) might result in different results. Furthermore, the covariates used for PSM are limited. Due to data availability issues, only herd size, farm intensity, and milk yield (for milk yield analysis, the first two were used) were selected to match case and control herds. The matching outcome will be more accurate if more covariates are included, such as breeding, region, etc., although this will also result in the exclusion of more herds from the analysis (Bryson et al., 2002).

Our empirical analysis shows no significant change in production and economic performance of dairy herds changed from 'unknown' to 'BVDV free'. This result was unexpected, as previous observational studies found an increase in SCC (Lindberg and Emanuelson, 1997; Tschopp et al., 2017) and calving interval (Niskanen et al., 1995; Burgstaller et al., 2016a) and a decrease in milk yield (Lindberg and Emanuelson, 1997; Beaudeau et al., 2004) in BVDV-infected herds. On the other hand, other published empirical studies on the effects of the BVDV control programme also did not find significant differences in SCC (Berends et al., 2008), calving interval (Burgstaller et al., 2016a), and milk yield (Tschopp et al., 2017) between case and control herds. An important reason for such non-significant findings in these and our study may be the uncertain infection dynamics. Berends et al. (Berends et al., 2008), Burgstaller et al. (Burgstaller et al., 2016a), and Tschopp et al. (Tschopp et al., 2017) all mentioned that case herds may have developed immunity prior to the eradication of BVDV, thereby protecting the herd from bigger losses. Information about the infection dynamics of case herds before the eradication of BVDV is often not available in retrospective data, which makes it difficult to detect significant results or to explain non-significant results. Although previous studies have reported negative effects of BVDV infection on gross margin (Fourichon et al., 2005; Knific and Zgajnar, 2014; Thomann et al., 2017), these were all based on normative simulation models. These ex-ante studies can support decisions regarding BVDV control programmes and are often conducted before the implementation of such programmes. However, for future decision making, it would also be useful to perform ex-post studies once the BVDV control programmes are being carried out. Such economic empirical ex-post studies have not been conducted to date, which reflects the need for additional studies in the future.

Two more specific reasons may explain the absence of effects upon BVDV-free certification in the present study: the definition of the case herds as well as the frequency of observations. First, case herds were defined as herds where the BVDV status changed from ‘unknown’ to ‘BVDV-free’ during the study period. However, the real BVDV infection situation of case herds in the unknown period cannot be accurately defined without knowing the presence of PI animals (the main reservoir of BVDV and shed a large number of viruses to susceptible animals throughout their lives) and the antibody prevalence. On the one hand, if PI animals present in the case herds in the unknown period, it is expected that economic and production performance will improve after BVDV-free certification, as the negative impact of BVDV infection has been reported to be larger in herds with PI animals than without (Houe, 2003; Moennig et al., 2007; Evans et al., 2019). On the other hand, if the antibody prevalence of case herds was relatively high in the unknown period, the changes in economic and production performance are likely to be small. The high antibody prevalence associated with lifelong immunity in the majority of the cows in the herd could protect the herd from serious negative effects (Brownlie et al., 1987; Baker, 1990; Pinior et al., 2019; Yue et al., 2021a; b). Another possibility is that case herds whose BVDV status changed directly from unknown to BVDV free may have already implemented some control measures before participating in the BVDV-free programme. Second, this study was based on annual herd performance and accounting data, and only 3 yearly observations per herd were included. If more frequent data with more observations will be available, it will be possible to analyse economic and production performance before and after the BVDV-free certification more precisely.

The real BVDV infection situation of case herds before BVDV-free certification is unknown, therefore, sub-analyses were conducted on the herds with BVDV-not-free status to further investigate the effect of BVDV-free certification. Specifically, the performance of herds that changed the BVDV status from BVDV-not-free to free was compared with the performance of herds that have always been BVDV-free. The matching and analysis process of the sub-analyses were the same as the main analysis of this study. It has to be noted that the number of case herds in these sub-analyses was very small (e.g., only 17 case herds in the sub-analysis of gross margin, Supplementary materials Table 2.S3). Results of the sub-analyses (shown in Supplementary materials Table 2.S4) also showed non-significant changes in the four analysed parameters when herds became BVDV-free-certified. The results of the sub-analyses support the results of the non-significant effects in the main analysis.

In our study, no differences in gross margin were found when the herds change from unknown status to BVDV-free. In addition to the possible general reasons discussed above, another potential explanation for the economic indicator is that the costs of BVDV-free certification have levelled out the potential positive economic consequences of being BVDV-free. In both the voluntary (prior to 2018) or mandatory (after 2018) BVDV control programme in the Netherlands, dairy farmers pay all costs related to BVDV control, such as virus testing costs of new-born calves for ten months in the intake phase, the virus or antibody testing costs in the monitoring phase, and the costs of removing PI animals (if any, van Duijn et al., 2019). Therefore, these animal health costs may balance the positive economic consequences of BVDV-free certification (e.g., increased milk sales, decreased premature culling, etc.). In addition, gross margin is a useful indication to compare the economic performance of different herds, but it can be strongly influenced by management factors other than BVDV-free certification. The management factors can be partly triggered by policy alterations (Vredenberg et al., 2021). During the study period, the milk quota system was abolished in 2015, and phosphate regulation was implemented in 2017 (Jongeneel et al., 2017; CRV, 2018; Kulkarni et al., 2021). As a consequence, different study herds may have taken different strategic management decisions, thereby affecting gross margin (Steeneveld et al., 2015; Vredenberg et al., 2021). So, while herd and year effects were included in the DID model, it is difficult to eliminate the impact of management changes on gross margin due to the large heterogeneity of farm management decisions.

The effects of the Dutch BVDV-free programme may have been underestimated due to the study period. During the study period, the BVDV control campaign in the Netherlands came to the tail end with the implementation of the compulsory schemes in 2018. On the one hand, the voluntary BVDV control started in 1997 has made effective progress before the study period. A prevalence study from GD animal health in 2013/2014 showed that only 14% of dairy farms had a recent BVDV circulation (GD Animal Health, 2014), so the case herd may not have the BVDV circulation in the period with the unknown status. On the other hand, BVDV control became mandatory in Dutch dairy herds during the study period, so even the dairy herds that had never experienced BVD related issues were obliged to participate in the programme and to achieve the official free or unsuspected status. Such dairy herds may also be included in the case herds, resulting in an underestimation of the effectiveness of BVDV control.

Author contributions

XY, JW, MV, WS and HH: design of the study. XY, JW and HH: data analysis. XY: drafting the manuscript. MV and WS: drafting the manuscript and critical revision of the article. HH: critical revision of the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary materials

Table 2.S1. Comparison of mean value, % bias[1], t-value, and p-value of the matching covariates for the case[2] and control herds[3] before and after propensity score matching for each sub-data set for the analysis of calving interval and gross margin

Sub-data set	Variables	Unmatched/ Matched	Mean		%bias	t	*p*-value
			Case herds	Control herds			
2015	Farm intensity, n/ha	Unmatched	1.91	2.18	−54.7	−1.13	0.260
		Matched	1.91	1.91	0.3	0.01	0.992
	Herd size	Unmatched	103	117	−34.6	−0.74	0.463
		Matched	103	100	9.7	0.27	0.789
	Milk yield, kg/cow/year	Unmatched	8918	8720	30.5	0.61	0.542
		Matched	8918	8824	14.4	0.21	0.837
2016	Farm intensity, n/ha	Unmatched	1.91	2.22	−58.9	−1.74	0.085
		Matched	1.96	1.91	10.6	0.39	0.700
	Herd size	Unmatched	115	126	−22.8	−0.74	0.462
		Matched	113	111	2.9	0.08	0.940
	Milk yield, kg/cow/year	Unmatched	8419	8853	−52.4	−1.82	0.072
		Matched	8618	8731	−13.6	−0.38	0.711
2017	Farm intensity, n/ha	Unmatched	2.22	2.07	27	0.98	0.327
		Matched	2.07	2.08	−2.1	−0.07	0.944
	Herd size	Unmatched	112	127	−30.9	−0.91	0.366
		Matched	115	115	0.1	0.00	0.998
	Milk yield, kg/cow/year	Unmatched	8776	9050	−23.6	−0.96	0.341
		Matched	9051	9037	1.2	0.04	0.972
2018	Farm intensity, n/ha	Unmatched	2.47	2.05	50.2	2.07	0.041
		Matched	2.09	2.09	−0.8	−0.03	0.981
	Herd size	Unmatched	103	123	−50.2	−0.98	0.329
		Matched	98	98	−0.5	−0.01	0.990
	Milk yield, kg/cow/year	Unmatched	9305	9150	20.8	0.47	0.639
		Matched	9157	9180	−3.1	−0.05	0.961
2019	Farm intensity, n/ha	Unmatched	2.22	2.07	37.6	0.68	0.497
		Matched	2.22	2.23	−3.5	−0.05	0.964
	Herd size	Unmatched	135	128	9.3	0.22	0.828
		Matched	135	138	−3.8	−0.05	0.963
	Milk yield, kg/cow/year	Unmatched	8582	9195	−76	−1.44	0.153
		Matched	8582	8621	−4.9	−0.08	0.941

[1] % bias = the standardized percentage bias, which is the percentage difference of the sample means in the case and control sub-samples as a percentage of the square root of the average of the sample variances in the case and control herds (Leuven; Rosenbaum and Rubin, 1985).
[2] Case herds = herds for which the BVDV status changed from unknown to BVDV-free during the study period.
[3] Control herds = herds that were BVDV-free during the entire study period.

Table 2.S2. Comparison of mean value, % bias[1], t-value, and p-value of the matching covariates for the case[2] and control herd[3] before and after propensity score matching for each sub-data set for the analysis of milk yield and somatic cell count

Sub-data set	Variables	Unmatched /Matched	Mean		%bias [3]	t	p-value
			Case herds[1]	Control herds[2]			
2015	Farm intensity, n/ha	Unmatched	1.91	2.18	−54.7	−1.13	0.260
		Matched	1.91	1.92	−1.9	−0.06	0.950
	Herd size	Unmatched	103	117	−34.6	−0.74	0.463
		Matched	103	103	0.3	0.01	0.995
2016	Farm intensity, n/ha	Unmatched	1.91	2.22	−58.9	−1.74	0.085
		Matched	1.91	1.92	−1.7	−0.07	0.944
	Herd size	Unmatched	115	126	−22.8	−0.74	0.462
		Matched	115	115	−1.2	−0.03	0.974
2017	Farm intensity, n/ha	Unmatched	2.22	2.07	27	0.98	0.327
		Matched	2.07	2.05	3.3	0.12	0.906
	Herd size	Unmatched	112	127	−30.9	−0.91	0.366
		Matched	115	111	8.9	0.29	0.775
2018	Farm intensity, n/ha	Unmatched	2.47	2.05	50.2	2.07	0.041
		Matched	2.09	2.13	−4.7	−0.14	0.888
	Herd size	Unmatched	103	123	−50.2	−0.98	0.329
		Matched	98	98	0.4	0.01	0.991
2019	Farm intensity, n/ha	Unmatched	2.22	2.07	37.6	0.68	0.497
		Matched	2.22	2.21	2.6	0.04	0.968
	Herd size	Unmatched	135	128	9.3	0.22	0.828
		Matched	135	128	9.2	0.13	0.900

[1] % bias = the standardized percentage bias, which is the percentage difference of the sample means in the case and control sub-samples as a percentage of the square root of the average of the sample variances in the case and control herds (Leuven; Rosenbaum and Rubin, 1985).
[2] Case herds = herds for which the BVDV status changed from unknown to BVDV-free during the study period.
[3] Control herds = herds that were BVDV-free during the entire study period.

Table 2.S3. Summary of the matched sub-data sets using the property score matching method and the merged final data sets for the sub-analysis

Analysed parameters	Data set	No. of case herds[1] (No. of obs.)	No. of control herds[2] (No. of obs.)	Total no. of studied herds (Total no. of obs.)
Calving interval, gross margin	2015	2 (6)	3 (9)	5 (15)
	2016	3 (7)	26 (78)	29 (85)
	2017	7 (20)	79 (237)	86 (257)
	2018	1 (3)	64 (192)	65 (195)
	2019	4 (8)	9 (18)	13 (26)
	Data set 1[3]	17 (44)	99 (372)	116 (416)
Milk yield, somatic cell count	2015	3 (9)	37 (111)	40 (120)
	2016	4 (10)	15 (45)	19 (55)
	2017	8 (23)	78 (234)	86 (257)
	2018	1 (3)	4 (12)	5 (15)
	2019	4 (8)	13 (26)	17 (34)
	Data set 2[3]	20 (53)	94 (351)	114 (404)

[1] Case herds = herds of which the BVDV status changed from BVDV-not-free to BVDV-free during the study period. The not-free status refers to a herd that participated in the BVDV-free programme but has not yet obtained the BVDV-free certification.
[2] Control herds = herds that were BVDV-free during the entire study period.
[3] The final data set is panel data, so duplicate records in different sub-data set were removed.

Table 2.S4. Summarized results of the sub-analysis for the effects on calving interval (days), gross margin (euros/kg milk/year), milk yield (kg/cow/year) and somatic cell count (1,000 cells/mL) of Dutch dairy herds becoming bovine viral diarrhoea virus (BVDV)-free between 2014 and 2019

Effects	Categories	Calving interval		Gross margin		Milk yield		Somatic cell count	
		Exponent of estimated coefficient	*p*-value	Exponent of estimated coefficient	*p*-value	Exponent of estimated coefficient	*p*-value	Exponent of estimated coefficient	*p*-value
Intercept		431	0.00	0.36	0.00	8455	0.00	200	0.00
BVDV certification status	BVDV-free	Referent							
	Not-free[1]	0.998	0.81	0.968	0.29	0.985	0.34	0.972	0.65
Herd size, n cows		1.000	0.52	1.001	0.35	1.000	0.75	0.999	0.72
Farm intensity, n cows/ha/year	Small[2]	Referent							
	Medium[2]	1.005	0.25	0.993	0.82	0.984	0.34	0.949	0.27
	Large[2]	0.991	0.27	0.981	0.57	0.978	0.27	0.917	0.13
Milk yield, kg/cow/year		1.000	0.07	1.000	0.15	-	-	-	-
Year	2014	Referent							
	2015	1.000	0.99	0.746	0.00	1.014	0.11	0.905	0.00
	2016	0.990	0.47	0.656	0.00	1.030	0.01	0.953	0.27
	2017	0.992	0.58	0.941	0.23	1.065	0.00	0.880	0.00
	2018	0.984	0.29	0.907	0.06	1.072	0.00	0.823	0.00
	2019	0.978	0.14	0.887	0.03	1.058	0.00	0.774	0.00

[1] The not-free status refers to a herd that participated in the BVDV-free programme but has not yet obtained the BVDV-free certification.

[2] The farm intensity variable consists of three categories: small ($n \leq 1.6$ cows/ha/year), medium ($1.6 < n \leq 2.6$ cows/ha/year), and large ($2.6 < n \leq 5$ cows/ha/year).

3

CHAPTER 3

The Effect of Bovine Viral Diarrhoea Virus Introduction on Milk Production of Dutch Dairy Herds

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Abstract

Dairy cows are negatively affected by the introduction of bovine viral diarrhoea virus (**BVDV**), and consequently, produce less milk. Existing literature on potential milk production losses is based on relatively outdated data and hardly evaluates milk production loss in relation to a new BVDV infection in a surveillance system. This study determined the annual and quarterly loss in milk production of BVDV introduction in 3,126 dairy herds participating in the Dutch BVDV-free programme between 2007 and 2017. Among these herds, 640 were “breakdown-herds” that obtained and subsequently lost their BVDV-free status during the study period, and 2,486 herds obtained and retained their BVDV-free status during the study period. Milk yields before and after BVDV introduction were compared through annual and quarterly linear mixed models. The fixed variables for both models included herd type (breakdown-herd or free-herd), bovine viral diarrhoea status (on an annual and quarterly basis), year, season, and a random herd effect. The dependent variable was the average daily milk yield on the test day. To define the possible BVDV-introduction dates, 4 scenarios were developed. In the default scenario, the date of breakdown (i.e., loss of the BVDV-free status) was assumed as the BVDV-introduction date. For the other 3 scenarios, the BVDV-introduction dates were set at 4, 6, and 9 months before the date of breakdown, based on the estimated birth date of a persistently infected calf. In the default scenario, the loss in milk yield due to BVDV introduction occurred mainly in the first year after breakdown, with a reduction in yield of 0.08 kg/cow per day compared with the last year before breakdown. For the other 3 scenarios, the greatest yield reduction occurred in the second year after BVDV introduction, with a loss of 0.09, 0.09, and 0.1 kg/cow per day, respectively. For the first 4 quarters after BVDV introduction in the default scenario, milk yield loss was 0.14, 0.09, 0.02, and 0.08 kg/cow per day, respectively. These quarterly results indicated that milk yield loss was greatest in the first quarter after BVDV introduction. Overall, BVDV introduction had a negative, but on average a relatively small, effect on milk yield for herds participating in the BVDV-free programme. This study will enable dairy farmers and policymakers to have a clearer understanding of the quantitative milk production effect of BVDV on dairy farms in a control programme.

Keywords: bovine viral diarrhoea virus, bovine viral diarrhoea virus introduction, control programme, milk production

3.1 Introduction

Bovine viral diarrhoea (**BVD**) is an endemic bovine disease in many countries across the world and is caused by bovine viral diarrhoea virus (**BVDV**, Houe, 2003; Lindberg et al., 2006). BVD could have major impact on cattle health. Next to diarrhoea, BVD can lead to fever, pneumonia, growth retardation, immunosuppression, and reproductive disorders, which can contribute to a reduction of milk production and consequently economic losses (Baker, 1995; Ridpath et al., 2000). Richter et al. (2017) systematically reviewed the direct economic loss caused by BVD, which can vary widely from 2 to 625 EUR per cow per year (Sørensen et al., 1995; Stelwagen and Dijkhuizen, 1998).

To reduce BVDV infection and its negative impact, some European countries and regions, such as Switzerland, Austria, Denmark, Germany, Ireland, and Scandinavia, have successfully implemented eradication or control programmes with reductions in BVDV prevalence and associated production losses (Scharnböck et al., 2018; Richter et al., 2019). In the Netherlands, Royal GD (Deventer, the Netherlands) initiated a voluntary BVDV control programme (i.e. BVDV-free programme) in 1997 (Mars and Van Maanen, 2005). Herds participating in this control programme are certified as BVDV-free if they succeed in identifying and removing persistently infected (**PI**) animals, and follow up with a monitoring phase surveilling BVDV status at the herd level. When monitoring indicates BVDV has circulated, i.e. BVDV was (re)introducted in these previously BVDV-free herds, the herd will lose its BVDV-free status. In 2007/2008, 7% of the herds certified as BVDV-free in the programme lost their BVDV-free status (i.e. experienced a breakdown), while in 2015/2016 this was only true for 4% of the certified herds (Veldhuis et al., 2018). Overall, the implementation of the BVDV-free control programme reduced the percentage of Dutch dairy farms that had an indication of BVDV circulation, from 19.4% in 2007 to 8.7% in 2017 (GD, 2016, 2017). Although some research has been carried out on the BVDV-free programme in the Netherlands (Berends et al., 2008; Veldhuis et al., 2018; van Duijn et al., 2019), little is known about the effect of BVDV (re)introduction on milk production. Moreover, estimating such milk production losses is complicated because the period at risk starts from the moment BVDV is introduced, which in itself is difficult to accurately determine.

The key to determine the moment of BVDV introduction is BVDV transmission. BVDV can be transmitted horizontally and vertically. Horizontal infection occurs when susceptible cows are infected by transiently infected (**TI**) or PI animals. Vertical infection occurs when the foetus is infected in early gestation and a PI calf is born (Pasman et al., 1994; Peterhans et al., 2010; Foddai et al., 2014). PI animals are the most important source for the spread of the virus (Gunn et al., 2005; Tinsley et al., 2012). Not only is the infection period longer for PI animals than for TI animals, significantly increasing the probability of transmission, the amount of viruses that PI animals continuously shed throughout their lifetime is much larger as well (Niskanen et al., 2000; Lindberg and Houe, 2005; Sarrazin et al., 2014). Susceptible cows in the herds are exposed to BVDV through direct or indirect contact with PI or TI animals, and can lead to subclinical infection manifestations, such as reduced milk production (Baker, 1995).

Reduced milk production due to BVDV introduction has been studied both at cow and herd level. For individual cows, studies show a dramatic reduction in milk production: milk production of PI cows is 48 to 76% lower compared to non-PI cows (Voges et al., 2006; Knific and Zgajnar, 2014). A 50-day longitudinal study by Moerman et al. (1994) showed that the moving average of daily milk production per TI cow decreased by more than 10% within 10 days after seroconversion. At the level of the herd, milk production of BVDV antibody positive herds is 0 to 1.7 kg lower per cow per day, and 368 to 394 kg lower per cow per 305 days, compared to BVDV antibody negative herds (Tiwari et al., 2005, 2007). Beaudeau et al. (2004) identified a milk yield reduction of 0.58 kg/cow/day for cows in recently infected herds compared with cows in not recently infected herds.

While several studies (e.g., Lindberg and Emanuelson, 1997; Beaudeau et al., 2004; Fourichon et al., 2005; Compton, 2006) have compared different herds based on BVDV infection status, changes in milk production within the same herd (i.e. before and after a BVDV introduction) have rarely been investigated. Moreover, previous research on milk production losses relies on relatively outdated data obtained before the introduction of BVDV control programmes. As such, it is unclear what the impact of new BVDV infection on milk production has been from BVDV control programmes, such as the Dutch BVDV-free programme. Therefore, the objectives of this study are to determine the annual and quarterly loss in milk production upon BVDV introduction for dairy herds participating in the Dutch BVDV-free programme between 2007 and 2017.

3.2 Materials and methods

3.2.1 Data Collection

Dairy farms participating in the Dutch BVDV-free programme between September 4, 2006 and June 15, 2016 were included in this study. Longitudinal herd-level BVDV surveillance data of all 4,334 dairy herds were previously described in Veldhuis et al. (2018). To obtain the

BVDV-free status, all cattle in the herds participating in the programme are tested and PI animals (if any) are removed, followed by a 10-month period of virus testing of all new-born calves. If no PI calf is detected during this 10-month period, the herd is certified as BVDV-free and enters the monitoring phase. In the monitoring phase, 5 calves are tested every 6 months for BVDV antibodies, or all new-born calves in the herd are tested for BVDV (explained below). When the monitoring indicates BVDV has been introduced, the herd loses its BVDV-free status. In this study, herds that obtained the BVDV-free status and did not have a breakdown until the end of the study period were defined as ‘free-herds’. The date on which the herd obtained the BVDV-free status was defined as the ‘free-date’. Herds that obtained and subsequently lost their BVDV-free status during the study period were defined as ‘breakdown-herds’. The date of losing the BVDV-free status was defined as ‘breakdown-date’. Cattle Improvement Cooperative (**CRV**, Arnhem, the Netherlands) provided milk production data for 20,553 Dutch dairy herds. This data included information per ‘test-day’ on average daily milk yield per cow (**ADMY**), milk fat, protein and lactose percentage, 305-day milk yield, 305-day milk fat and protein, and average DIM, based on information collected from each herd at monthly intervals between January 1, 2007 and December 31, 2017.

3.2.2 Data Editing

Data of the farms in the BVDV-free programme (4,334 herds) were merged with monthly test-day data on milk production (20,553 herds) based on a unique herd number. The preliminary merged dataset contained 472,523 test-days of 4,211 dairy herds, as not all herds in the dataset of BVDV-free programme participated in CRV test-day sampling. Subsequently, another 1,085 herds were excluded: 507 herds because of leaving the BVDV-free programme for different reasons (e.g. stopped dairy farming); 429 herds because of incomplete milk production records; 37 herds because the herd size was less than 20 cows, because a herd with less than 20 lactating cows is not considered a commercial dairy farm; 26 herds because the ADMY was out of the range of 0.1^{th} and 99.9^{th} percentile of the total, and 86 herds for which (sufficient) pre or post-breakdown-date was lacking as the breakdown occurred prior to January 1, 2008 or post December 31, 2014. Since herds have to undergo a 10-month virus test on all new-born calves before obtaining the BVDV-free status, test-day milk production data earlier than 10 months before the free-date were removed to ensure that the study herds are indeed free of BVDV before its defined introduction. Therefore, data for 85,363 test-days were removed. The final dataset includes 3,126 Dutch dairy herds with information on 244,701 monthly test-days from January 1, 2007 to December 31, 2017, of which 41,650 test-days for 640 breakdown-herds and 203,051 test-days for 2,486 free-herds.

3.2.3 Scenarios of BVDV Introduction

Since the exact moment of BVDV introduction was unknown, 4 scenarios were developed. To have a clear insight on the possible BVDV-introduction-date, we developed a timeline (Figure 3.1) based on the Dutch BVDV-free programme (van Duijn et al., 2019) and existing BVD epidemiological knowledge and expert opinion. In the monitoring phase of the BVDV-free programme, blood samples are collected every 6 months from 5 randomly selected 8- to-12-month-old calves and tested for BVDV antibodies. Alternatively, all new-born calves in the herd are tested for the presence of BVDV (for more detail see van Duijn et al., 2019). The monitoring results will determine if the herd loses its BVDV-free status.

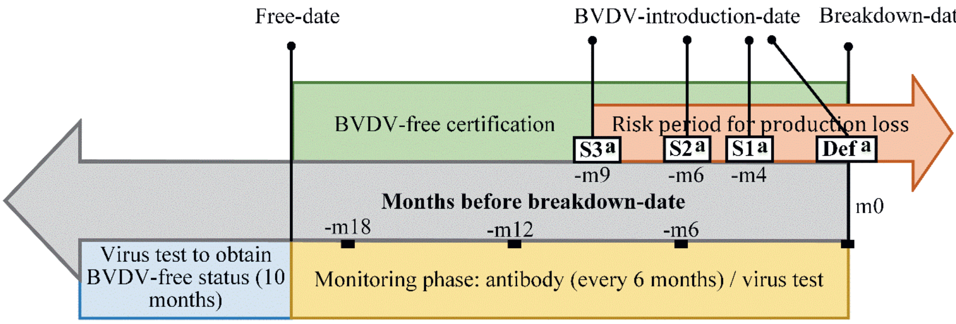

Figure 3.1. The timeline of bovine viral diarrhoea virus (BVDV) introduction in dairy herds participating in the BVDV-free programme.
[a] Def (default scenario): The risk period for production loss starts from the breakdown-date. S1, S2 and S3: The risk period for production loss starts from the birth of the persistently infected (PI) calf, which could be 4 months (S1, scenario 1), 6 months (S2, scenario 2), or 9 months (S3, scenario 3) before the breakdown-date (i.e., the date when the BVDV antibody/virus test was positive, and the farm lost its BVDV-free status).

In this study, 4 scenarios were developed under the assumption that herd breakdown can only be caused by a PI animal, and transient infections that did not result in the birth of a PI animal would not lead to a breakdown. The BVDV-introduction-date defines from which point in time milk production is at risk. In the default scenario, the BVDV-introduction-date was assumed to coincide with the breakdown-date, i.e., the date when the herd loses its BVDV-free status. For the other 3 scenarios, the BVDV-introduction-date was set at the estimated date of birth of a PI calf. This information was not available for the herds in our sample, but a study by van Duijn et al. (2019) indicates that in 25% of the herds, PI calves are born within the last 4 months prior to the breakdown-date; in 50% of the herds, PI calves are born within the last 6 months prior to the breakdown-date; and in 75% of the herds, they are born within 9 months before the breakdown-date. Thus, to account for this distribution, the BVDV-introduction-date was set 4 months (Scenario 1), 6 months (Scenario 2), and 9 months (Scenario 3) prior to the breakdown-date.

3.2.4 Statistical Analysis

In order to estimate the impact of BVDV on milk yield in breakdown-herds, the milk production before and after virus introduction was compared. To correct for fluctuation over time, the milk production of free-herds was included in the analysis as well. To compare breakdown-herds with free-herds, it was assumed that free-herds lost their BVDV-free status on a random breakdown-date, artificially generated by simple random sampling from the distribution of the breakdown-dates of the breakdown-herds. A random artificial BVDV-introduction-date of the free-herd was therefore derived from the random artificial breakdown-date in the 4 scenarios. Consequently, the changes in milk production due to BVDV introduction could be calculated by comparing the differences in milk production before and after the BVDV-introduction-date in the breakdown-herds, taking into account differences in milk production before and after the artificial BVDV-introduction-date of the free-herds. Data editing and analysis were conducted in R version 3.5.0 (R Core Team, Vienna, Austria).

Annual Effect of BVD. For the annual effect of BVD on milk production, the 2 years prior and 3 years post introduction were taken into account. Descriptive statistics were performed on herd size and milk production performance for both breakdown-herds and free-herds in the default scenario.

A linear mixed model was applied as follows:

$$ADMY_{ij} = \beta_0 + \beta_1 BH_{FH_i} + \beta_2 BVD\ status_{ij} + \beta_3(BH_{FH_i} \times BVD\ status_{ij}) + \beta_4 Year_{ij} + \beta_5 Season_{ij} + \mu_{herd(i)} + \varepsilon_{ij} \qquad [3.1]$$

For herd $i \in \{1, \dots, 3{,}126\}$ and test-day $j \in \{01/01/2007, \dots, 12/31/2017\}$, where $ADMY_{ij}$ is the average daily milk production in kilograms on test-day j of herd i. $\boldsymbol{BH\_FH_i}$ is a dummy variable that represents herd type (breakdown-herd versus free-herd). $BVD\ status_{ij}$ is a defined categorical variable, which indicates the BVDV infection status of herd i on test-day j. $BVD\ status_{ij}$ was defined based on the BVDV-introduction-date (real and artificial) and consists of 5 categories: 2nd last year before BVD, last year before BVD, 1st year after BVD, 2nd year after BVD and 3rd year after BVD. The category 'last year before BVD' was used as reference category. The effect of BVD on milk production within the breakdown-herd can be explained by the coefficients of the interaction term BH_FH × BVD status in the model results.

$Year_{ij}$ (2007–2017) is a categorical variable that corrects for variation in milk production across different calendar years, with 2007 as the reference category. $Season_{ij}$ is a categorical variable defined as Spring (March–May), Summer (June–August, reference category), Autumn (September–November) and Winter (December to next February). $\mu_{herd(i)}$ refers to the random herd-effect in the i^{th} herd that takes into account repeated measures within 1 herd (Dohoo and Martin, 2003). Further, the errors $\varepsilon_{1j,\ldots,}\varepsilon_{3,126j}$ are assumed to be independent with $\sim \mathrm{N}(0, \sigma^2)$. Maximum likelihood estimates of the parameters in the linear mixed model were determined using the lmer function in the *lme4* package for R (Bates et al., 2014). The annual linear mixed model was repeated for all 4 BVDV infection scenarios.

To include the uncertainty of generating the random artificial breakdown-date for the free-herds, the process of generating a random breakdown date for the free-herds and fitting the linear mixed model was performed with 200 iterations. The number of 200 iterations was considered sufficient if the differences between the average coefficients of the first 100 iterations and those of the last 100 iterations were less than 0.01. The modelling results for each of the 200 iterations were combined to provide a final outcome, which included the mean, standard deviation, minimum, maximum and 2.5th to 97.5th percentile of the coefficients of the 200 iterations. The significance of the model results was indicated by this summary of coefficients instead of the P-value. The 95-percentile interval was considered as the range of parameter estimates that reflects the situation closest to the "fact". This interval can inform the decision to (not) reject the hypothesis about a systematic increase or decrease of milk production. Independent variables were checked for multicollinearity by calculation of variance inflation factors using the check_collinearity function in R package performance (Lüdecke et al., 2019). The independent variable $BVD\ status_{ij}$ and $Year_{ij}$ had variance inflation factors more than 10 in the annual analysis, indicating the presence of multicollinearity, there were no multicollinearity problem among other independent variables. Although the $BVD\ status_{ij}$ variable was correlated with the $Year_{ij}$ variable that was used to correct for natural fluctuations in milk production, they were both retained in the final model due to the importance and indispensability of the 2 variables. To measure the explanatory power of the model, conditional R^2, which is the proportion of the total variance explained by fixed and random effects, were also calculated using *performance* package (Lüdecke et al., 2019). The residuals of the annual linear mixed model did meet the normal distribution and were evaluated by visual inspection.

Quarterly Effect of BVD. Similarly to the annual effect of BVD, the presence of quarterly effects was also analysed for the first year after BVDV introduction. The BVD status variable for the quarterly analysis consisted of 5 categories representing the first 4 quarters (Q1–Q4) of the first year after the BVDV-introduction-date, and the last year before the BVDV-introduction-date is the reference category (last year before BVD). Except for a different BVD status variable, the quarterly linear mixed model was similar to the annual linear mixed model. Again, 200 iterations were run in the quarterly linear mixed model, and the adequacy test for the number of iterations was the same as for the annual model. Multicollinearity was not an issue in the quarterly analysis model. The residuals of the quarterly linear mixed model did meet the normal distribution.

Sensitivity Analysis. In order to understand how initial prevalence in the herd affects the change in milk production after a new BVDV infection (Pinior et al., 2019), a sensitivity analysis was performed. The duration of the BVDV-free status, defined as the number of days between the free-date and the breakdown-date, was used as an indicator of the initial antibody prevalence levels in the herd. The longer the herd had been BVDV-free, the lower the initial antibody prevalence levels in the herd. In the sensitivity analysis, therefore, only herds which had been BVDV-free for more than 3 years were included. The sensitivity analysis was carried out for both the annual and quarterly linear mixed models, with each model running 200 iterations, in all 4 BVDV infection scenarios.

3.3 Results

3.3.1 Descriptive Analysis

Table 3.1 presents herd size and milk production performance by BVDV status in breakdown-herds, and overall in free-herds in the default scenario. The mean ADMY in a breakdown-herd is 0.3 kg lower than in a free-herd in the study years, and 40 kg lower for the mean 305-day milk production. Within the breakdown-herds, the mean ADMY is 0.1 kg per cow lower in the first year after breakdown compared to the last year before breakdown.

Table 3.1. Average herd size and milk production performance for the 3,126 Dutch dairy herds participating in the bovine viral diarrhoea virus (BVDV)-free programme for the years 2007 to 2017 in the default scenario. The risk period for milk production loss started from the BVDV-introduction-date. In the default scenario, the breakdown-date (i.e., the date of losing the BVDV-free status) was assumed as the BVDV-introduction-date

Variables	Unit	Breakdown-herds[1] (n = 640)						Free-herds[2] (n = 2,486)
		2nd last year before breakdown	Last year before breakdown	1st year after breakdown	2nd year after breakdown	3rd year after breakdown	Overall	Overall
		Mean (SD)						
Herd size	Number	78 (35)	79 (36)	81 (38)	84 (40)	87 (44)	82 (39)	80 (38)
ADMY[3]	kg/cow/day	27.2 (3.1)	27.2 (3.2)	27.1 (3.2)	27.1 (3.2)	27.1 (3.3)	27.1 (3.2)	27.4 (3.4)
305d milk	kg/cow/305 day	8,800 (833)	8,810 (829)	8,800 (853)	8,790 (862)	8,810 (888)	8,800 (854)	8,840 (917)
Fat	%	4.39 (0.30)	4.40 (0.30)	4.39 (0.30)	4.39 (0.30)	4.39 (0.30)	4.39 (0.30)	4.39 (0.29)
Protein	%	3.54 (0.13)	3.54 (0.13)	3.55 (0.14)	3.55 (0.14)	3.55 (0.14)	3.55 (0.14)	3.55 (0.14)

[1] Breakdown-herds = herds that lost the BVDV-free status during the study period.
[2] Free-herds = herds that did not lose the BVDV-free status during the study period.
[3] ADMY = average daily milk yield per cow.

3.3.2 Annual Effect of BVD on Milk Production

Table 3.2 shows the annual modelling results of 200 iterations for the default scenario, and Figure 3.2 provides the results of all 4 scenarios including the free-herds as the reference. In the default scenario, the mean ADMY is 0.08 kg/cow (2.5th and 97.5th percentile: −0.15; −0.02 kg/cow) lower in the first year after breakdown (the coefficients of the interaction term BH_FH × BVD status) compared to the last year before breakdown. In the second and third year after breakdown, the negative effects of BVDV introduction on mean ADMY in the default scenario decreased gradually, to 0.05 and 0.03 kg/cow (2.5th and 97.5th percentile: −0.12; 0.03 and −0.10; 0.04 kg/cow), respectively. Thus, milk production is most affected in the first year after BVDV introduction, and losses gradually decrease in the following 2 years. The results for scenario 1, 2 and 3 (i.e., setting the BVDV-introduction-date at 4, 6 or 9 months before the breakdown-date) are presented in supplementary material Table 3.S1. In these scenarios, the mean ADMY in the first year after introduction is respectively 0.04, 0.02 and 0.04 kg/cow/day lower compared to the year leading up to BVDV introduction. However, in the second year after introduction, the negative effects increased. The mean ADMY reductions for the second year in scenarios 1, 2 and 3 were 0.09, 0.09 and 0.1 kg/cow/day, respectively.

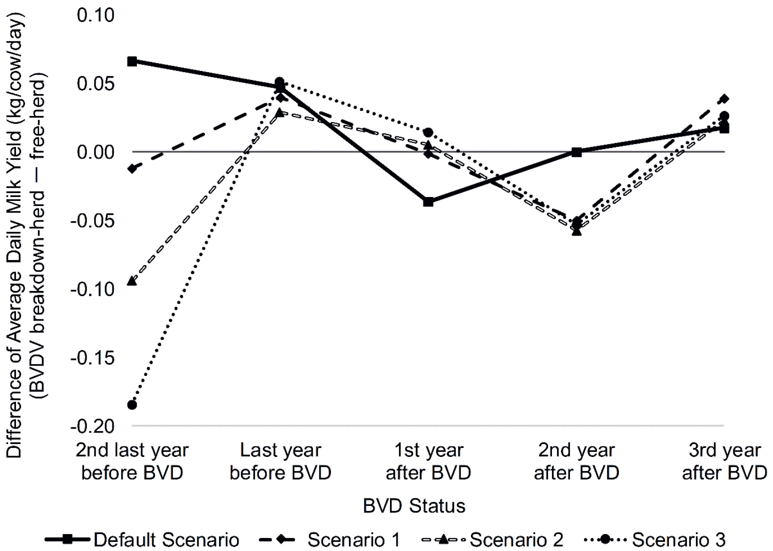

Figure 3.2. The estimates of mean Average Daily Milk Yield (kg/cow) of bovine viral diarrhoea virus (BVDV) breakdown-herds in the years before and after BVDV introduction. The ordinate 0 is the reference level of free-herds, there is no difference in ADMY of free-herds. A breakdown-herd is a dairy herd that obtained and subsequently lost the BVDV-free status, while a free-herd is a dairy herd that did not breakdown during the study period. 4 scenarios were developed to define the BVDV-introduction-date. In the default scenario, the BVDV-introduction date was set to coincide with the breakdown-date (i.e., the date of losing the BVDV-free status). In scenario 1, 2 and 3, the BVDV-introduction date was set at 4, 6 and 9 months prior to the breakdown-date.

Table 3.2. Estimates of the linear mixed model for the annual effect of bovine viral diarrhoea virus (BVDV) introduction on average daily milk yield (kg) per cow with 200 iterations in the default scenario. In this scenario, the breakdown-date (i.e., the date of losing the BVDV-free status) was used as the BVDV-introduction-date, and signified the start of the period with potential milk production loss

Effects	Categories	Parameter Estimate				
		Mean	SD	Min	95% PI[1]	Max
Intercept		26.20	0.07	26.10	26.10; 26.40	26.50
BH_FH[2]	Free-herd	ref.				
	Breakdown-herd	0.05	0.03	−0.04	−0.01; 0.11	0.13
BVD status	Last year before BVD	ref.				
	2nd last year before BVD	0.23	0.04	0.13	0.15; 0.30	0.34
	1st year after BVD	−0.21	0.03	−0.31	−0.28; −0.15	−0.11
	2nd year after BVD	−0.46	0.05	−0.59	−0.55; −0.36	−0.32
	3rd year after BVD	−0.65	0.07	−0.88	−0.78; −0.53	−0.48
BH_FH ×BVD status	BH_FH × Last year before BVD	ref.				
	BH_FH × 2nd last year before BVD	0.02	0.04	−0.10	−0.05; 0.09	0.10
	BH_FH × 1st year after BVD	−0.08	0.03	−0.17	−0.15; −0.02	0.00
	BH_FH × 2nd year after BVD	−0.05	0.04	−0.15	−0.12; 0.03	0.05
	BH_FH × 3rd year after BVD	−0.03	0.04	−0.14	−0.10; 0.04	0.08
Year	2007	ref.				
	2008	0.18	0.04	0.04	0.08; 0.25	0.30
	2009	0.92	0.06	0.74	0.80; 1.02	1.07
	2010	1.30	0.06	1.11	1.18; 1.43	1.48
	2011	1.41	0.08	1.16	1.26; 1.58	1.62
	2012	1.08	0.09	0.80	0.91; 1.27	1.35
	2013	1.32	0.11	0.98	1.13; 1.53	1.63
	2014	1.86	0.13	1.48	1.62; 2.11	2.18
	2015	2.19	0.14	1.80	1.88; 2.46	2.59
	2016	2.60	0.16	2.17	2.29; 2.92	3.04
	2017	3.43	0.21	2.85	3.03; 3.84	3.99
Season[3]	Summer	ref.				
	Autumn	−0.91	0.01	−0.94	−0.93; −0.89	−0.88
	Winter	0.03	0.01	−0.02	0.00; 0.05	0.06
	Spring	0.39	0.01	0.36	0.37; 0.41	0.41
Conditional R^2 (%)		70.9	0.3	70.2	70.3; 71.4	71.6

[1] 95% PI = 2.5th percentiles to 97.5th percentiles of the parameter estimate, the significance of the model results was indicated by this interval.
[2] BH_FH = a dummy variable indicating breakdown-herd and free-herd.
[3] Season = Spring (March-May), Summer (June-August), Autumn (September-November), Winter (December to next February).

3.3.3 Quarterly Effect of BVD on Milk Production

Table 3.3 presents the results of the quarterly linear mixed model for the default scenario, and Figure 3.3 shows the quarterly effect of BVDV introduction on milk production among all 4 scenarios, involving the free-herds as the reference. In the default scenario, the mean ADMY is 0.14 kg/cow (2.5th and 97.5th percentile: −0.21; −0.06 kg/cow) lower in the first quarter (Q1) after breakdown, compared to the last year before breakdown. Further, for Q2, Q3 and Q4 after breakdown, the mean ADMY is respectively 0.09, 0.02 and 0.08 kg/cow (2.5th and 97.5th percentile: −0.18; 0.00, −0.10; 0.07, and −0.16; 0.02 kg/cow) lower than the last year before breakdown. The estimates of scenario 1, 2 and 3 are presented in Supplementary material Table 3.S2. Although the quarterly effects of BVD differ in scenarios 1, 2 and 3, the milk production of the breakdown-herds declines after BVDV introduction in all 3 scenarios.

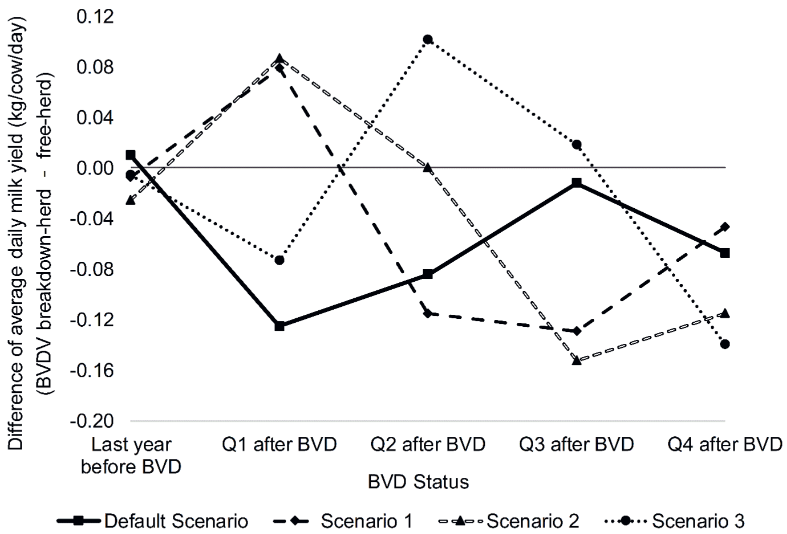

Figure 3.3. The estimates of mean Average Daily Milk Yield (kg/cow) of bovine viral diarrhoea virus (BVDV) breakdown-herds per quarter for four BVDV introduction scenarios. The ordinate 0 is the reference level of free-herds, there is no difference in ADMY of free-herds. A breakdown-herd is a dairy herd that obtained and subsequently lost the BVDV-free status, while a free-herd is a dairy herd that did not breakdown during the study period. 4 scenarios were developed to define the BVDV-introduction-date. In the default scenario, the BVDV-introduction date was set to coincide with the breakdown-date (i.e., the date of losing the BVDV-free status). In scenario 1, 2 and 3, the BVDV-introduction date was set at 4, 6 and 9 months prior to the breakdown-date. Q1, Q2, Q3 and Q4 represent the 1st, 2nd, 3rd and 4th quarters after BVDV introduction.

Table 3.3. Estimates of the quarterly effect linear mixed model of average daily milk yield (kg) per cow with 200 iterations in the default scenario. In this scenario, the breakdown-date (i.e., the date of losing the bovine viral diarrhoea virus (BVDV)-free status) was used as the BVDV-introduction-date, and signified the start of the period with potential milk production loss

Effects	Categories	Parameter estimate				
		Mean	SD	Min	95% PI[1]	Max
Intercept		26.30	0.10	25.90	26.10; 26.40	26.60
BH_FH[2]	Free-herd	ref.				
	Breakdown-herd	0.01	0.04	−0.10	−0.06; 0.08	0.12
BVD status	Last year before BVD	ref.				
	Q1[3] after BVD	−0.12	0.04	−0.23	−0.21; −0.04	−0.02
	Q2[3] after BVD	−0.17	0.05	−0.30	−0.27; −0.07	−0.04
	Q3[3] after BVD	−0.18	0.05	−0.30	−0.29; −0.09	−0.07
	Q4[3] after BVD	−0.27	0.05	−0.39	−0.36; −0.17	−0.14
BH_FH × BVD status	BH_FH × Last year before BVD	ref.				
	BH_FH × Q1 after BVD	−0.14	0.04	−0.24	−0.21; −0.06	−0.05
	BH_FH × Q2 after BVD	−0.09	0.05	−0.23	−0.18; 0.00	0.02
	BH_FH × Q3 after BVD	−0.02	0.05	−0.14	−0.10; 0.07	0.14
	BH_FH × Q4 after BVD	−0.08	0.05	−0.19	−0.16; 0.02	0.04
Year	2007	ref.				
	2008	0.25	0.06	0.10	0.14; 0.38	0.46
	2009	0.88	0.08	0.65	0.72; 1.02	1.10
	2010	1.18	0.09	0.91	0.99; 1.34	1.41
	2011	1.33	0.11	1.05	1.12; 1.54	1.63
	2012	1.09	0.13	0.77	0.87; 1.35	1.52
	2013	1.30	0.14	0.90	1.02; 1.55	1.94
	2014	1.73	0.16	1.31	1.43; 2.02	2.27
	2015	1.83	0.19	1.29	1.43; 2.20	2.31
Season[4]	Summer	ref.				
	Autumn	−0.85	0.02	−0.90	−0.89; −0.81	-0.80
	Winter	0.11	0.03	0.02	0.05; 0.16	0.18
	Spring	0.46	0.02	0.39	0.42; 0.50	0.52
Conditional R^2 (%)		73.3	0.3	72.6	72.7; 74.1	74.4

[1] 95% PI = 2.5th percentiles to 97.5th percentiles of the parameter estimate, the significance of the model results was indicated by this interval.
[2] BH_FH = a dummy variable containing breakdown-herd and free-herd.
[3] Q1, Q2, Q3, Q4 = the 1st, 2nd, 3rd, 4th quarters after the BVDV-introduction-date.
[4] Season = Spring (March-May), Summer (June-August), Autumn (September-November), Winter (December to next February).

3.3.4 Sensitivity Analysis

The sensitivity analysis modelled herds had been BVDV-free for more than 3 years. Figure 3.4 shows the estimates of the sensitivity analysis and the overall analysis (i.e., all herds) in the default scenario. Estimates of the sensitivity analysis for all 4 scenarios are listed in Supplementary material Table 3.S3. In the sensitivity analysis on annual effect, ADMY decreased by an average of 0.08 kg/cow (2.5th and 97.5th percentile: −0.15; −0.01 kg/cow) in the first year after breakdown in the default scenario, the same result as the one obtained in the overall annual effect analysis. In the second year after breakdown of the annual sensitivity analysis, the reduction in mean ADMY is 0.07 kg/cow (2.5th and 97.5th percentile: −0.14; 0.02 kg/cow), which is 0.02 kg/cow more than the overall annual effect analysis results (i.e., 0.05 kg/cow reduction in milk yield). It was also found that the annual production levels of herds that remained BVDV-free for at least 3 years are lower than that of all herds where herds with shorter BVDV-free periods were included. In the sensitivity analysis on quarterly effect, in the default scenario, the mean ADMY in the first 3 quarters after breakdown is 0.16, 0.14 and 0.1 kg/cow (2.5th and 97.5th percentile: −0.26; −0.04, −0.25; −0.04, and −0.22; 0.03 kg/cow) lower than that of the year before breakdown. These reductions in milk yield are 0.02, 0.05, 0.08 kg/cow/day greater than the overall quarterly effect analysis results (i.e., 0.14, 0.09, 0.02 kg/cow/day reduction in milk yield). Overall, the trends found in the annual sensitivity analysis are comparable to the annual linear mixed model results, whereas there is a clear divergence between the quarterly sensitivity analysis and the quarterly linear mixed model results in the fourth quarter after breakdown.

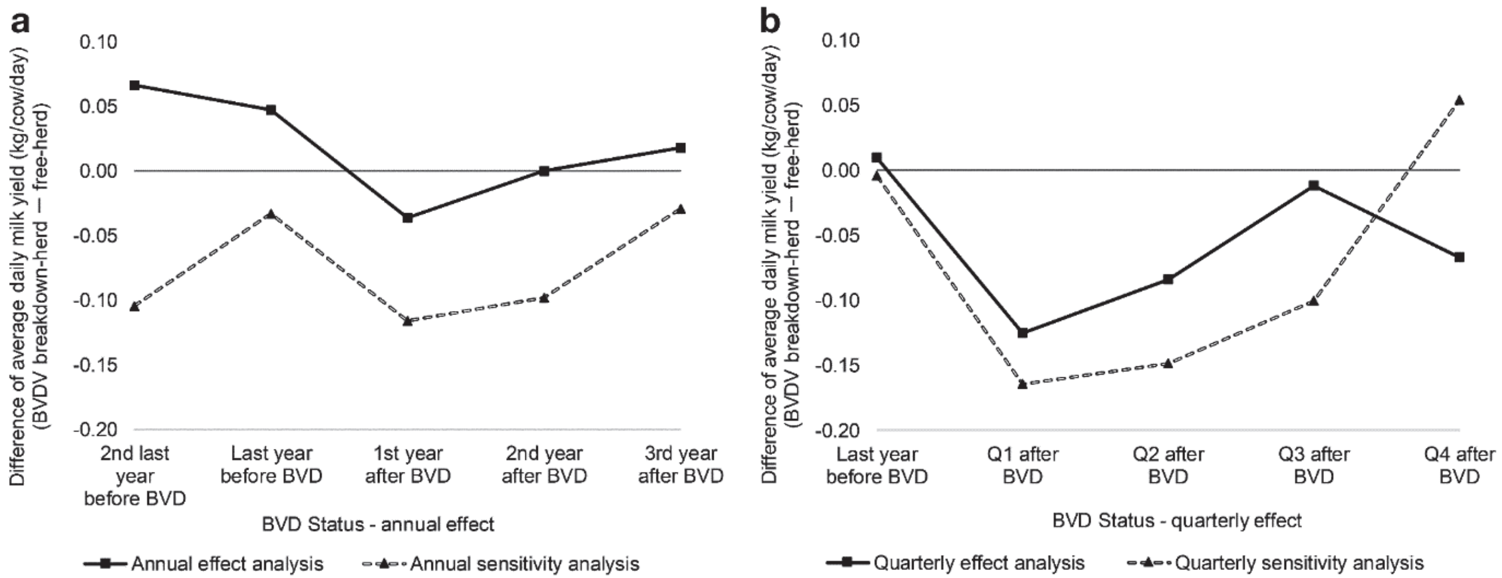

Figure 3.4. Comparison of the annual (a) and quarterly (b) impact of bovine viral diarrhoea virus (BVDV) introduction on the estimates of mean Average Daily Milk Yield of all study herds and of herds that remained BVDV-free for at least 3 years (sensitivity analysis) in the default scenario. The ordinate 0 is the reference level of free-herds, there is no difference in ADMY of free-herds. Annual effects are based on the yields obtained in the 2 years prior and 3 years post BVDV introduction, while quarterly effects are based on milk yields in the first 4 quarters (Q1–Q4) after BVDV-introduction-date and the last year before that date.

3.4 Discussion

This paper presents the effect of a BVDV (re)introduction on milk production of dairy herds by combining herd-level BVDV surveillance data and milk production data of 3,216 Dutch dairy herds from 2007 to 2017. Our findings help to understand annual and quarterly milk losses that occur upon BVDV introduction. The ADMY decreased by 0.02–0.14 kg/cow in the first year after BVDV introduction in the default scenario. At the herd level, the average milk yield loss in the first year after the breakdown was 2,394 kg/herd/year (SD = 1,139 kg/herd/year), which was calculated based on the average herd size in this study (mean = 82, SD = 39, Table 3.1). This demonstrates that BVDV introduction has a negative but on average a relatively small impact on milk production in herds involved in the BVDV control programme.

The impact of BVDV introduction on milk production in dairy farms in this study was smaller compared to other studies, which included herds with or without BVDV control measures. For herds without BVDV control measures, Lindberg and Emanuelson (1997) found a milk production loss of 0.7 kg/cow/day, higher than the loss in our study. Beaudeau et al. (2004) also reported bigger losses: cows in recently recovered herds produced 0.41 kg/cow/day less milk compared with cows in not recently infected herds. These differences in the findings may be explained by the fact that PI animals were removed quickly from the herds in the BVDV-free programme in our study. In the herds that were analysed by Beaudeau et al. (2004), bulk tank milk was periodically tested for BVDV antibodies, but no intervention measures were taken. This interpretation is also supported by Pasman et al. (1994), who already pointed out that intervention measures can save direct losses caused by BVD, including those attributed to milk production. For herds in which BVDV control measures were applied, small milk production losses due to BVDV infection were also reported by Marschik et al. (2018), who presented that the milk production of BVDV infected herds was 0.18 kg/cow/day lower than that of uninfected herds in Styria, Austria. Tschopp et al., (2017) analysed herds with at least 2 PI animals but the data on milk yield after the eradication phase was inconclusive. Tiwari et al. (2007) found that cows in BVDV-antibody-positive herds produced 368 kg milk less per 305 days (≈0.21 kg/cow/day), compared with cows in BVDV-antibody-negative herds. Differences in research results can partly be explained by variations in BVDV control measures, milk production levels, breed, study area, etc. (Eurostat, 2017), as well as the study design, i.e. inter- vs intra-herd analysis.

The impact of BVDV introduction on milk production can be considered relatively small on average in the current study and can be explained by several BVDV epidemiological factors.

First, milk production loss due to BVDV infection may be affected by the amount of virus and duration of the infection (Pinior et al., 2019). A study by van Duijn et al. (2019) indicates that in almost half of breakdown-herds, PI animals were not identified, which may be explained by PI animal that died or moved to a veal farm before the detection. The fewer PI animals in the herd, the smaller the impact of a BVDV introduction on milk production. Second, the duration of BVDV circulation, which depends on when PI animals died or were removed, also affects the impact of BVDV introduction on milk production. In the BVDV-free programme, new-born calves of the herd are tested until no BVDV-positive animal is detected for 10 months (van Duijn et al., 2019). On average, PI animals are removed within 8 weeks after detection. When PI animals are swiftly removed from the herd, BVDV circulation within the herd is shorter, which means fewer cows are infected and milk yield losses are relatively small. The negative impact of the introduction of BVDV on milk production may also be underestimated. Generally, dairy farms involved in both CRV milk production registration and BVDV-free programme are better managed (expert opinion) and may be able to detect and remove the PI animals more quickly than farms that are not participating in both programmes. Therefore, the introduction of BVDV may have a larger impact on milk production of Dutch dairy farms not included in this study.

BVDV introduction has a greater impact on milk production in herds that have been BVDV free for a longer time period because the herd will consist of more naive cows (depending also on the replacement rate of the herd), with lower initial antibody prevalence. In our sensitivity analysis, only herds that were BVDV-free for at least 3 years were included and these herds were considered to have a relatively low initial antibody prevalence. This assumption is supported by the research of Houe, (1999), showing that the average BVDV antibody level in 10 herds decreased slowly by 15% over the 1,000 days following removal of the last PI animal from the herd. The sensitivity analysis indicates that BVDV introduction indeed has a higher impact on milk production in herds that were BVDV-free for a longer period of time. Herds in the sensitivity analysis lost 0.02 kg/cow/day more milk than the average milk loss of all herds in the second year after BVDV introduction (default scenario). The negative effects observed in the quarterly sensitivity analysis are also greater than the quarterly analysis results of all herds in the first, second and third quarters after the introduction of BVDV (default scenario). These results are in line with those of Pinior et al. (2019) who also found that BVDV infection is less damaging when the herd is still protected by high BVDV antibody levels, compared to a herd with a low initial antibody prevalence.

The risk period for milk production loss due to BVDV is mostly in the first 2 years after BVDV introduction. In each of the 4 scenarios with different ways of defining the moment of introduction, there was a reduction in milk production over the next 2 years after BVDV introduction. These results reflect those of Lindberg and Emanuelson (1997), Valle et al. (2000) and Beaudeau et al. (2004), all of whom presented a decline in milk production in the year of BVDV infection detection and 1 year after. It should be noted that the data of these 3 studies are limited to a maximum duration of 5 years, so the longer-term annual impact of BVDV introduction may not be detected due to insufficient data. Our study includes surveillance data from 2007 to 2017, and the results of the default scenario show that in the third year after BVDV introduction, the impact on milk production loss is indeed small (−0.02 kg/cow/day, 95% percentiles interval: −0.10; 0.04 kg/cow/day). While our findings validate previous studies, the long-term impact of BVDV on milk production may be underestimated in our study because all herds participated in the BVDV-free programme. This means the presence of BVDV was likely detected before more serious clinical problems, causing long-term impacts on production, could occur. Furthermore, we analysed the quarterly effects of BVDV introduction on milk production within the first year after introduction. The results of the default scenario show that milk production loss is highest (i.e., 0.16 kg/cow /day) in the first quarter. Previous studies have shown that the impact of BVDV infection on milk production occurs mainly in the first 3 weeks after infection (David et al., 1994; Moerman et al., 1994; Bennett et al., 1999). We also found that the annual milk production losses are smaller than the quarterly losses, since milk production decreased significantly in the first few months after infection, but was levelled out in the annual impact analysis. Quarterly analyses may help us to better understand the duration of the impact of BVDV introduction on milk production in a controlled situation.

Of the 4 scenarios developed in this study, the default scenario on average appears to be most closely aligned with the true period of BVDV infection. Previous research has shown that milk production tends to decrease most in the time period when a PI animal appears on a dairy farm and causes transient infections (Bennett et al., 1999; Houe, 2003). The results of the annual and quarterly impact analysis of the default scenario are consistent with this fact. The results of the annual impact analysis in Scenarios 1–3 are fairly consistent: milk production losses all start from the first year after BVDV introduction, with greater losses in the second year. It may be because scenario 1, 2 and 3 are all assuming that the BVDV introduction started before the breakdown-date, so the milk production losses of these scenarios are delayed compared to the default scenario. Given the above, each herd has its own true scenario of (re)introduction, the time of BVDV introduction cannot be precisely defined, but the average situation can be approached from different infection scenarios.

Although the linear mixed model used in this study has been widely used in veterinary epidemiology, there are limitations to the model used in this study. The $Year_{ij}$ variable may not be able to correct all fluctuations in milk production during the study period. The milk production of Dutch dairy farms is affected by many factors such as weather and policy changes. For instance, a single year category may not completely correct the impact of the abolition of the EU milk quota system in 2015 on dairy farms. Nevertheless, the effects of weather and policy changes can be different on each farm. So the $Year_{ij}$ variable is a proxy for many unmeasured effects. Another limitation is the multicollinearity between 2 variables $BVD\ status_{ij}$ and $Year_{ij}$ in the annual analysis model. This is because $BVD\ status_{ij}$ is a categorial variable with year as unit. Both variables retained in the final linear mixed model because $BVD\ status_{ij}$ is one of the variables of interest in this study, and the $Year_{ij}$ variable is used to control the natural fluctuation of milk production over time, which cannot be ignored. Although multicollinearity may lead to unstable estimates of coefficients, it's only a problem for the collinear variables $Year_{ij}$ and $BVD\ status_{ij}$. The coefficient of the interaction term $BH\_FH_i \times BVD\ status_{ij}$ (the main variable of interest) will not be affected, and the performance of the control variables $Year_{ij}$ and $BVD\ status_{ij}$ as controls will not be impaired (Allison, 2012). Furthermore, there are other factors that affect the milk production at the herd level, such as grazing, the use of automatic milking systems, breeds, feeding systems, etc. These factors will most likely remain stable within the farm over time, so estimates of milk yield changes within the breakdown-herd will not be largely affected by these factors.

The estimated impact of the BVDV introduction on milk production is based on monthly test-days in our study and may not accurately determine milk yield loss. In future research, a study that includes more frequent measures of both milk production and virus introduction would allow to more accurately track BVDV introduction and its impact, which will in turn help develop a full picture of BVD consequences for milk production. In addition, there is abundant room for further study in determining the overall production and economic impact of BVDV introduction on dairy herds including losses due to reproduction, culling, mortality and indirect production diseases.

3.5 Conclusion

The introduction of bovine viral diarrhoea virus has a negative but on average a relatively small impact on milk production for Dutch dairy herds participating in the BVDV-free control programme. This impact was mainly observed during the first and second year, especially in the first quarter, after dairy herds lost their BVDV-free status. Our results provide dairy farms and policy makers with information on the annual and quarterly loss of milk production due to BVDV introduction in the BVDV-free programme, which can be used to develop more effective prevention and control plans.

Acknowledgements

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Supplementary materials

Table 3.S1. Estimates of the linear mixed model for the annual effect of bovine viral diarrhoea virus (BVDV) introduction on average daily milk yield (kg) per cow with 200 iterations in scenarios 1, 2 and 3. In scenario 1, 2 and 3, the BVDV-introduction date was set at 4, 6 and 9 months prior to the breakdown-date, and signified the start of the period with potential milk production loss

Effects	Categories	Parameter estimate					
		Scenario 1		Scenario 2		Scenario 3	
		Mean	SD	Mean	SD	Mean	SD
Intercept		26.40	0.08	26.50	0.07	26.50	0.06
BH_FH[1]	Free-herd	ref.					
	Breakdown-herd	0.04	0.04	0.03	0.04	0.05	0.04
BVD status	Last year before BVD	ref.					
	2nd last year before BVD	0.20	0.04	0.16	0.04	0.21	0.04
	1st year after BVD	−0.22	0.04	−0.19	0.04	−0.21	0.04
	2nd year after BVD	−0.44	0.05	−0.36	0.05	−0.40	0.05
	3rd year after BVD	−0.63	0.07	−0.54	0.06	−0.60	0.06
BH_FH ×BVD status	BH_FH × Last year before BVD	ref.					
	BH_FH × 2nd last year before BVD	−0.05	0.04	−0.12	0.04	−0.24	0.04
	BH_FH × 1st year after BVD	−0.04	0.03	−0.02	0.03	−0.04	0.04
	BH_FH × 2nd year after BVD	−0.09	0.04	−0.09	0.04	−0.10	0.04
	BH_FH × 3rd year after BVD	0.00	0.04	−0.01	0.04	−0.02	0.04
Year	2007	ref.					
	2008	0.15	0.04	0.12	0.04	0.14	0.04
	2009	0.88	0.06	0.80	0.06	0.85	0.05
	2010	1.24	0.07	1.14	0.07	1.20	0.06
	2011	1.34	0.09	1.20	0.08	1.29	0.08
	2012	1.01	0.10	0.84	0.10	0.96	0.09
	2013	1.23	0.12	1.01	0.12	1.14	0.11
	2014	1.76	0.14	1.51	0.14	1.67	0.13
	2015	2.07	0.15	1.78	0.16	1.97	0.15
	2016	2.48	0.17	2.18	0.19	2.41	0.18
	2017	3.13	0.24	2.69	0.29	2.65	0.30
Season[2]	Summer	ref.					
	Autumn	−0.89	0.01	−0.90	0.01	−0.86	0.01
	Winter	0.05	0.01	0.08	0.01	0.10	0.01
	Spring	0.43	0.01	0.44	0.01	0.46	0.01
Conditional R^2 (%)		70.6	0.3	70.3	0.3	70.5	0.3

[1] BH_FH = a dummy variable containing breakdown-herd and free-herd, the significance of the model results was indicated by this interval.
[2] Season = Spring (March-May), Summer (June-August), Autumn (September-November), Winter (December to next February).

Table 3.S2. Estimates of the quarterly effect linear mixed model of average daily milk yield (kg) per cow with 200 iterations in scenario 1, 2 and 3. In scenario 1, 2 and 3, the bovine viral diarrhoea virus (BVDV)-introduction date was set at 4, 6 and 9 months prior to the breakdown-date, and signified the start of the period with potential milk production loss

Effects	Categories	Parameter estimate					
		Scenario 1		Scenario 2		Scenario 3	
		Mean	SD	Mean	SD	Mean	SD
Intercept		26.40	0.08	26.60	0.08	26.50	0.07
BH_FH[1]	Free-herd	ref.					
	Breakdown-herd	−0.01	0.03	−0.03	0.04	−0.01	0.04
BVD status	Last year before BVD	ref.					
	Q1[2] after BVD	−0.14	0.05	−0.10	0.05	−0.13	0.05
	Q2[2] after BVD	−0.15	0.05	−0.16	0.05	−0.16	0.05
	Q3[2] after BVD	−0.21	0.05	−0.18	0.05	−0.23	0.05
	Q4[2] after BVD	−0.21	0.05	−0.21	0.05	−0.26	0.05
BH_FH × BVD status	BH_FH × Last year before BVD	ref.					
	BH_FH × Q1 after BVD	0.09	0.05	0.11	0.05	−0.07	0.05
	BH_FH × Q2 after BVD	−0.11	0.05	0.03	0.04	0.11	0.05
	BH_FH × Q3 after BVD	−0.12	0.05	−0.13	0.04	0.02	0.05
	BH_FH × Q4 after BVD	−0.04	0.05	−0.09	0.05	−0.13	0.05
Year	2007	ref.					
	2008	0.15	0.06	0.08	0.06	0.07	0.05
	2009	0.80	0.07	0.72	0.07	0.72	0.07
	2010	1.07	0.09	0.96	0.09	0.99	0.08
	2011	1.19	0.10	1.07	0.10	1.14	0.10
	2012	0.95	0.12	0.80	0.11	0.94	0.11
	2013	1.10	0.13	0.98	0.13	1.16	0.12
	2014	1.52	0.15	1.40	0.16	1.67	0.15
	2015	1.49	0.21	1.07	0.23	1.29	0.28
Season[3]	Summer	ref.					
	Autumn	−0.83	0.02	−0.82	0.02	−0.81	0.02
	Winter	0.13	0.02	0.16	0.02	0.19	0.03
	Spring	0.49	0.02	0.51	0.02	0.50	0.02
Conditional R^2 (%)		72.9	0.4	72.7	0.4	72.8	0.4

[1] BH_FH = a dummy variable containing breakdown-herd and free-herd, the significance of the model results was indicated by this interval.
[2] Q1, Q2, Q3, Q4 = the 1st, 2nd, 3rd, 4th quarters after the BVDV-introduction-date.
[3] Season = Spring (March-May), Summer (June-August), Autumn (September-November), Winter (December to next February).

Table 3.S3. Estimates of the annual and quarterly effect linear mixed model of average daily milk yield (kg) per cow of all study herds and of herds that remained bovine viral diarrhoea virus (BVDV)-free for at least 3 years (sensitivity analysis) with 200 iterations in 4 scenarios. 4 scenarios were developed to define the BVDV-introduction-date

Effects	Categories	Parameter estimate mean							
		Annual effect				Quarterly effect			
		Def[1]	S1[1]	S2[1]	S3[1]	Def	S1	S2	S3
Intercept		23.70	26.30	26.50	26.30	25.40	26.60	26.90	26.80
BH_FH[2]	Free-herd	ref.							
	Breakdown-herd	−0.03	−0.05	−0.05	−0.02	−0.00	−0.02	−0.03	−0.02
BVD status	Last year before BVD	ref.							
	2nd last year before BVD	0.23	0.17	0.14	0.21	-	-	-	-
	1st year after BVD	−0.29	−0.27	−0.23	−0.26	-	-	-	-
	2nd year after BVD	−0.58	−0.52	−0.47	−0.55	-	-	-	-
	3rd year after BVD	−0.83	−0.79	−0.70	−0.83	-	-	-	-
	Q1[3] after BVD	-	-	-	-	−0.24	−0.23	−0.17	−0.21
	Q2[3] after BVD	-	-	-	-	−0.37	−0.31	−0.29	−0.26
	Q3[3] after BVD	-	-	-	-	−0.45	−0.44	−0.35	−0.38
	Q4[3] after BVD	-	-	-	-	−0.54	−0.49	−0.46	−0.44
BH_FH× BVD status	BH_FH × Last year before BVD	ref.							
	BH_FH × 2nd last year before BVD	−0.07	−0.16	−0.27	−0.48	-	-	-	-
	BH_FH × 1st year after BVD	−0.08	−0.07	−0.02	−0.02	-	-	-	-
	BH_FH × 2nd year after BVD	−0.07	−0.03	−0.03	−0.06	-	-	-	-
	BH_FH × 3rd year after BVD	0.00	0.02	−0.01	−0.06	-	-	-	-
	BH_FH × Q1 after BVD	-	-	-	-	−0.16	0.13	0.16	−0.08
	BH_FH × Q2 after BVD	-	-	-	-	−0.14	−0.12	0.06	0.17
	BH_FH × Q3 after BVD	-	-	-	-	−0.10	−0.18	−0.16	0.07
	BH_FH × Q4 after BVD	-	-	-	-	0.06	−0.11	−0.15	−0.17
Year	2007	ref.				-	-	-	-
	2008	2.83	0.40	0.27	0.38	ref.			
	2009	3.51	1.09	0.93	1.09	1.66	0.55	0.39	0.50
	2010	3.88	1.44	1.24	1.47	2.05	0.96	0.76	0.90
	2011	4.06	1.59	1.37	1.65	2.39	1.27	1.03	1.19
	2012	3.75	1.25	1.02	1.36	2.30	1.18	0.89	1.08
	2013	4.02	1.49	1.22	1.59	2.55	1.41	1.13	1.33
	2014	4.61	2.08	1.79	2.20	3.07	1.88	1.64	2.00
	2015	4.97	2.43	2.12	2.58	3.39	1.98	1.55	1.79
	2016	5.44	2.86	2.53	3.05	-	-	-	-
	2017	6.38	3.57	3.07	3.36	-	-	-	-
Season[4]	Summer	ref.							
	Autumn	−0.95	−0.94	−0.95	−0.89	−1.00	−0.96	−0.97	−0.92
	Winter	−0.01	0.02	0.05	0.07	−0.01	−0.01	0.02	0.03
	Spring	0.39	0.46	0.47	0.49	0.48	0.50	0.51	0.50
Conditional R^2 (%)		69.4	69.1	68.9	69.0	73.1	72.8	72.7	72.9

[1] Def, S1, S2, S3 = In the default scenario (Def), the BVDV-introduction date was set to coincide with the breakdown-date (i.e., the date of losing the BVDV-free status). In scenario 1, 2 and 3 (S1, S2, S3), the BVDV-introduction date was set at 4, 6 and 9 months prior to the breakdown-date. Q1, Q2, Q3 and Q4 represent the 1st, 2nd, 3rd and 4th quarters after BVDV introduction.

[2] BH_FH = a dummy variable containing breakdown-herd and free-herd.

[3] Q1, Q2, Q3, Q4 = the 1st, 2nd, 3rd, 4th quarters after the BVDV-introduction-date.

[4] Season = Spring (March-May), Summer (June-August), Autumn (September-November), Winter (December to next February).

4

CHAPTER 4

The Effect of New Bovine Viral Diarrhoea Virus Introduction on Somatic Cell Count, Calving Interval, Culling, and Calf Mortality of Dairy Herds in the Dutch Bovine Viral Diarrhoea Virus–Free Programme

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Abstract

Bovine viral diarrhoea virus (**BVDV**) infection has a major effect on the health of cows and consequently on herd performance. Many countries have implemented control or eradication programmes to mitigate BVDV infection and its negative effects. These negative effects of BVDV infection on dairy herds are well documented, but there is much less information about the effects of new introduction of BVDV on dairy herds already participating in a BVDV control programme. The objective of our study was to investigate the effect of a new BVDV introduction in BVDV-free herds participating in the Dutch BVDV-free programme on herd performance. Longitudinal herd level surveillance data were combined with herd information data to create four unique datasets, including a monthly test-days somatic cell count (**SCC**) dataset, annual calving interval (**CIV**) and culling risk (**CR**) datasets, and a quarterly calf mortality rate (**CMR**) dataset. Each database contained two types of herds: herds remained BVDV-free during the whole study period (defined as 'free-herds'), and herds lost their BVDV-free status during the study period (defined as 'breakdown-herds'). The date of losing the BVDV-free status was defined as 'breakdown-date'. To compare breakdown-herds with free-herds, a random breakdown-date was artificially generated for free-herds by simple random sampling from the distribution of the breakdown-month of the breakdown-herds. The SCC and CIV before and after a new introduction of BVDV were compared through linear mixed-effects models with a gaussian distribution, and the CR and CMR were modelled using a negative binomial distribution in generalized linear mixed-effects models. The explanatory variables for all models included herd type, BVDV status, year, and a random herd effect. Herd size was included as an explanatory variable in the SCC, CIV and CMR model. Season was included as an explanatory variable in the SCC and CMR model. Results showed that free-herds have lower SCC, CR, CMR and shorter CIV than the breakdown-herds. Within the breakdown-herds, the new BVDV introduction affected the SCC and CMR. In the year post BVDV introduction, the SCC was higher than that in the year prior to BVDV introduction, with a factor of 1.011 (2.5th to 97.5th percentile (95% **PCTL**): 1.002, 1.020). Compared with the year prior to BVDV breakdown, the CMR in the year of breakdown and the year post breakdown was higher, with factors of 1.170 (95% PCTL: 1.120; 1.218) and 1.096 (95% PCTL: 1.048; 1.153), respectively. This study reveals that a new introduction of BVDV had a negative but on average relatively small effect on herd performance in herds participating in a BVDV control programme.

Keywords: bovine viral diarrhoea virus, control programme, somatic cell count, calving interval, culling, calf mortality

4.1 Introduction

Bovine viral diarrhoea (**BVD**) is endemic in many cattle-raising countries around the world (Houe, 1995; Pinior et al., 2019). The disease is caused by an infection with bovine viral diarrhoea virus (**BVDV**), which results in diverse clinical manifestations, such as fever, reproductive dysfunctions, congenital defects, growth retardation, and death (Baker, 1995; Houe, 2003; Khodakaram-Tafti and Farjanikish, 2017). Through these manifestations, BVDV infection negatively affects the productivity and economic benefits of dairy herds (Richter et al., 2017).

It is well established that BVDV infection causes poor herd performance, resulting in decreased udder health, premature culling, extended calving intervals and increased mortality among cows and calves (Baker, 1995; Houe, 1995; Gunn et al., 2005; Richter et al., 2017). The bulk tank milk somatic cell count (**SCC**) in BVDV infected herds is higher than in uninfected herds (Laureyns et al., 2013; Tschopp et al., 2017), ranging from 6,000 to 27,000 cells/mL (Lindberg and Emanuelson, 1997; Beaudeau et al., 2005; Laureyns et al., 2013).The calving interval (**CIV**) of the BVDV infected herd was found 7 to 9 days longer than that of uninfected herds (Niskanen et al., 1995; Burgstaller et al., 2016), while a non-significant difference in the CIV between the BVDV infected and uninfected herds was found (Berends et al., 2008; Tschopp et al., 2017). The time to first calving is 14 to 16 days longer in herds seroconverted to BVDV (Valle et al., 2001). Some studies show that the incidence of premature culling in clinical cases of BVDV infection is between 2% to 11% (Pritchard et al., 1989; David et al., 1994; Bennett et al., 1999), while others find little evidence of an increased culling rate due to BVDV infection (Gates et al., 2013; Pinior et al., 2019). The calf mortality rate (**CMR**) in BVDV seropositive herds is 3 to 7 percentage points higher than that in negative herds (Ersbøll et al., 2003; Gates et al., 2013).

Many European countries and regions have implemented control or eradication programmes to reduce the prevalence of BVDV and related direct losses (Lindberg et al., 2006; Santman-Berends et al., 2017; Evans et al., 2019; van Roon et al., 2020a). In the Netherlands, a voluntary BVDV-free programme was launched in 1997, and with success: the number of “BVDV-free” herds increased and the new BVDV circulation in these herds declined (van Duijn et al., 2019). The percentage of dairy herds with BVDV-free or BVDV-unsuspected status increased from 29% in 2011 to 65% in 2018 (GD Animal Health, 2011, 2018). The percentage of dairy herds with recent BVDV circulation dropped from 19.6% in 2009–2010 to 8.7% in 2015–2016 (GD Animal Health, 2011, 2018). To further reduce BVDV infection and improve animal health and welfare in Dutch dairy herds, the compulsory national BVDV control programme was formally introduced on April 1, 2018 (ZuivelNL, 2020). In the second quarter of 2020, 81% of dairy herds had a BVDV-free or BVDV-unsuspected status (GD Animal Health, 2020).

Successful BVDV control programmes are characterized by a low rate of new introductions of BVDV. The probability of new viral introduction in a herd after previous eradication is particularly important when determining the direct loss due to BVDV and assessing the efficiency of biosecurity measures in the BVDV control programme (Lindberg et al., 2006; Stott et al., 2010). For herds participating in a BVDV control (or surveillance) programme, it is possible to detect the BVDV circulation earlier, which may prevent further outbreaks and reduce the negative effects. However, the effect of new introduction of BVDV on herd performance (e.g., udder health, reproduction, culling, calf mortality) in a BVDV control programme has not been quantified before.

The objective of our study was to investigate the effect of a new BVDV introduction on herd performance (i.e., SCC, CIV, culling risk (**CR**), and CMR) in BVDV-free herds participating in the Dutch BVDV-free programme.

4.2 Materials and methods

4.2.1 Data Collection

Two datasets were collected to quantify the effect of new BVDV introduction on the SCC, CIV, CR and CMR of dairy herds. The first dataset consists of longitudinal herd-level BVDV status data and was previously described in Yue et al. (2021a) and Veldhuis et al. (2018). The BVDV status dataset includes 4,334 dairy herds that participated in the Dutch BVDV-free programme between September 4, 2006 and June 15, 2016. Figure 4.1 shows the three phases that make up the BVDV-free programme procedure. Phase I is the test and cull phase. If no new-born calves test positive for BVDV for 10 consecutive months, the herd is certified as BVDV-free and enters the monitoring phase (Phase II). If BVDV is detected during Phase II, the dairy herd loses its BVDV-free certificate and enters the removal phase for persistently infected (PI) animals (Phase III). Two important dates in the BVDV-free programme are: the date on which a herd is certified as BVDV-free (i.e., when the herd enters Phase II), the so-called ‘free-date’; and the date on which a herd loses its BVDV-free certificate (i.e., when the herd enters Phase III), the so-called ‘breakdown-date’. A herd that is certified BVDV-free and stays in Phase II until the end of the study period is defined as a ‘free-herd’. A herd entering Phase III is defined as a ‘breakdown-herd’ (Figure 4.1). The BVDV status dataset also includes

CMR records from January 1, 2011 to June 30, 2016 (i.e., the number of ear-tagged calves up to 1 year old that is reported 'dead' in a quarter, divided by the number of calf-quarters at risk during that same time period. The calf-quarters at risk is calculated by taking the number of calves per months, and then averaging that to a number per quarter).

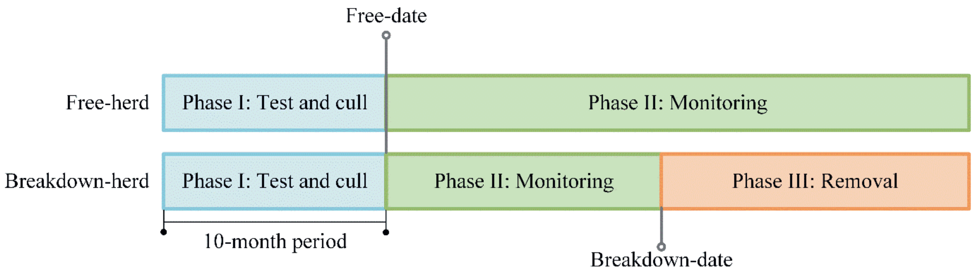

Figure 4.1. Three phases of the BVDV-free programme in the Netherlands and the definition of free-herds and breakdown-herds. A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.

The second dataset includes herd information and was obtained from CRV (Cattle Improvement Cooperative, Arnhem, the Netherlands), including herd-level monthly or annual records of 20,796 Dutch dairy herds between January 1, 2007 and December 31, 2016. The monthly test-day records contain information on average cow SCC and the number of cows sampled for SCC on that test day. The annual records include the number of removed and present cows, the average CIV and the number of cows used to calculate the average CIV. No animals were used in this study, so there is no experimental protocol that needs to be approved.

4.2.2 Data Editing

Four different datasets (for SCC, CIV, CR and CMR) were created. The detailed data editing process of each dataset is provided in Supplementary material Figure 4.S1 (https://doi.org/10.17026/dans-2zc-7w88). For the SCC, CIV and CR datasets, the herd information was merged with the BVDV status based on an anonymized unique herd number. The following herds were excluded: herds that quit the BVDV-free programme before the end of the study period; herds with a breakdown-date before January 1, 2008 or after December 31, 2014, to ensure sufficient pre- or post-breakdown-date records; herds with meaningless values (e.g., SCC=0, CIV=0, CR>1, number of present cows=0, CMR<0) or records with missing data; and herds with <20 cows as they were not considered commercial farms. In addition, all records before the 10-mo period prior to the free-date (Phase I) were excluded to ensure that the studied herds are indeed free of BVDV before its defined new introduction. Records earlier than 2 years prior and later than 3 years post the breakdown-date were not used in the statistical analysis.

The sample size was not calculated, all herds that met the enrolment criteria were included in the study. The final four datasets include SCC data for 3,332 Dutch dairy herds, CIV data for 3,318 herds, CR data for 3,262 herds and CMR data for 3,167 herds, from January 1, 2007 to December 31, 2016 (for CMR dataset, from January 1, 2011 to June 30, 2016). The SCC dataset comprises information on 234,367 monthly test days. The CIV and CR dataset contain 23,231 and 23,431 annual records, respectively. The CMR dataset consisted of 62,721 quarterly records.

4.2.3 Statistical Analysis

Descriptive statistics were performed on SCC, CIV, CR and CMR for both breakdown- and free-herds. In order to estimate the effect of BVDV breakdown on the herd performance on the breakdown-herds, the herd performance was compared before and after breakdown. To correct for other effects in the outcome besides the change in BVDV status, such as weather, policy and management decisions, free-herds were also included in the analysis. Random breakdown-dates were generated for free-herds by simple random sampling from the distribution of the breakdown-month of the breakdown-herds. Consequently, the changes in herd performance due to BVDV breakdown could be calculated by comparing the differences in herd performance before and after the breakdown-date on the breakdown-herds, taking into account differences in herd performance before and after the artificial BVDV breakdown-date of the free-herds. Data editing and analysis were conducted in R version 3.5.0 (R Core Team, 2018).

Somatic cell count. The effect of BVDV breakdown on SCC was analysed per year and per quarter. For the former, the two years prior and three years post BVDV breakdown were taken into account. A linear mixed effects model was applied as follows:

$$\ln(SCC)_{ij} = \beta_0 + \beta_1 BH_{FH_i} + \beta_2 BVDV\ status_{ij} + \beta_3 (BH_{FH_i} \times BVDV\ status_{ij}) \\ + \beta_4 No.animal_{ij} + \beta_5 Year_{ij} + \beta_6 Season_{ij} + \mu_{herd(i)} + \varepsilon_{ij} \qquad [4.1]$$

For herd $i \in \{1, \ldots, 3{,}332\}$ and test-day $j \in \{01/01/2007, \ldots, 12/31/2016\}$, where SCC_{ij} is the average SCC per cow on test day j of herd i, in units of 1,000 cells/mL. Because of the right skewed distribution of the SCC value, it was natural log-transformed. $\boldsymbol{BH\_FH_i}$ is a dummy variable that represents herd type (breakdown-herd or free-herd). $BVDV\ status_{ij}$ is a defined categorical variable, which indicates the BVDV status of herd i on test day j. $BVDV\ status_{ij}$ was defined based on the BVDV breakdown-date (real and artificial) and consists of five categories: 2 years prior breakdown, 1 year prior breakdown, 1 year post breakdown, 2 years post breakdown and 3 years post breakdown. The category ‘1 year prior breakdown’ was used as reference category. The effect of BVDV introduction on SCC within the breakdown-herd can be explained by the coefficients of the interaction term BH_FH × BVDV status in the model results. $No.animal_{ij}$ is the number of cows sampled on the test day for SCC. $Year_{ij}$ (2007–2016) is a categorical variable that corrects for variation in SCC across different calendar years, with 2007 as the reference year. $Season_{ij}$ is a categorical variable defined as Spring (March–May), Summer (June–August, reference category), Autumn (September–November) and Winter (December to next February). In the Netherlands, dairy farms have a year-round calving pattern (Derks et al., 2013), thus the impact of the time of BVDV introduction on the seasonal calving system was not considered. $\mu_{herd(i)}$ refers to the random herd effect in the i^{th} herd that takes into account repeated measures within one herd (Dohoo et al., 2003). Further, the errors $\varepsilon_{1j,\ldots,}\varepsilon_{3,332j}$ are assumed to be independent with $\sim \mathrm{N}(0, \sigma^2)$. Maximum likelihood estimates of the parameters in the linear mixed model were determined using the lmer function in the lme4 package for R (Bates et al., 2014).

For the quarterly effect of BVDV breakdown on SCC, the model is similar, the only difference being the definition of the BVDV status variable. For the quarterly analysis it consisted of 5 categories representing the year prior to the BVDV breakdown-date (reference category) and the first four quarters (Q1–Q4) of the year post BVDV breakdown.

The process of generating the random breakdown-date and fitting the annual and quarterly SCC models was iterated 200 times, as were the models of the other studied parameters. Two hundred iterations were considered sufficient when the differences between the average transformed coefficients of the first 100 iterations and those of the last 100 iterations were less than 0.01. To include the uncertainty of generating the random artificial breakdown-date for the free-herds, a random breakdown-date for the free-herds was generated within each iteration. In addition, each iteration included a data editing step before running the model to ensure that all studied herds have data on the year prior and the year post BVDV breakdown. The modelling results for each of the 200 iterations were combined to provide a final outcome, which included the mean, SD, and 2.5th to 97.5th percentile (**95% PCTL**) of the natural exponential transformed coefficients of the 200 iterations. As the artificial breakdown-date generated for free-herds in each iteration is random, the significance of the model results was indicated by the summary of coefficients of 200 iterations instead of the P-value of each iteration. This 95% PCTL can inform the decision to (not) reject the hypothesis about a systematic increase or decrease of SCC or other herd performance variables. The normal distribution of the residuals of one iteration of the linear mixed model outcome was evaluated by visual inspection. The performance of the model was checked using the check_model function in R package performance (Lüdecke et al., 2019). The conditional R^2, which indicates how much the model variance is explained by both fixed and random factors (Nakagawa and Schielzeth, 2013) was also calculated with the performance package.

Calving interval. As CIV data is available per year, the effect of a new BVDV introduction on CIV was analysed per year as well. In line with the SCC model, a linear mixed effects model was applied to the CIV analysis, and specific model composition and variable definitions are shown in Table 4.1. The model-fitting procedure was the same as the SCC model. The modelling results were summarized with the mean, SD, minimum, maximum and 95% PCTL of the natural exponential transformed coefficients of the 200 iterations.

Culling risk. Culling risk is available per year, so the effect of new introduction of BVDV on CR was analysed per year. The herd-level CR was estimated using negative binomial distribution, and a logit-link function was used in a generalized linear mixed effects model:

$$\begin{aligned} Culling\ Risk_{ik} &= \beta_0 + \beta_1 BH_{FH_i} + \beta_2 BVDV\ status_{ik} \\ &+ \beta_3 (BH_{FH_i} \times BVDV\ status_{ik}) + \beta_4 Year_{ik} + Zu_{ik} \end{aligned} \quad [4.2]$$

For herd $i \in \{1, \ldots, 3{,}262\}$ and year $k \in \{2007, \ldots, 2016\}$, where $Culling\ Risk_{ik}$ was calculated by dividing the number of removed cows by the number of present cows on year k of herd i. The definition of explanatory variables BH_FH_i, $BVDV\ status_{ik}$ and $Year_{ik}$ is shown in Table 4.1. The random herd effect is u_{ik} and Z is the design matrix for the random part of the model (Dohoo et al., 2003). The random herd effect was assumed to be normally distributed. Maximum likelihood estimates of the parameters in the generalized linear mixed model were determined using the glmmTMB function in the glmmTMB package for R (Magnusson et al., 2017). The model fitting procedure was the same as for the SCC model. Overdispersion of the model was checked using the testDispersion function in the DHARMa package (Hartig and Hartig, 2017). The theoretical conditional R2 that can be used for the binomial distribution was calculated with the r.squaredGLMM function in package MuMIn (Barton and Barton, 2019). The intercept term was transformed back to the probability, and the modelling results of fixed variables were summarized in the same way as for the CIV model.

Calf mortality rate. The CMR data was recorded quarterly, thus the effect of a new BVDV introduction on CMR was analysed per year and per quarter. A generalized linear mixed effects model was applied (Table 4.1). The calf mortality data were fitted to a negative binomial distribution. The modelling results were summarized in the same way as for the CR model.

Table 4.1. Model composition summary of all 6 models, including the average cow somatic cell count (SCC), average calving interval (CIV), culling risk (CR) and calf mortality rate (CMR) analysis. The symbol × represents inclusion of the variable in the model

Model	Period of analysis	Regression type[1]	Regression	Dependent variable	Independent variable						
					BH_FH[2]	BVDV status	BH_FH × BVDV status	No. animal[6]	Year[7]	Season[8]	Herd[9]
SCC	Quarter	LMM	Linear	ln (SCC)	×	Quarterly[3]	×	×	×	×	×
	Annual	LMM	Linear	ln (SCC)	×	Yearly_1[4]	×	×	×	×	×
CIV	Annual	LMM	Linear	ln (CIV)	×	Yearly_2[5]	×	×	×		×
CR	Annual	GLMM	Negative binomial	CR	×	Yearly_2[5]	×		×		×
CMR	Quarter	GLMM	Negative binomial	CMR	×	Quarterly[3]	×	×	×	×	×
	Annual	GLMM	Negative binomial	CMR	×	Yearly_2[5]	×	×	×	×	×

[1] LMM = linear mixed effects model; GLMM = generalized linear mixed effects model.
[2] A dummy variable that represents herd type (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.
[3] BVDV status-Quarterly = 5 categories including the year prior to the BVDV breakdown-date (reference category) and the first four quarters (Q1–Q4) of the year post BVDV breakdown.
[4] BVDV status-Yearly_1 = 5 categories including 2 years prior breakdown, 1 year prior breakdown (reference categories), 1 year post breakdown, 2 years post breakdown and 3 years post breakdown.
[5] BVDV status-Yearly_2 = 6 categories including the 5 categories of BVDV status-Yearly_1, and a category "year of breakdown".
[6] For the SCC analysis: number of cows sampled on the test day, For the CIV analysis: number of cows used to calculate the average CIV, for the CMR analysis: herd size.
[7] A categorical variable, 2007–2016 for the SCC, CIV and CR analysis, and 2011–2016 for the CMR analysis.
[8] A categorical variable defined as Spring (March–May), Summer (June–August, reference category), Autumn (September–November) and Winter (December to next February).
[9] A random herd effect that takes into account repeated measures within one herd.

Sub-analysis. Although all studied herds participated in the BVDV-free programme, the antibody prevalence within each herd will vary, depending on when BVDV last circulated. The initial antibody prevalence can moderate the effect of BVDV introduction on herd performance. Therefore, a sub-analysis was performed to determine the effect of initial BVDV antibody prevalence on the effects of BVDV introduction. The length of BVDV-free time (defined as the number of days between the free-date and breakdown-date) was used as an indicator of the BVDV antibody prevalence. The longer a herd is BVDV-free, the lower the BVDV antibody prevalence within the herd is. Therefore, in the sub-analysis, only herds that had a BVDV-free status for more than 3 years were included. After 3 years of BVDV-free, the antibody prevalence in the herd was considered to be reduced to a low level (approx. 28%, according to the control experience of infectious bovine rhinotracheitis in the Netherlands (Noordegraaf et al., 1998). The sub-analysis was carried out for all six models mentioned in Table 4.1.

4.3 Results

4.3.1 Descriptive results

Table 4.2 presents descriptive results of the herd performance (SCC, CIV, CR and CMR) in relation to the BVDV status. The descriptive results show that the herd performance of free-herds was generally better than of breakdown-herds. The overall average SCC for breakdown-herds and free-herds was 198,000 cells/mL (SD ± 87,000) and 187,000 cells/mL (SD ± 87,000), respectively. The overall average CIV of cows in breakdown-herds was on average 3 days longer than in free-herds. The overall average CR in breakdown-herds was 23.5% (SD ± 8.4%), which was 0.3% higher than in free-herds. The average CMR in breakdown-herds was 0.44% higher than that in free-herds. In addition, within the breakdown-herds, SCC, CIV, CR and CMR differed by years prior or post BVDV breakdown.

Table 4.2. The descriptive statistics of the average herd level cow somatic cell count (SCC), calving interval (CIV), culling risk (CR) and calf mortality rate (CMR) in Dutch dairy herds from 2007 to 2016[1]

Variables	Breakdown-herd[2]							Free-herd[3]
	Years prior and post bovine viral diarrhoea virus (BVDV) breakdown						Average	Average
	−2	−1	0	1	2	3		
	Mean (SD)							
SCC								
Number of herds in the analysis				703				2,629
Number of animals sampled for SCC	77 (34)	79 (35)	-	81 (37)	84 (40)	87 (43)	82 (38)	80 (37)
SCC[4], 1,000 cells/mL	209 (89)	205 (88)	-	202 (90)	190 (84)	185 (83)	198 (87)	187 (87)
CIV								
Number of herds in the analysis				706				2,612
Number of cows to calculate average CIV	64 (31)	64 (30)	66 (31)	68 (34)	71 (36)	73 (38)	68 (34)	67 (32)
Average CIV, days	415 (21)	417 (26)	417 (26)	417 (25)	415 (25)	414 (24)	416 (25)	413 (23)
CR								
Number of herds in the analysis				700				2,562
Number of removed cows per year	21 (13)	21 (13)	22 (13)	23 (13)	23 (14)	23 (14)	22 (13)	21 (12)
Number of present cows per year	88 (41)	89 (41)	92 (43)	95 (44)	98 (49)	101 (53)	94 (46)	92 (43)
CR, %	23.0 (8.5)	23.1 (8.4)	23.4 (9.0)	24.3 (8.6)	23.7 (8.2)	23.1 (7.9)	23.5 (8.4)	23.2 (8.3)
CMR								
Number of herds in the analysis				327				2,840
Number of dead calves, n/quarter[5]	1 (2)	1 (2)	1 (2)	1 (2)	2 (2)	2 (2)	1 (2)	1 (2)
Number of present calves, n/quarter[6]	38 (21)	41 (24)	42 (24)	43 (25)	45 (27)	46 (29)	43 (25)	41 (22)
CMR[7], %	2.96 (4.35)	2.99 (4.25)	3.34 (4.64)	3.29 (4.64)	3.50 (5.25)	3.55 (4.96)	3.33 (4.76)	2.89 (4.26)

[1] For SCC, CIV and CR, from January 1, 2007 to December 31, 2016; for CMR, from January 1, 2011 to June 30, 2016.
[2] Breakdown-herd = herd lost its BVDV-free status during the study period.
[3] Free-herd = herd remained BVDV-free during the whole study period.
[4] SCC is the average SCC per cow on the test day.
[5] The number of ear-tagged calves up to 1 year old that is reported 'dead' in a quarter.
[6] The number of calf-quarters at risk.
[7] CMR (%) is defined as the number of ear-tagged calves up to 1 year old that is reported 'dead' in a quarter, over the number of calf-quarters at risk during that same time period.

4.3.2 Somatic cell count

Table 4.3 shows the summarized results of the SCC analysis. Figure 4.2a compares SCC in relation to BVDV breakdown in breakdown-herds and free-herds. Figure 4.3a presents the results of the quarterly analysis. In the annual analysis, the SCC for breakdown-herds was 1.008 (95% PCTL: 1.000; 1.017) times higher than in free-herds. The interaction term BH_FH × BVDV status indicated the effect of BVDV introduction on SCC within the breakdown-herds. In the year post BVDV breakdown, the SCC was 1.011 (95% PCTL: 1.002; 1.020) times higher than in the year prior to BVDV breakdown. The SCC decreased by a factor of 0.997 (95% PCTL: 0.985; 1.008) in the second year post BVDV breakdown. In the quarterly analysis, the SCC increased mainly in the second quarter post BVDV breakdown, with a factor of 1.014 (95% PCTL: 1.001; 1.027). Both the annual and quarterly analysis indicated that BVDV introduction has negative effects on SCC in breakdown-herds.

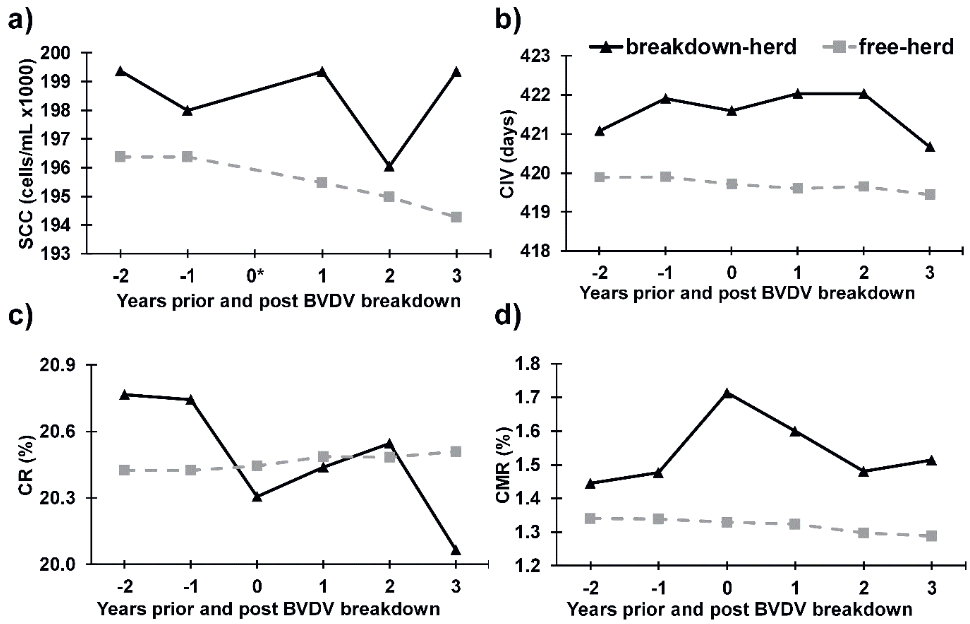

Figure 4.2. Effect of new introduction of bovine viral diarrhoea virus (BVDV) on average cow somatic cell count (SCC) (a), calving interval (CIV) (b), culling risk (CR) (c) and calf mortality rate (CMR) (d) for breakdown-herds and free-herds in the Netherlands. A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.
*Year 0 is not defined in the SCC analysis, and therefore there is no Y value. For SCC analysis, the BVDV status corresponding to the monthly SCC records was defined according to the breakdown-date. In other analyses (CIV, CR, CMR), the BVDV status corresponding to the yearly or quarterly records was defined according to the breakdown-year.

Table 4.3. Summarized natural exponentiated regression coefficients of the linear mixed effects model with 200 iterations for the effects of bovine viral diarrhoea virus (BVDV) breakdown on somatic cell count (SCC, 1,000 cells/mL) per cow in 703 breakdown-herds[4] and 2,629 free-herds[4] in the Netherlands

Effects	Categories	Exponent[1] of estimated coefficients					
		Annual analysis			Quarterly analysis		
		Mean	SD	95% PCTL[2]	Mean	SD	95% PCTL
SCC Intercept[3]		196	2	192; 200	198	3	192; 202
BH_FH[4]	Free-herd	Ref.					
	Breakdown-herd	1.008	0.005	1.000; 1.017	1.010	0.004	1.002; 1.019
No. animal[5]		1.001	0.000	1.000; 1.001	1.000	0.000	1.000; 1.001
BVDV status	1 year prior breakdown	Ref.					
	2 years prior breakdown	1.000	0.006	0.990; 1.012	-	-	-
	1 year post breakdown	0.995	0.005	0.987; 1.004	-	-	-
	2 years post breakdown	0.993	0.007	0.980; 1.006	-	-	-
	3 years post breakdown	0.989	0.008	0.975; 1.004	-	-	-
	Q1 post breakdown [6]	-	-	-	0.996	0.006	0.985; 1.007
	Q2 post breakdown [6]	-	-	-	0.995	0.007	0.982; 1.008
	Q3 post breakdown [6]	-	-	-	0.995	0.006	0.983; 1.008
	Q4 post breakdown [6]	-	-	-	0.996	0.007	0.984; 1.010
BH_FH × BVDV status	BH_FH × 1 year prior breakdown	Ref.					
	BH_FH × 2 years prior breakdown	1.007	0.005	0.996; 1.016	-	-	-
	BH_FH × 1 year post breakdown	1.011	0.004	1.002; 1.020	-	-	-
	BH_FH × 2 years post breakdown	0.997	0.006	0.985; 1.008	-	-	-
	BH_FH × 3 years post breakdown	1.018	0.006	1.006; 1.029	-	-	-
	BH_FH × Q1 post breakdown	-	-	-	1.007	0.006	0.996; 1.019
	BH_FH × Q2 post breakdown	-	-	-	1.014	0.007	1.001; 1.027
	BH_FH × Q3 post breakdown	-	-	-	1.005	0.006	0.993; 1.018
	BH_FH × Q4 post breakdown	-	-	-	1.300	0.006	0.038; 2.460
Year	2007	Ref.					
	2008	1.050	0.007	1.036; 1.064	1.039	0.007	1.021; 1.060
	2009	1.031	0.008	1.015; 1.046	1.022	0.008	1.001; 1.044
	2010	1.038	0.009	1.021; 1.055	1.036	0.008	1.013; 1.061
	2011	0.976	0.009	0.958; 0.993	0.981	0.009	0.957; 1.007
	2012	0.833	0.009	0.815; 0.849	0.837	0.008	0.811; 0.859
	2013	0.826	0.010	0.807; 0.845	0.824	0.009	0.795; 0.850
	2014	0.853	0.012	0.830; 0.875	0.840	0.011	0.814; 0.868
	2015	0.803	0.013	0.776; 0.825	0.783	0.012	0.742; 0.817
	2016	0.819	0.015	0.788; 0.848	-	-	-
Season[7]	Summer	Ref.					
	Autumn	0.939	0.002	0.936; 0.942	0.937	0.003	0.931; 0.943
	Winter	0.878	0.002	0.875; 0.882	0.883	0.003	0.877; 0.889
	Spring	0.887	0.002	0.884; 0.890	0.894	0.003	0.888; 0.899
Conditional R^2 (%)		36.60	0.45	35.80; 37.50	38.50	0.65	37.30; 39.80

[1] The natural exponentiated regression coefficient (expect for the intercept term) is the ratio between the mean level of a specific category and the mean level of the reference category.
[2] 2.5th percentile to 97.5th percentile of the parameter estimate.
[3] The geometric mean of SCC.
[4] A dummy variable indicating herd status (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.
[5] Number of cows sampled on the test day for SCC.
[6] The 1st, 2nd, 3rd and 4th quarter following the BVDV breakdown-date.
[7] Spring (March–May), Summer (June–August), Autumn (September–November), Winter (December to next February).

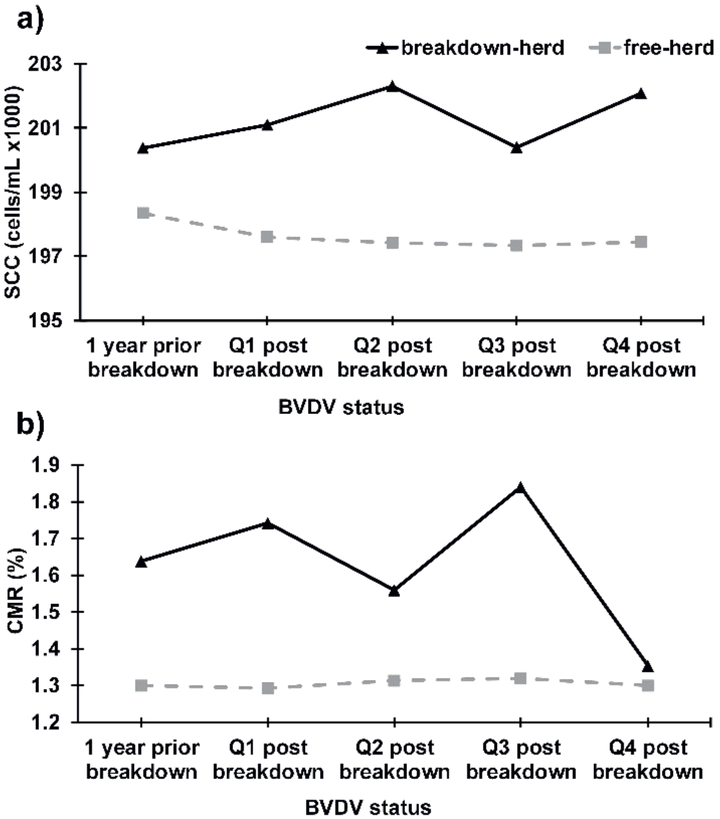

Figure 4.3. Effect of new introduction of bovine viral diarrhoea virus (BVDV) on average cow somatic cell count (SCC) (a) and calf mortality rate (CMR) (b) for breakdown-herds and free-herds in the first year after breakdown in the Netherlands. A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.

4.3.3 Calving Interval

Table 4.4 shows the summarized modelling results for the CIV analysis. Figure 4.2b compares the CIV in relation to the BVDV breakdown in breakdown-herds and free-herds. The CIV in breakdown-herds was 1.005 (95% PCTL: 1.003; 1.007) times higher than in free-herds. Within the breakdown-herds, there is no significant change in the average CIV, whether it is in the year of the breakdown (mean ratio 1.000, 95% PCTL: 0.998; 1.002) or on the first two years post BVDV breakdown.

Table 4.4. Summarized exponentiated regression coefficients of the linear mixed effects model with 200 iterations for the annual effect of (bovine viral diarrhoea virus) BVDV breakdown on average calving interval (CIV) (days) per cow in 706 breakdown-herds[4] and 2,612 free-herds[4] in the Netherlands

Effects	Categories	Exponent[1] of estimated coefficients				
		Mean	SD	Min	95% PCTL[2]	Max
CIV Intercept[3]		420	1	420	420; 420	424
BH_FH[4]	Free-herd	Ref.				
	Breakdown-herd	1.005	0.001	1.003	1.003; 1.007	1.008
No. animal[5]		1.000	0.000	1.000	1.000; 1.000	1.000
BVDV status	1 year prior breakdown	Ref.				
	2 years prior breakdown	1.000	0.001	0.996	0.997; 1.002	1.004
	Year of breakdown	1.000	0.001	0.996	0.997; 1.002	1.003
	1 year post breakdown	0.999	0.001	0.996	0.997; 1.002	1.003
	2 years post breakdown	0.999	0.002	0.995	0.996; 1.003	1.004
	3 years post breakdown	0.999	0.002	0.993	0.995; 1.003	1.004
BH_FH × BVDV status	BH_FH × 1 year prior breakdown	Ref.				
	BH_FH × 2 years prior breakdown	0.998	0.001	0.995	0.996; 1.001	1.002
	BH_FH × Year of breakdown	1.000	0.001	0.997	0.998; 1.002	1.003
	BH_FH × 1 year post breakdown	1.001	0.001	0.998	0.999; 1.003	1.004
	BH_FH × 2 years post breakdown	1.001	0.001	0.997	0.998; 1.003	1.005
	BH_FH × 3 years post breakdown	0.998	0.001	0.994	0.996; 1.000	1.001
Year	2007	Ref.				
	2008	1.007	0.001	1.004	1.005; 1.008	1.010
	2009	1.013	0.001	1.009	1.010; 1.015	1.016
	2010	1.002	0.001	0.998	0.999; 1.005	1.006
	2011	1.006	0.002	1.000	1.002; 1.009	1.010
	2012	1.006	0.002	1.001	1.002; 1.010	1.011
	2013	1.005	0.002	0.999	1.001; 1.010	1.012
	2014	0.999	0.003	0.992	0.994; 1.005	1.007
	2015	0.999	0.003	0.991	0.992; 1.005	1.007
	2016	0.993	0.004	0.984	0.986; 0.999	1.002
Conditional R^2 (%)		68.90	0.51	67.70	67.90; 69.90	70.10

[1] The natural exponentiated regression coefficient (expect for the intercept term) is the ratio between the mean level of a specific category and the mean level of the reference category.
[2] 2.5th percentile to 97.5th percentile of the parameter estimate.
[3] The geometric mean of average CIV.
[4] A dummy variable indicating herd status (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.
[5] Number of cows used to calculate the average CIV.

4.3.4 Culling risk

Table 4.5 shows the modelling results for the CR analysis. Figure 4.2c compares the CR in relation to BVDV breakdown in breakdown- and free-herds. The mean intercept of CR is 20.4%, and the CR in breakdown-herds was on average 1.020 (95% PCTL: 1.001; 1.040) times higher than in free-herds. For the breakdown-herds, the CR in the year of breakdown is lower than in the year prior to BVDV breakdown, with a factor of 0.972 (95% PCTL: 0.949; 0.996). There was no significant effect of BVDV introduction on CR in the two years post breakdown.

Table 4.5. Summarized exponentiated regression coefficients of the generalized linear mixed effects model (with logit-link function and negative binomial distribution) with 200 iterations for the annual effect of bovine viral diarrhoea virus (BVDV) breakdown on culling risk (CR) (%) in 700 breakdown-herds[4] and 2,562 free-herds[4] in the Netherlands

Effects	Categories	Exponent[1] of estimated coefficients				
		Mean	SD	Min	95% PCTL[3]	Max
CR Intercept[2] (%)		20.4	0.4	19.8	19.9; 20.9	21.1
BH_FH[4]	Free-herd	Ref.				
	Breakdown-herd	1.020	0.010	0.993	1.001; 1.040	1.046
BVDV status	1 year prior breakdown	Ref.				
	2 years prior breakdown	1.000	0.014	0.960	0.975; 1.027	1.043
	Year of breakdown	1.001	0.014	0.964	0.975; 1.027	1.036
	1 year post breakdown	1.004	0.015	0.965	0.980; 1.035	1.049
	2 years post breakdown	1.004	0.017	0.968	0.972; 1.035	1.050
	3 years post breakdown	1.005	0.019	0.958	0.968; 1.042	1.057
BH_FH × BVDV status	BH_FH × 1 year prior breakdown	Ref.				
	BH_FH × 2 years prior breakdown	1.001	0.014	0.959	0.975; 1.027	1.045
	BH_FH × Year of breakdown	0.972	0.013	0.940	0.949; 0.996	1.010
	BH_FH × 1 year post breakdown	0.978	0.013	0.946	0.951; 1.003	1.011
	BH_FH × 2 years post breakdown	0.984	0.012	0.948	0.960; 1.006	1.013
	BH_FH × 3 years post breakdown	0.954	0.013	0.913	0.931; 0.980	0.996
Year	2007	Ref.				
	2008	0.943	0.011	0.917	0.921; 0.963	0.974
	2009	1.265	0.016	1.228	1.231; 1.292	1.311
	2010	1.239	0.018	1.195	1.202; 1.275	1.288
	2011	1.275	0.021	1.229	1.234; 1.315	1.331
	2012	1.163	0.022	1.113	1.123; 1.204	1.218
	2013	1.009	0.022	0.957	0.968; 1.050	1.059
	2014	1.224	0.029	1.147	1.168; 1.279	1.292
	2015	1.045	0.028	0.981	0.994; 1.096	1.112
	2016	1.163	0.037	1.055	1.097; 1.232	1.261
Conditional R^2 (%)		71.70	0.34	70.80	71.10; 72.50	72.70

[1] The natural exponentiated regression coefficient (expect for the intercept term) is the ratio between the mean level of a specific category and the mean level of the reference category.

[2] The intercept was transformed back to the probability by using the equation $p(Intercept) = \frac{exp\ (\beta_0)}{1+\exp\ (\beta_0)}$.

[3] 2.5th percentile to 97.5th percentile of the parameter estimate.

[4] A dummy variable indicating herd status (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.

4.3.5 Calf Mortality Rate

Table 4.6 shows the annual and quarterly modelling results for the CMR analysis. Figure 4.2d compares the CMR in relation to BVDV breakdown in breakdown- and free-herds. Figure 4.3b presents the results of the quarterly analysis. The mean intercept of CMR in annual and quarterly results is 1.34% and 1.30%, respectively, and the CMR in the breakdown-herds was on average 1.105 (95% PCTL: 1.062; 1.150) and 1.265 (95% PCTL: 1.231; 1.292) times higher than in free-herds, respectively. For the annual analysis results, the CMR in the year of the breakdown and the year post BVDV breakdown was 1.170 (95% PCTL: 1.120; 1.218) and 1.096 (95% PCTL: 1.048; 1.153) times higher than the year prior to BVDV breakdown, respectively. In the quarterly modelling results, the CMR increased in the first and third quarter after BVDV breakdown, which was on average 1.070 (95% PCTL: 1.009; 1.134) and 1.108 (95% PCTL: 1.048; 1.179) times higher than the CMR in the year prior to BVDV breakdown, respectively. In the second and fourth quarter, the CMR was on average 0.941 (95% PCTL: 0.890; 0.991) and 0.824 (95% PCTL: 0.768; 0.889) times lower than the CMR in the year prior to BVDV breakdown, respectively. Both the annual and quarterly analysis indicate that BVDV introduction has a negative effect on CMR in breakdown-herds.

Table 4.6. Summarized exponentiated regression coefficients of the generalized linear mixed effects model (with logit-link function and negative binomial distribution) with 200 iterations for the annual effect of BVDV breakdown on calf mortality rate (CMR, %) in 327 breakdown-herds[4] and 2,840 free-herds[4] in the Netherlands

Effects	Categories	Exponent[1] of estimated coefficients					
		Annual analysis			Quarterly analysis		
		Mean	SD	95% PCTL[3]	Mean	SD	95% PCTL
CMR Intercept (%)[2]		1.34	0.06	1.22; 1.43	1.30	0.05	1.20; 1.38
BH_FH[4]	Free-herd	Ref.			Ref.		
	Breakdown-herd	1.105	0.023	1.062; 1.150	1.265	0.016	1.231; 1.292
Herd size		1.001	0.000	1.001; 1.001	1.001	0.000	1.001; 1.001
BVDV status	1 year prior breakdown	Ref.			Ref.		
	2 years prior breakdown	1.002	0.037	0.937; 1.081	-	-	-
	Year of breakdown	0.993	0.033	0.924; 1.047	-	-	-
	1 year post breakdown	0.988	0.053	0.889; 1.093	-	-	-
	2 years post breakdown	0.969	0.069	0.821; 1.089	-	-	-
	3 years post breakdown	0.961	0.083	0.796; 1.106	-	-	-
	Q1 post breakdown [5]	-	-	-	0.995	0.030	0.936; 1.052
	Q2 post breakdown [5]	-	-	-	1.011	0.031	0.958; 1.072
	Q3 post breakdown [5]	-	-	-	1.015	0.034	0.951; 1.081
	Q4 post breakdown [5]	-	-	-	1.000	0.042	0.922; 1.078
BH_FH × BVDV status	BH_FH × 1 year prior breakdown	Ref.			Ref.		
	BH_FH × 2 years prior breakdown	0.976	0.029	0.913; 1.034	-	-	-
	BH_FH × Year of breakdown	1.170	0.026	1.120; 1.218	-	-	-
	BH_FH × 1 year post breakdown	1.096	0.030	1.048; 1.153	-	-	-
	BH_FH × 2 years post breakdown	1.034	0.026	0.987; 1.087	-	-	-
	BH_FH × 3 years post breakdown	1.067	0.031	1.001; 1.131	-	-	-
	BH_FH × Q1 post breakdown	-	-	-	1.070	0.030	1.009; 1.134
	BH_FH × Q2 post breakdown	-	-	-	0.941	0.026	0.890; 0.991
	BH_FH × Q3 post breakdown	-	-	-	1.108	0.033	1.048; 1.179
	BH_FH × Q4 post breakdown	-	-	-	0.824	0.032	0.768; 0.889
Year	2011	Ref.			Ref.		
	2012	1.045	0.031	0.991; 1.113	1.071	0.022	1.027; 1.116
	2013	1.161	0.056	1.058; 1.278	1.192	0.037	1.137; 1.266
	2014	1.131	0.080	0.996; 1.307	1.130	0.046	1.041; 1.224
	2015	1.255	0.112	1.075; 1.516	1.224	0.066	1.099; 1.373
	2016	1.454	0.159	1.198; 1.811	-	-	-
Season[6]	Summer	Ref.			Ref.		
	Autumn	1.381	0.020	1.344; 1.418	1.368	0.029	1.317; 1.430
	Winter	1.619	0.022	1.579; 1.660	1.618	0.032	1.562; 1.685
	Spring	1.476	0.020	1.439; 1.513	1.530	0.028	1.481; 1.582
Conditional R^2 (%)		85.70	0.33	85.10; 86.30	86.50	0.28	85.90; 87.00

[1] The natural exponentiated regression coefficient (expect for the intercept term) is the ratio between the mean level of a specific category and the mean level of the reference category.

[2] The intercept was transformed back to the probability by using the equation $p(Intercept) = \frac{exp\ (\beta_0)}{1+\exp\ (\beta_0)}$.

[3] 2.5th percentile to 97.5th percentile of the parameter estimate.

[4] A dummy variable indicating herd status (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.

[5] Q1, Q2, Q3, Q4 = the 1st, 2nd, 3rd and 4th quarter following BVDV breakdown.

[6] Spring (March–May), Summer (June–August), Autumn (September–November), Winter (December to next February).

4.3.6 Sub-analysis

The sub-analysis comprised herds that were BVDV-free for more than 3 years. The descriptive results and estimates of the sub-analysis for all six models are listed in Supplementary material Table 4.S1, 4.S2 and 4.S3 (https://doi.org/10.17026/dans-2zc-7w88). For the sub-analysis of SCC, the SCC in breakdown-herds in the first, second and third year post BVDV breakdown was 1.021 (95% PCTL: 1.010; 1.032), 1.013 (95% PCTL: 1.002; 1.023) and 1.042 (95% PCTL: 1.033; 1.053) times higher than in the year prior to BVDV breakdown, respectively. The results show that, compared with the SCC for all studied herds, the SCC in herds that had the BVDV-free status for more than 3 years increased more after BVDV introduction. The average CIV of breakdown-herds in the first and second year post breakdown was 1.005 (95% PCTL: 1.003; 1.007) and 1.003 (95% PCTL: 1.001; 1.005) times the average CIV in the year prior to BVDV breakdown in the sub-analysis. Compared with the effect of BVDV introduction on the average CIV of all studied herds, BVDV introduction had a larger effect on the average CIV in herds that had a longer BVDV-free status. The sub-analysis of the CR model showed that after BVDV introduction the reduction in CR was higher than in the overall analysis. In the year of breakdown, the CR in breakdown-herds was 0.941 (95% PCTL: 0.922; 0.961) times lower than in the year prior to breakdown. The CMR of breakdown-herds increased with a factor of 1.223 (95% PCTL: 1.158; 1.280) and 1.156 (95% PCTL: 1.094; 1.224) in the year of breakdown and the year post breakdown, respectively, compared with the CMR in the year prior to BVDV breakdown. Similar to the other parameters (i.e., SCC, CIV), the estimated negative effects of BVDV introduction on CMR increased for herds which were BVDV-free for a longer time period.

4.4 Discussion

The effect of a new BVDV introduction on herd performance was quantified by examining SCC, CIV, CR, and CMR in Dutch dairy herds participating in the BVDV-free programme. This study combined the herd-level BVDV surveillance data and herd performance information from January 1, 2007 to December 31, 2016. Both descriptive and multivariable model results show that BVDV-free herds perform better than breakdown-herds. Free-herds had lower SCC, CR, CMR and shorter CIV. For the breakdown-herds, our results indicate that a new BVDV introduction has a negative, but on average relatively small, effect on herd performance (mainly on SCC and CMR) in dairy herds participating in the BVDV control programme.

The effect of BVDV infection on SCC is smaller in our study than in other studies. Beaudeau et al. (2005) and Laureyns et al. (2013) reported that the SCC in BVDV-infected herds was 6,000 cells/mL to 31,400 cells/mL higher than in non-infected herds. A possible explanation for the smaller effect of BVDV infection in our findings might be that all the studied herds in our study participated in the BVDV-free programme. The studied herds were able to detect BVDV infection at an early stage. Moreover, in the BVDV-free programme, they were obligated to detect and cull the PI animals, so as to prevent more susceptible animals from being infected (and subsequent increase in cow SCC). These activities most probably will lead to relatively small effects of BVDV infections on herd performance. Another possible explanation for the smaller effect in our results is that previous studies were mostly cross-sectional studies and evaluated the effect of BVDV infection by comparing SCC in herds with different BVDV status. Few studies have investigated changes in SCC within BVDV infected herds. Tschopp et al. (2017) assessed the effect of BVDV eradication on bulk milk SCC in Swiss dairy farms by matching case herds with more than one PI animal with control herds free of BVDV. After the eradication of BVDV, bulk milk SCC in case herds showed a slight decrease (Tschopp et al., 2017). However, other studies did not find a significant association between bulk milk SCC and BVDV status of the herd (Waage et al., 1994; Heuer et al., 2007; Rola et al., 2014; Shafaei et al., 2020). The effect of BVDV introduction on SCC in our study mainly appeared in the first year post introduction in our study, and this is in accordance with the findings of Beaudeau et al. (2005) and Laureyns et al. (2013).

Another finding is that CMR in breakdown-herds increased significantly after a new BVDV introduction. These results are in accordance with previous studies indicating that BVDV infection attributes to mortality in young stock (Houe and Meyling, 1991; Bennett et al., 1999; Dieguez et al., 2009; Graham et al., 2013). However, the effect of BVDV infection on CMR found in our study is smaller than previous studies. Ersbøll et al. (2003) and Gates et al. (2013) reported that the CMR in herds affected with BVDV was 3.05 to 7.3 percentage points (calculated to be 1.47 to 2 times) higher than in herds free from BVDV. One possible reason for the difference in results is the fact that herds in our study can detect virus circulation and cull PI animals more quickly. In addition, a different definition of CMR was used in our study. In the studies by Ersbøll et al. (2003) and Gates et al. (2013), annual rather than quarterly CMR data were used. The annual CMR is higher than the quarterly CMR (Santman-Berends et al., 2014, 2019). We used quarterly CMR data in our analysis to determine the short-term effects of new BVDV introductions.

The effect of a new introduction of BVDV on CIV was only statistically significant (95% PCTL >1 or <1) for herds that had been BVDV-free for at least 3 years, as was shown in the sub-analysis. Prior studies had conflicting results. Berends et al. (2008), Valle et al. (2001) and Gates et al. (2013) found no apparent effects, however, other studies observed a longer CIV (ranging from 7 to 9 days) as a consequence of BVDV infection (Niskanen et al., 1995; Burgstaller et al., 2016). These different results may be due to the heterogeneity of the studied herds. In our study, herds that had been BVDV-free for a longer time period had more susceptible cows. When BVDV was introduced into these herds, more naive cows could be transiently infected. This may further lead to increased abortion rates, decreased conception rates, and increased early embryonic deaths, etc. (Houe et al., 1993; Berends et al., 2008; Burgstaller et al., 2016), resulting in an extended average CIV.

The CR was lower in breakdown-herds in the year when BVDV was introduced, this finding is contrary to previous studies which suggested that BVDV infection results in higher risk of culling (Bennett et al., 1999; Valle et al., 2001; Tiwari et al., 2005) or has no significant effect on culling (Niskanen et al., 1995; Gates et al., 2013). A possible explanation may be that in the BVDV-free programme, a new infection usually starts with a small number of PI animals that will be quickly detected and culled. Herds that are certified BVDV-free have no PI animal (Figure 4.1). After obtaining the BVDV-free certificate, the herd enters the monitoring phase (Phase II) and is monitored by testing 5 randomly selected young stock at the age of 8-12 months with an antibody ELISA every 6 months or testing all new-born calves in the herd with an antigen ELISA (Veldhuis et al., 2018; van Duijn et al., 2019). Furthermore, in 49% of breakdown-herds antigen-positive animals are detected, and only 3.87% (782/20,213) were confirmed as PI animals (van Duijn et al., 2019). Therefore, BVDV breakdown is more likely to be due to transient infection. Transiently infected cows will develop antibodies in two to three weeks after infection, which often leads to lifelong seropositivity, and therefore the transiently infected cows do not need to be culled (Houe et al., 2006; Scharnböck et al., 2018). In addition, the few herds that have detected PI calves only need to cull a small number of PI calves. The small number of PI animals has only a limited impact on the annual CR of breakdown-herds.

The main reason for the limited effects of a new BVDV introduction on herd performance is the effective control measures of the BVDV-free programme. In this study, the specific reasons or animals introducing BVDV into each herd could not be determined due to lack of data on this. The route on how BVDV was introduced can however be indirectly inferred through the control measures of the BVDV-free programme. In the test and cull phase (phase I) of the BVDV-free programme, all cattle in the herd are tested for virus, and the detected PI animals are culled. The herd can be certified as BVDV-free only if the virus is not detected in new-born calves for 10 consecutive mo. This process ensures that there are no PI animals in the herd when the herd is certified as BVDV-free. After being certified as BVDV-free, the herd has to perform antigen ELISA tests on the purchased animals if the animals are purchased from a herd with a lower BVDV status (Veldhuis et al., 2018). This measure prevents PI animals from entering the lactating herd. Furthermore, after the BVDV breakdown, the herd needs to quickly test and confirm whether there are PI animals in the herd and remove the PI animals (if any) to obtain the BVDV-free certification again. In the study of van Duijn et al. (2019), the average age of detected PI animals was 7 months, and the 99th percentile was 16 months. Hence, PI animals are already removed before entering the lactating herd, which prevents them from infecting susceptible cows and causing a negative impact on herd performance. Without a BVDV-free programme, BVDV introduction may be noticed and detected when clinical signs appear or when herd performance is notably worsened. Clearly, the effects of the new introduction of BVDV may have a greater negative effect on herd performance of dairy herds that do not participate in a control programme. The relatively minor effects of BVDV introduction, as found in our study, show the value of BVDV surveillance. Participation in a BVDV surveillance programme can be seen as insurance to limit the negative effects of the introduction of BVDV in a free-herd. In addition, all studied herds participated in both the CRV data registration and the BVDV-free programme. The overall management of such herds may be better, compared with herds that did not participate in these programmes (expert opinion). Therefore, the effects of a new BVDV introduction may be underestimated in this study.

In this study, the breakdown-date was assumed to be the date of BVDV introduction. Most free-herds (3,811/4,334) monitor their BVDV status with antibody tests twice a year. The exact moment of introduction of BVDV may lie somewhere before the breakdown-date. (Yue et al. (2021a) developed four different scenarios to determine which period is closest to the true period of BVDV spread in the herd. In the default scenario, the BVDV introduction date is assumed to be the same as the BVDV breakdown-date, and in the other scenarios the BVDV introduction date is set at 3, 6 or 9 months prior to BVDV breakdown-date. The authors showed that the default scenario most closely resembles the true period of BVDV infection. In the current study, the same scenarios were tested. However, the model results and conclusion in different scenarios were nearly identical, therefore these results are not presented.

Our statistical model may have potential limitations due to the nature of some variables. Multicollinearity between the explanatory variable $BVDV\ status$ and $Year$ is a common issue in the annual analysis of both the linear mixed models (SCC and CIV) and generalized linear mixed models (CR and CMR). This is a foreseeable problem because BVDV status is a categorical variable on a yearly basis (e.g., a breakdown-herd was BVDV-free in the early years and at some point in time changed to breakdown and kept that status afterwards). However, due to the indispensability of the $BVDV\ status$ and $Year$ variables, they are both retained in the final model. Although multicollinearity could reduce the precision of the estimated coefficients, this will only be a problem for the collinear variables. The coefficient of the variable of interest, the interaction item BH_FH×BVDV status, will not be affected, and the performance of the collinear variable BVDV status and Year as controls will not be impaired (Allison, 2012). Furthermore, we tested the overdispersion in the CR model. This is a problem that often appears in models with count data, and influences the standard errors of the indices and other parameters (McCullagh and Nelder, 1989; Hougaard et al., 1997) rather than affecting the coefficients. In our study, from each iteration only the coefficients are stored (not the standard errors) and the obtained distribution of coefficients was used to summarize the model results. Therefore, we considered that overdispersion did not affect the final results of the CR model. In addition, we ran the SCC, CIV, CR and CMR models with the duration of BVDV-free as a categorical variable, but the models did not improve, and therefore results for this analysis were not provided.

4.5 Conclusion

In the Dutch BVDV-free programme, BVDV-free herds had lower SCC, CR, CMR and shorter CIV than breakdown-herds. Within breakdown-herds, a new BVDV introduction had a negative but on average relatively small effect on herd performance (mainly on SCC and CMR). The modest effect is likely due to the fact that within the BVDV-free programme these herds did monitor BVDV and were obliged to detect and cull PI animals. Our results inform that implementing the BVDV surveillance programme is expected to limit the negative effects of BVDV introduction at the herd level substantially.

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Supplementary material

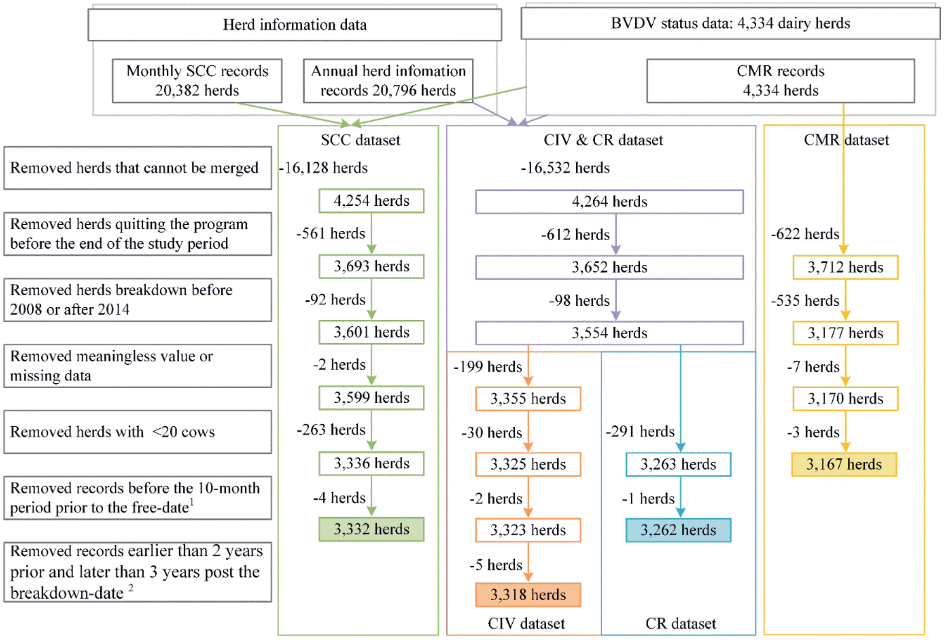

Figure 4.S1. Data editing process for the creation of four datasets of SCC, calving interval (CIV), culling risk (CR) and calf mortality rate (CMR).

[1] Free-date = the date on which the herd was certified as BVDV-free.

[2] Breakdown-date = the date on which the herd loses its BVDV-free certificate.

Table 4.S1. The descriptive statistics of the average herd level cow somatic cell count (SCC), calving interval (CIV), culling risk (CR), and calf mortal ity rate (CMR) from 2007 to 2016[1] of Dutch dairy herds that were bovine viral diarrhoea virus (BVDV)-free for more than 3 years (sub-analysis)

Variables	Breakdown-herd[2]							Free-herd[3]
	Years prior and post BVDV breakdown						Average	Average
	-2	-1	0	1	2	3		
SCC								
Number of herds in the analysis				221				2,629
Number of animals sampled for SCC	79 (37)	81 (39)	-	83 (41)	86 (44)	90 (48)	84 (42)	80 (37)
SCC[4], 1,000 cells/mL	211 (89)	202 (86)	-	194 (85)	180 (81)	182 (83)	194 (86)	187 (87)
CIV								
Number of herds in the analysis				216				2,612
Number of cows used to calculate the average CIV	66 (34)	67 (33)	68 (35)	70 (37)	74 (40)	76 (43)	70 (37)	67 (32)
Average CIV, days	414 (21)	417 (21)	413 (22)	418 (23)	415 (22)	413 (23)	415 (22)	413 (23)
CR								
Number of herds in the analysis				213				2,562
Number of removed cows per year	21 (13)	23 (14)	23 (13)	23 (13)	23 (14)	23 (14)	23 (14)	21 (12)
Number of present cows per year	89 (43)	92 (46)	94 (48)	97 (51)	101 (55)	106 (59)	96 (51)	92 (43)
CR, %	23.3 (8.6)	25.4 (8.6)	24.4 (9.3)	24.5 (8.3)	23.0 (7.5)	22.4 (7.1)	23.9 (8.3)	23.2 (8.3)
CMR								
Number of herds in the analysis				149				2,840
Number of dead calves, n/quarter[5]	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	2 (2)	1 (2)	1 (2)
Number of present calves, n/quarter[6]	37 (16)	43 (26)	43 (24)	44 (25)	46 (28)	47 (30)	44 (26)	41 (22)
CMR[7], %	2.82 (4.08)	2.96 (3.98)	3.11 (4.34)	3.07 (4.44)	3.41 (5.36)	3.41 (4.73)	3.19(4.62)	2.89 (4.26)

[1] For SCC, CIV and CR, from January 1, 2007 to December 31, 2016; for CMR, from January 1, 2011 to June 30, 2016.
[2] Breakdown-herd = herd lost its BVDV-free status during the study period.
[3] Free-herd = herd remained BVDV-free during the whole study period.
[4] SCC is the average SCC per cow on the test day.
[5] The number of ear-tagged calves up to 1 year old that is reported 'dead' in a quarter.
[6] The number of calf-quarters at risk.
[7] CMR (%) is defined as the number of ear-tagged calves up to 1 year old that is reported 'dead' in a quarter, over the number of calf-quarters at risk during that same time period.

Table 4.S2. Summarized natural exponentiated regression coefficients of the (generalized) linear mixed model with 200 iterations for the annual effect of bovine viral diarrhoea virus (BVDV) breakdown on somatic cell count (SCC, 1,000 cells/mL) per cow, calving interval (days) per cow, culling risk (%) per herd and calf mortality rate (%) per herd of Dutch dairy herds that were BVDV-free for more than 3 years (sub-analysis)

		Exponent[1] of estimated coefficients							
Effects	Categories	SCC (1000 cells/mL)		Calving interval (days)		Culling risk (%)		Calf mortality rate (%)	
		Mean	95% PCTL[2]	Mean	95% PCTL	Mean	95% PCTL	Mean	95% PCTL
Intercept[3]		215	179; 257	420	412; 424	0.211	0.187; 0.244	1.33	1.19; 1.46
BH_FH[4]	Free-herd	Ref.		Ref.		Ref.		Ref.	
	Breakdown-herd	1.000	0.992; 1.009	1.004	1.002; 1.005	1.051	1.036; 1.066	1.082	1.035; 1.132
Herd size/ No. animal[5]		1.001	1.000; 1.001	1.000	1.000; 1.000	-	-	1.001	1.000; 1.001
BVDV status	1 year prior breakdown	Ref.		Ref.		Ref.		Ref.	
	2 years prior breakdown	1.002	0.990; 1.014	1.000	0.997; 1.003	1.001	0.973; 1.032	1.005	0.923; 1.091
	Year of breakdown	-		0.999	0.997; 1.001	1.000	0.976; 1.025	0.982	0.904; 1.060
	1 year post breakdown	0.995	0.984; 1.006	0.998	0.995; 1.002	1.003	0.973; 1.032	0.978	0.877; 1.085
	2 years post breakdown	0.988	0.973; 1.003	0.998	0.993; 1.003	1.004	0.971; 1.042	0.956	0.832; 1.114
	3 years post breakdown	0.987	0.969; 1.003	0.997	0.992; 1.004	1.006	0.965; 1.052	0.957	0.786; 1.135
BH_FH × BVDV status	BH_FH × 1 year prior breakdown	Ref.		Ref.		Ref.		Ref.	
	BH_FH × 2 years prior breakdown	1.009	1.000; 1.018	0.994	0.992; 0.996	0.965	0.940; 0.989	0.929	0.862; 0.998
	BH_FH × Year of breakdown	-	-	0.997	0.995; 0.998	0.941	0.922; 0.961	1.223	1.158; 1.280
	BH_FH × 1 year post breakdown	1.021	1.010; 1.032	1.005	1.003; 1.007	0.985	0.967; 1.006	1.156	1.094; 1.224
	BH_FH × 2 years post breakdown	1.013	1.002; 1.023	1.003	1.001; 1.005	0.969	0.953; 0.989	1.021	0.973; 1.074
	BH_FH × 3 years post breakdown	1.042	1.033; 1.053	1.001	0.999; 1.003	0.935	0.913; 0.953	1.074	1.020; 1.141

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Table 4.S2. Summarized natural exponentiated regression coefficients of the (generalized) linear mixed model with 200 iterations for the annual effect of bovine viral diarrhoea virus (BVDV) breakdown on somatic cell count (SCC, 1,000 cells/mL) per cow, calving interval (days) per cow, culling risk (%) per herd and calf mortality rate (%) per herd of Dutch dairy herds that were BVDV-free for more than 3 years (sub-analysis)

Effects	Categories	Exponent[1] of estimated coefficients							
		SCC (1000 cells/mL)		Calving interval (days)		Culling risk (%)		Calf mortality rate (%)	
		Mean	95% PCTL[2]	Mean	95% PCTL	Mean	95% PCTL	Mean	95% PCTL
Year	2007	Ref.		Ref.		Ref.		-	-
	2008	0.970	0.807; 1.156	1.012	1.001; 1.025	0.903	0.755; 1.053	-	-
	2009	0.952	0.791; 1.135	1.019	1.008; 1.031	1.207	1.005; 1.412	-	-
	2010	0.958	0.795; 1.142	1.008	0.996; 1.021	1.189	0.989; 1.388	-	-
	2011	0.899	0.748; 1.069	1.012	0.999; 1.024	1.224	1.019; 1.426	Ref.	
	2012	0.769	0.640; 0.913	1.012	0.998; 1.026	1.104	0.914; 1.285	1.067	1.003; 1.138
	2013	0.765	0.634; 0.908	1.012	0.997; 1.026	0.964	0.795; 1.121	1.183	1.080; 1.315
	2014	0.789	0.653; 0.938	1.007	0.989; 1.020	1.183	0.977; 1.374	1.157	1.017; 1.322
	2015	0.746	0.618; 0.891	1.006	0.990; 1.020	0.995	0.813; 1.176	1.287	1.100; 1.548
	2016	0.763	0.627; 0.891	1.002	0.982; 1.016	1.124	0.929; 1.319	1.471	1.172; 1.828
Season[6]	Summer	Ref.		-	-	-	-	Ref.	
	Autumn	0.937	0.934; 0.940	-	-	-	-	1.380	1.330; 1.429
	Winter	0.870	0.867; 0.874	-	-	-	-	1.626	1.573; 1.680
	Spring	0.879	0.876; 0.882	-	-	-	-	1.477	1.428; 1.522
Conditional R^2 (%)		37.90	37.10; 38.80	67.90	66.80; 68.80	0.71	0.70; 0.71	85.80	84.90; 86.70

[1] The natural exponentiated regression coefficient (expect for the intercept term) is the ratio between the mean level of a specific category and the mean level of the reference category.
[2] 2.5th percentile to 97.5th percentile of the parameter estimate.
[3] The intercept of SCC and calving interval is the geometric mean, and the intercept of culling risk and calf mortality rate was transformed back to the probability by using the equation $p(Intercept) = \frac{exp\ (\beta_0)}{1+\exp\ (\beta_0)}$.
[4] A dummy variable indicating herd status (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.
[5] Herd size variable was included in the calf mortality model, No. animal variable was involved in the SCC and calving interval models, representing the number of animals in control for SCC or calving interval.
[6] Spring (March–May), Summer (June–August), Autumn (September–November), Winter (December to next February).

Table 4.S3. Summarized exponentiated regression coefficients of the (generalized) linear mixed effects model with 200 iterations for the quarterly effect of BVDV breakdown on somatic cell count (1,000 cells/mL) per cow and calf mortality rate (%) per herd of Dutch dairy herds that were BVDV-free for more than 3 years (sub-analysis)

Effects	Categories	Exponent[1] of estimated coefficients			
		SCC (1,000 cells/mL)		Calf mortality rate (%)	
		Mean	95% PCTL[2]	Mean	95% PCTL
Intercept[3]		235	198; 276	1.29	1.20; 1.38
BH_FH[4]	Free-herd	Ref.		Ref.	
	Breakdown-herd	1.002	0.994; 1.010	1.168	1.141; 1.195
Herd size/ No. animal[5]		1.000	1.000; 1.001	1.001	1.000; 1.001
BVDV status	1 year prior breakdown	Ref.		Ref.	
	Q1[4] after breakdown	0.992	0.979; 1.004	1.004	0.945; 1.073
	Q2[4] after breakdown	0.992	0.977; 1.006	1.029	0.971; 1.100
	Q3[4] after breakdown	0.987	0.971; 1.006	1.031	0.974; 1.089
	Q4[4] after breakdown	0.988	0.972; 1.005	1.016	0.936; 1.113
BH_FH × BVDV status	BH_FH × 1 year prior breakdown	Ref.		Ref.	
	BH_FH × Q1[6] after breakdown	1.008	0.996; 1.021	1.095	1.033; 1.163
	BH_FH × Q2[6] after breakdown	1.037	1.025; 1.052	0.914	0.862; 0.966
	BH_FH × Q3[6] after breakdown	1.011	0.996; 1.026	1.068	1.007; 1.125
	BH_FH × Q4[6] after breakdown	1.024	1.011; 1.037	0.899	0.838; 0.972
Year	2008	Ref.		-	-
	2009	0.864	0.738; 1.027	-	-
	2010	0.880	0.748; 1.044	-	-
	2011	0.834	0.710; 0.992	Ref.	
	2012	0.717	0.602; 0.857	1.082	1.039; 1.129
	2013	0.713	0.599; 0.849	1.207	1.139; 1.278
	2014	0.734	0.619; 0.876	1.149	1.047; 1.239
	2015	0.685	0.572; 0.824	1.261	1.108; 1.422
Season[7]	Summer	Ref.		Ref.	
	Autumn	0.944	0.938; 0.950	1.353	1.302; 1.404
	Winter	0.875	0.868; 0.881	1.636	1.573; 1.704
	Spring	0.890	0.883; 0.896	1.543	1.495; 1.598
Conditional R^2 (%)		39.40	38.00; 40.60	86.30	85.80; 86.90

[1] The natural exponentiated regression coefficient (expect for the intercept term) is the ratio between the mean level of a specific category and the mean level of the reference category.
[2] 2.5th percentile to 97.5th percentile of the parameter estimate.
[3] The intercept of SCC is the geometric mean, and the intercept of calf mortality rate was transformed back to the probability by using the equation $p(Intercept) = \frac{exp\ (\beta_0)}{1+\exp\ (\beta_0)}$.
[4] A dummy variable indicating herd status (breakdown-herd or free-herd). A breakdown-herd lost its BVDV-free status during the study period, a free-herd remained BVDV-free during the whole study period.
[5] Herd size variable was included in the calf mortality model, No. animal variable was involved in the SCC model, representing the number of animals in control for SCC.
[6] The 1st, 2nd, 3rd and 4th quarter following the BVDV breakdown-date.
[7] Spring (March–May), Summer (June–August), Autumn (September–November), Winter (December to next February).

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CHAPTER 5

Seroprevalence of Bovine Viral Diarrhoea Virus in 3 Large Dairy Herds in North China

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Abstract

Bovine viral diarrhoea (**BVD**) is one of the most common cattle diseases in dairy herds. To date, there is little information on the prevalence of the bovine viral diarrhoea virus (**BVDV**) in large-scale dairy herds in North China. A study on the seroprevalence of BVDV was carried out in 3 large commercial dairy herds in North China in July 2019. Blood samples collected from 98 random dairy cows in the first and second parity were tested for BVDV antibodies by enzyme-linked immunosorbent assay. The results showed that the true BVDV seroprevalence was 96.3% in one herd and 100.0% in the other two herds. These high values indicated the high within-herd seroprevalence of BVDV. Results of this study provide Chinese dairy farmers with insight into the circulation of BVDV within the dairy herds, even though there are no clear signs of BVDV infection.

Bovine viral diarrhoea (**BVD**) is an infectious cattle disease, which is endemic in most cattle-raising countries worldwide (Scharnböck et al., 2018). BVD is caused by bovine viral diarrhoea virus (**BVDV**), and it can be transmitted vertically and horizontally. Vertical transmission occurs when a dam is infected with BVDV in the first trimester of pregnancy, resulting in the birth of a persistently infected (**PI**) calf (Brownlie et al., 1998). PI animals cannot produce BVDV antibodies by themselves, and spread a large amount of viruses every day during their entire life, making them the main reservoir of BVDV infections (Baker, 1995). Horizontally, susceptible animals exposed to BVDV can be transiently infected (**TI**). After 2 to 3 weeks, these TI animals will seroconvert and induce lifelong immunity (Brownlie et al., 1987; Baker, 1990). TI animals also shed virus during infection, but compared to PI animals, the amount of virus is negligible (Foddai et al., 2014).

Economically, BVD may result in significant losses in dairy herds, which were reported to vary between 0 to 658 euros per cow per year (Yarnall and Thrusfield, 2017). These economic losses are attributed to the negative effects of BVDV on dairy cows: poor reproductive performance (extended calving intervals, stillbirth, abortion, etc.), increased calf mortality, growth retardation, premature culling, increased susceptibility to other diseases, and reduced milk production (Houe, 2003; Pinior et al., 2017, 2019). Despite these listed negative effects, both PI and TI animals may stay in the herd without manifestations of clinical signs, not noticed by the dairy farmers, and can only be detected through laboratory tests (Baker, 1995; Moennig and Yarnall, 2021).

To have a better understanding of the BVDV infection status, many BVDV prevalence studies have been conducted in the past decades, especially in European and American countries (Houe, 1995). However, there is little published data on the prevalence of BVDV in Chinese dairy herds (e.g., Deng et al. 2015). The pooled BVDV prevalence in dairy cows was reported 53% by Ran et al. (2019), and varied greatly (19.7%%–85.3%) in different provinces and regions, with the highest in North China (including Beijing, Tianjin, Hebei Province, Shanxi Province and Inner Mongolia Autonomous Region). North China is the area with the highest milk production among the three major dairy farming industry areas (North, Northeast, and Northwest) in China (Intelligence Research Group, 2021). Although some prevalence studies on BVDV have been conducted in North China (Zhang et al., 2010; Fu et al., 2012; Qi et al., 2013; Li et al., 2014, 2017), prevalence studies specifically on large dairy farms are lacking. With the General Office of the State Council issued the "Opinions on Promoting the Revitalization of the Milk Industry and Ensuring the Quality and Safety of Dairy Products" in

2018, the number of large-scale dairy farms in China has rapidly increased (Wang et al., 2021). This indicates a need to understand the prevalence of BVDV on large-scale dairy farms.

The aim of this study was to investigate the within-herd seroprevalence (prevalence of antibodies) of BVDV in 3 large commercial dairy herds in North China. The results of this study will provide both dairy farmers and policy maker with insights about BVDV infection within the herds, which can be used to formulate control plans.

The experiment procedures of this study were carried out under the approval of the Animal Welfare Body of Wageningen University and Research and the Animal Ethics Committee of China Agricultural University (Permit number: AW12049102-2).

Commercial farms were selected through personal communication. The farm screening criteria included: (1) located in North China, (2) using an advanced milking system and being able to retrieve data of dairy cows, (3) not having been vaccinated against BVDV, (4) having at least 400 milking cows, and (5) the within-herd prevalence of BVDV is estimated to be between 30% and 70% by the dairy farmer. Three dairy herds located in North China (2 from Inner Mongolia Autonomous Region and 1 from Hebei Province) were selected to investigate the within-herd seroprevalence of BVDV.

A total of 98 blood samples were collected from milking cows (between 35 to 400 DIM, reason discussed below) during July 2019 (Table 5.1). Only cows in the first and second parities were sampled because the next parities are more likely to have been infected with BVDV and cannot reflect the infection situation in the past 2 to 3 years. In the 3 sampling herds, cows in the first parity were kept in separate pens, and the cows in second parity were housed together with cows in parity 3 and higher. In each pen and for each parity, equal number of animals were sampled randomly (Table 5.1).

Table 5.1. Herd size and sample size of 3 dairy herds in North China.

Herd	Location	Herd size			Sample size				
					1st parity		2nd parity		
		1st parity	2nd parity	Total	No. pens	No. animals	No. pens	No. animals	Total
1	Inner Mongolia	622	485	1,107	6	3	9	2	36
2	Inner Mongolia	496	626	1,122	5	3	5	3	30
3	Hebei	510	373	883	4	4	8	2	32

Blood samples were collected and centrifuged. One sample in herd 1 was excluded as it was jelly-like after centrifugation. In total 97 serum samples were tested for BVDV antibodies by blocking enzyme-linked immunosorbent assay (**ELISA**) using commercial test kits PrioCHECK® BVDV Antibody ELISA (Thermo Fisher, Lelystad, The Netherlands).

The true BVDV seroprevalence was estimated based on the method described by Rogan and Gladen (1978), taking into account the sensitivity (97.89%) and specificity (99.16%) of the BVDV antibody ELISA kit. Sensitivity and specificity were provided by Thermo Fisher Scientific (2017), calculated based on the test of 1,000 field serum samples. A confidence interval (**CI**) at 95% level for the true prevalence was calculated using the method proposed by Lang and Reiczigel (2014).

The test results of the sampling and the estimated true seroprevalence of BVDV are presented in Table 5.2. The estimated true seroprevalence of BVDV was 96.3% (95% CI: 88.3% - 100.0%) in herd 1 and 100.0% (95% CI: 98.7% - 100.0%) in herd 2 and 3, respectively.

Table 5.2. The apparent and estimated true seroprevalence of BVDV in 3 dairy herds in North China.

Herd	Parity	No. tested	No. positive	No. negative	Apparent prevalence (%)	Estimated true seroprevalence (%)	
						Mean	95% CI
1	1	17	17	0	94.3	96.3	[88.3, 100.0]
	2	18	16	2			
2	1	15	15	0	100.0	100.0	[98.7, 100.0]
	2	15	15	0			
3	1	16	16	0	100.0	100.0	[98.7, 100.0]
	2	16	16	0			

The high seroprevalence found in this study is comparable to other studies conducted in North China. Ran et al. (2019) indicated that among the six administrative regions in China, the pooled prevalence of BVDV in North China is the highest (72.2%, 95% CI 59.2%–85.3%). The within-herd seroprevalence was shown to be as high as 94.1% in the study of Zhang et al. (2010) in 6 dairy herds in Beijing. In Inner Mongolia, the mean within-herd BVDV seroprevalence was reported 88.9% in 17 large-scale dairy herds (Li et al., 2014), among which the seroprevalence rates of the herds with more than 2,000 cows and herds with less than 500 cow were higher than that of the herds with 500 – 2,000 cows. Wang et al. (2014) found a within-herd seroprevalence in three dairy herds in Tianjin, Hebei, and Shanxi of 85.0%, 71.1%, and 95.2%, respectively. Nevertheless, there are also prevalence studies based in North China that show a relatively low BVDV seroprevalence within the herd. For instance, a seroprevalence of 58.4% in 6 dairy herds in Inner Mongolia (Tong et al., 2013), and a seroprevalence of 36.7% in 1 dairy herd in Beijing (Wang et al., 2014). The seroprevalence within the herd varies thus greatly in North China. This variability illustrates the necessity of within-herd BVDV seroprevalence investigations like this study, allowing farmers to understand the infection situation of their own herd and make personalized control plans on the disease. Yet, the collection and testing of more samples calculated based on the herd size and the priori estimate of the prevalence can estimate the true prevalence more accurately (Dohoo and Martin, 2003). In addition, the BVDV seroprevalence within the herd may also depend on the herd structure, breed, housing system, management decisions of the dairy farmers, sanitation regulations, pathogenicity of infecting virus strains, sampling period, the applied diagnostic methods, the presence of clinical sign in the tested animals, etc. (Houe, 1999; Deng et al., 2015; Scharnböck et al., 2018).

The seroprevalence was surprisingly high for the involved dairy farmers. They believed that their herd was (almost) free of BVDV because BVD related issues were not seen or maybe only a few cases. On the one hand, this may due to the limited dairy farmers' awareness of BVD. Up to now, there is no official national BVDV control programme in China (Deng et al., 2020). The lack of (official) information on the (economic) impact of BVDV infection may have led to a generally low level of awareness of BVD among Chinese dairy farmers. Some dairy farmers have limited knowledge of the clinical manifestations of BVDV infection (expert opinions, personal communication), and may fail to recognize BVDV circulation within the herd. In order to increase the awareness of Chinese dairy farmers on BVD, further studies estimating the (economic) impact of BVDV infection on Chinese dairy herds are necessary. On the other hand, the misjudgement of the status of BVDV infection by dairy farmers may also be attributed to the "unnoticed/stealthy" nature of a BVDV infection. BVDV may continue to circulate in dairy farms without attracting the attention of dairy farmers. In many cases TI animals only have subclinical mild symptoms or even no manifestations of clinical signs (Baker, 1995; Schweizer et al., 2021), and even PI animals can stay in the herd asymptomatic and unnoticed (Baker, 1995; Peterhans et al., 2010; Lanyon et al., 2014). Approximately half of PI animals are clinically normal and can only be detected using laboratory diagnostics (Moennig and Yarnall, 2021). In our study, the high seroprevalence in the first two parities proves the high proportion of TI animals in the tested herds, which implies that PI animals are likely to exist in the herds. Therefore, it is highly recommended to screen the whole herd to identify and cull the PI animal(s), thereby avoiding more production and economic losses.

Originally the aim of the research was to estimate milk production differences between groups of BVDV-infected and non-infected cows. As a result of the original study design, only cows between 35 to 400 DIM were randomly selected for sampling. The minimum DIM was set to be 35 days because the first 4 days of infection is the incubation period, followed by the loss of milk production lasting up to one month (Foddai et al., 2014). The maximum DIM was set to be 400 days because much less cows are available. Based on this original aim, sample size was calculated using EpiTools epidemiological calculators (Ausvet, 2019) with assumptions and inputs: (1) the difference in milk production of 0.5 kg/cow/day (Beaudeau et al., 2005), (2) the standard deviation of individual milk production of 6 kg/day (Noordhuizen et al., 2001), (3) the desired level of confidence 0.95, (4) the desired power of 0.8. The calculated sample size was 297 of each group of BVDV infected and non-infected cows (i.e., 594 samples per herd). In the sampling process, first only a pre-sampling procedure (i.e., collecting and testing approximately 5% of the sample size per herd) was developed to investigate the preliminary seroprevalence of BVDV within the herd. The idea was to continue the main sampling procedure (i.e., collecting and testing the rest of the samples size per herd) with a preliminary seroprevalence approximately between 30% and 70%. Otherwise, the BVDV infected/non-infected group will not have a sufficient number of samples. However, only pre-sampling was performed on site. The main sampling procedure was terminated because the preliminary seroprevalence of each of the 3 selected dairy herds was very high. Nevertheless, the original study design is still interesting for Chinese dairy farmers and related stakeholders to get more insights into the impact of BVDV infection on Chinese dairy herds.

Only the lactating cows of the first two parities were sampled to understand the infection situation in the herd in the past 2-3 years. A cow suffered from acute BVDV infection will develop long-term immunity (Moerman et al., 1993; Houe, 1995; Lindberg, 2003), so a cow that tested positive for BVDV antibodies at the fifth parity may have been infected during its calf period, which is not representative of the recent infection situation. The same number of samples for the first parity and the second parity were collected, and this is based on the housing structure. In the three sampled herds, cows in the first parity were kept separately from other parities. The high seroprevalence in the first parity may indicate that the cows have been infected before the start of lactation, and the seroprevalence of the second parity reflects the infection in the mixed parities. Furthermore, in the same parity, the same number of samples were collected from each pen. In this way, the BVDV infection situation in such large intensive dairy herds can be obtained more comprehensively.

The results of this study provide dairy farmers and their advisors with insight into the circulation of BVDV within the dairy herds, even though there are no clear signs of BVDV infection. The high within-herd seroprevalence found in this study also calls on dairy farmers to increase the awareness of BVDV prevention and control to reduce production and economic losses. To prevent BVDV from continuing to circulate in the herd, it is imperative to screen the whole herd, and cull the identified PI animals. Further, Chinese dairy herds could learn from existing BVDV control programmes in other countries to formulate and implement control measures adapted to their own (especially large-scale herds), so as to improve the (economic) performance of the herd.

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6

CHAPTER 6

Simulating the Production and Economic Impact of Bovine Viral Diarrhoea Virus Infection in Chinese Dairy Herds

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Abstract

Bovine viral diarrhoea virus (**BVDV**) infection is negatively affecting dairy cattle and results in substantial economic losses. To date, the effects of BVDV introduction in large-scale intensive Chinese dairy herds have not been quantified. The objective of this study was to simulate the effects of BVDV introduction on large-scale intensive dairy herds (300 cows) in China and estimate the production and economic effects of BVDV introduction. An individual cow-based dynamic, stochastic bio-economic simulation model was developed in daily time steps. The model simulated the average production and economic losses over 3 years after a persistently infected (**PI**) heifer entered into a fully susceptible herd. Production effects due to BVDV introduction consisted of a reduced milk production, reduced feed intake, increased probability of abortion, and a mortality probability of the PI animal. Subsequently, associated economic effects were calculated. Three scenarios were modelled: 1 scenario without BVDV introduction and 2 scenarios with BVDV introduction. In the literature-based scenario, the input values for the BVDV infection dynamics were retrieved from literature, while in the expertise-based scenario, the input values were calibrated based on expert opinion to mimic the situation in large Chinese dairy herds observed in the field. The effects of BVDV introduction were calculated by comparing the model outputs of the scenarios with and without BVDV introduction. The mean annual economic losses in the 3 years after BVDV introduction were 52, 98, 54 €/cow/year in the literature-based scenario, and 255, 89, 45 €/cow/year in the expertise-based scenario, respectively. Our estimates provide evidence that BVDV introduction causes significant losses in large-scale intensive dairy herds in China. Although we did lack accurate data on BVDV infection and herd performance for large Chinese dairy herds, we did develop a simulation model that is as accurate as possible, and thus can provide decision makers with more complete information on losses caused by BVDV infection.

6.1 Introduction

Bovine viral diarrhoea (**BVD**) is a global endemic disease in dairy cattle, negatively affecting the health, welfare, production, and profitability (Richter et al., 2017; Yarnall and Thrusfield, 2017). Infection with bovine viral diarrhoea virus (**BVDV**) may result in clinical signs like fever, diarrhoea, leukopenia, infertility, abortion, stillbirth, reduced milk yields, etc. (Baker, 1995). BVDV transmission occurs vertically and horizontally. Vertical transmission of BVDV occurs in a dam in the first trimester of pregnancy, leading to the birth of a persistently infected (**PI**) calf. The PI calf excretes large amounts of virus throughout its whole life. Horizontally, BVDV is transmitted from PI and transient infected (**TI**) animals to susceptible animals. Compared to PI animals, TI animals shed much less virus for a short period before developing immunity (Houe, 1999). Ongoing BVDV infection is often associated with inapparent or mild symptoms. (Moerman et al., 1994; Fourichon et al., 2005; Bachofen et al., 2010). Due to the inconspicuous clinical appearance of BVD, dairy farmers, especially those in countries without BVDV control programmes (e.g., China), are often unaware of an ongoing BVDV infection and the associated production and economic losses.

Insight in the losses associated with BVD allows dairy farmers and policymakers to make more informed decisions regarding prevention and mitigation of the disease. We know that BVD results in reduced milk production, prolonged calving interval, and increased abortion rate in dairy herds (Houe et al., 1993a; Berends et al., 2008; Burgstaller et al., 2016b; Tschopp et al., 2017). A wide range of economic losses due to BVD were reported, ranging from 0 to 654 euros per cow per year (Yarnall and Thrusfield, 2017). The vast majority of the estimates of the losses of BVD on dairy herds come from European and North American countries, particularly those with compulsory or voluntary BVDV control programmes. Very little attention has been paid to the production and economic effects of BVDV introduction in countries without any national/regional BVDV intervention programmes (Richter et al., 2017; Scharnböck et al., 2018) as well as for farm systems with large herds (Smith et al., 2009; Foddai et al., 2014).

Simulation modelling has shown to be very useful in supporting animal health decisions. However, simulation models developed to estimate the effects of BVDV introduction were mainly targeted at European farming systems (i.e., herd size of approximately 100 cows, grazing in summer (Pasman et al., 1994; Sørensen et al., 1995; Gunn et al., 2005; Knific and Zgajnar, 2014). These models are not applicable for large-scale intensive dairy herds housed indoors year-round. China has such large-scale intensive dairy herds, and for these Chinese circumstances no simulation models exist and consequently there is a limited understanding of how BVDV introduction affects these dairy farming systems.

The objective of this study was, therefore, to simulate the effects of BVDV introduction on large-scale intensive dairy herds in China and estimate the production and economic effects of BVDV introduction.

6.2 Material and methods

6.2.1 Model overview

The bio-economic simulation model used in this study is an adaptation and extension of the simulation model described by Edwardes et al. (2021), which is an individual cow-based dynamic, stochastic model simulating a dairy herd in daily time steps. The model was developed in R (version 4.1.0, “Camp Pontanezen”, R Core Team, 2021). The model was adapted to a typical large-scale Chinese dairy herd with 300 milking cows, and the infection dynamics of BVDV as well as the associated production and economic effects were added. The herd layout and the herd characteristics assumed in this study were discussed with Chinese experts. The simulation model consists of 4 modules, including production and herd dynamics (milk yield, reproductive cycle and culling), BVDV infection dynamics, production effects due to BVD and associated economic calculations. The cow simulation model specifications are described below, with a specific emphasis on the new components (BVDV infection dynamics and effects of BVDV infection) and adaptations.

6.2.2 Simulation model

Herd layout. The model was designed to fit the layout of a closed herd with a constant number of milking cows, housed all year round. The 300 milking cows were divided over 3 pens (2 lactating cow pens and 1 dry cow pen, Figure 6.1). Lactating cows are divided over the 2 lactating cow pens based on their days in milk (**DIM**). Cows with DIM 0-180 are in one pen, and cows with DIM 181 to dry period are in the other lactating cow pen. The model did not simulate young stock.

Production and herd dynamics. The production and herd dynamics module, simulating milk yield, feed intake, body weight, reproductive cycle and culling was equal as described by Edwardes et al. (2021). Input values were adapted to the Chinese situation, being the number of milking cows (300 cows), the lactation curve, fat-protein corrected milk (**FPCM**), and the maximum parity number (5 parities). To fit lactation curves the Wilmink (1987) function was adapted to Chinese input values (Table 6.S1), resulting in a mean milk production level of 28.5 kg/cow/day (5^{th}; 95^{th} percentiles: 17.9; 38.7 kg/cow/day). The fat and protein content of each parity were also adapted to Chinese input values (Table 6.S1) for the calculation of FPCM. Parameters related to culling were also calibrated to the conditions of Chinese dairy herds, based on expert’s estimates. The overall culling rate was approximately 30%. The distributions for the 1st, 2nd, 3rd, 4th, and 5th parity in the herds is 40%, 20%, 15%, 15%, and 10%, respectively.

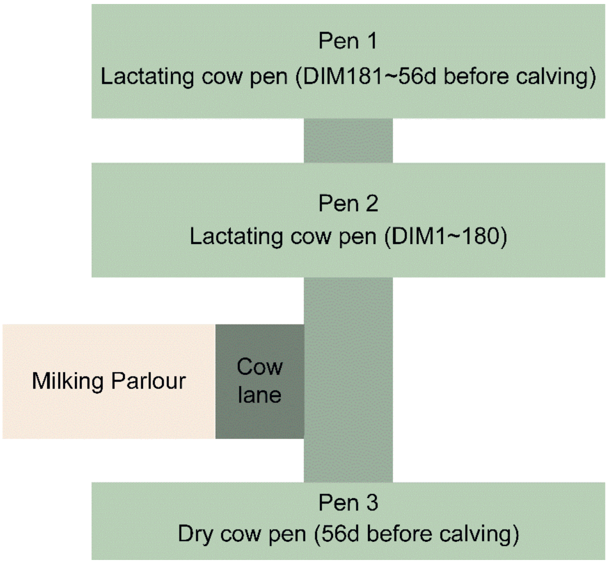

Figure 6.1. Layout of the simulated dairy herd with 300 milking cows

BVDV infection dynamics. A compartmental model (based on the Susceptible, Infected, Recovered (SIR) concept) was used to simulate the dynamics of BVDV after its introduction. The model consists of 3 compartments: susceptible cows (S), infected cows (TI or PI), and recovered cows (R). After infection, susceptible cows become TI cows for a short period and then recovered, and are assumed to develop lifelong immunity (Baker, 1990), whereas PI cows remain viraemic until death. At the start of each simulation, the herd was assumed to be fully susceptible to BVDV. A BVDV infection is simulated by a replacement heifer entering the herd that is a PI cow. It was assumed that no other PI cows enter the herd before the end of the simulation, and that all other replacement heifers are susceptible to BVDV. Moreover, it was assumed that there are no interventions towards BVD.

Transmission was assumed to occur horizontally from infected cows to susceptible cows both within and between pens, based on the layout of the studied herd (Figure 6.1). Transmission within the pen was assumed to be the most efficient, considering the high probability of direct and indirect contact of cows within the pen (Niskanen and Lindberg, 2003). Transmission between cows in different pens was assumed to be less efficient. Direct transmission between cows in two pens may occur around milking, for instance by nose-to-nose contact through barriers while waiting for milking alleyways to the milking parlour.

Indirect transmission may occur through a contaminated environment, because in practice the alleyways are not cleaned after the passage of cows in the first pen.

To simulate the infection dynamics, the probability of a new infection was calculated on a daily basis, based on the approach of Foddai et al. (2014) and is defined below (Eq.[6.1]):

$$P_j = 1 - \left[\begin{array}{c} \left(1 - \beta_{TIin} \times \frac{I_{TIj}}{N_j}\right) \times \left(1 - \beta_{PIin} \times \frac{I_{PIj}}{N_j}\right) \\ \times \left(1 - \beta_{TIbtw} \times \frac{I_{TIk}}{N_j}\right) \times \left(1 - \beta_{PIbtw} \times \frac{I_{PIk}}{N_j}\right) \end{array} \right] \qquad [6.1]$$

where P_j is the daily probability of a new infection in pen j; β_{TIin} and β_{PIin} are the daily effective contact rates[5] between pairs of cows within a pen with a TI/PI cow; β_{TIbtw} and β_{PIbtw} are the daily effective contact rates between pairs of cows between pens with a TI/PI cow; I_{TIj} , I_{PIj}, I_{TIk}, I_{PIk} are the number of TI/PI cows within pen j or k on the current day.

For the infection dynamics we simulated 2 scenarios, (i) a literature-based scenario and (ii) an expertise-based scenario. In the literature-based scenario, the aim was to resemble the infection dynamics using input values for infection dynamics as we could retrieve it from existing scientific literature. In the expertise-based scenario, the aim was to resemble the infection dynamics in such a way that they mimicked the situation in large Chinese dairy herds as was observed by Yue et al. (submitted). Therefore, input values for infection dynamics in the expertise-based scenario were calibrated based on expert opinion towards the following two infection outcomes: (i) when a PI cow stayed in the herd for more than a year, more than 90% of the cows in the herd were infected; (ii) when the PI cow left the herd, the transient infection continued, which has been reported to be up to 6 years in field studies (Moerman et al., 1993; Moen et al., 2005). Besides, the daily probability of recovery of TI animals was assumed to be the reciprocal of duration of transient infection (14 and 21 days in the 2 scenarios, respectively). The parameters used for infection dynamics are presented in Table 6.1.

[5] The effective contact rate is the total contact rate times the risk of infection, given contact with an infected animal.

Table 6.1. Parameters for the infection dynamics of bovine viral diarrhoea virus (BVDV)

Parameter	Description	Literature-based scenario		Expertise-based scenario
		Value	Source	Value
β_{PIin}	Daily effective contact rates between pairs of cows within a pen with a PI[1] cow	0.5	Viet et al. (2004); Ezanno et al. (2007); Foddai et al. (2014); Qi et al. (2019)	0.5
β_{PIbtw}	Daily effective contact rates from cows in another pen to this pen with a PI cow located in another pen	0.25	Expert opinion	0.25
β_{TIin}	Daily effective contact rates between pairs of cows within a pen with a TI[2] cow	0.03	Viet et al. (2004); Ezanno et al. (2007); Foddai et al. (2014); Qi et al. (2019)	0.3
β_{TIbtw}	Daily effective contact rates from cows in another pen to this pen with a TI cow located in another pen	0	Foddai et al. (2014)	0.15
γ	Daily probability of recovery	1/14	Baker, (1990); Mars et al. (1999)	1/21

[1] PI = persistent infection
[2] TI = transient infection

Production effects due to BVD. The effects of BVDV infection consisted of a reduced milk production, reduced feed intake, increased probability of abortion, and a mortality probability of the PI animal (Table 6.2, Table 6.3).

The reduction in milk yield was assumed to happen in both TI and PI cows. For TI cows, it was assumed that they develop either clinical or subclinical signs due to BVDV infection. The probability of developing clinical or subclinical signs is presented in Table 6.2. Cows with clinical and subclinical BVD signs were assumed to have different proportions of decreased milk production during BVDV infection (Table 6.2). During infection, cows with clinical and subclinical signs experience different proportions of reduced milk production (Table 6.2). After recovery, TI cows with clinical signs were assumed to have long-term milk production losses until the end of the lactation in which the infection happened (Table 6.2). The long-term loss assumption was based on the recent evidence of chronic milk loss in recovered TI animals (Schmitt–van de Leemput et al., 2020) and expert opinion. For the PI cow it was assumed that it had a lower milk production over its lifetime (Pasman et al., 1994).

Feed intake reduction, expressed in VEM[6] (feed unit for lactation, 1VEM=1.65 kcal of NEL[7]), was calculated as a function of the reduced daily FPCM. The calculation procedure was described in detail by Edwardes et al. (2021).

Assumptions about the BVDV induced abortion were based upon literature and expert opinion (Table 6.3). It was assumed that BVDV infection leads to an increased probability of abortion in dams, and this probability varies with stage of pregnancy. Subsequently, the management following abortion was modelled, dependent on the latest date of conception (**LDC**). The LDC is based on the relative production level of a cow and if a cow does not conceive before LDC, inseminations will end and the cow will be culled once its daily milk yield falls below a fixed yield threshold (i.e., 15 kg/cow/day). When abortion occurs in the 1st half of pregnancy (i.e., from conception to 144 days pregnancy), it was assumed that a farmer will restart heat detection and artificial insemination until LDC. If a cow aborts during the 2nd half of pregnancy (i.e., from 145 days pregnancy until calving), it was assumed that there is an 80% probability that the cow will be culled at the end of this lactation, otherwise it will be detected in heat until LDC.

[6] VEM is the feed requirements estimated as energy requirements for lactation, as defined by Van Es (1978).
[7] NEL is the net energy for lactation (Vermorel and Coulon, 1998).

Table 6.2. Parameters used to simulate the effects of bovine viral diarrhoea virus (BVDV) infection on milk yield and mortality in milking cows on a daily basis, applicable to both the literature- and expertise-based scenario

Parameter	Value (%)	Source
Milk yield reduction		
Probability of TI[1] cows with clinical sign	30	Expert opinion
Probability of TI cows with subclinical sign	70	Expert opinion
Proportion of milk yield reduction in TI cows with clinical sign during BVDV infection	20	Hasler et al. (2012)
Proportion of milk yield reduction in TI cows with clinical sign from recovery to the end of this lactation	2	Expert opinion
Proportion of milk yield reduction in TI cows with subclinical sign during BVDV infection	5	Expert opinion
Proportion of milk yield reduction in PI[2] cows during lifetime	10	Pasman et al. (1994)
Mortality		
Probability of death of the PI animal	0.14	Duffell and Harkness (1985); Viet et al. (2004); Foddai et al. (2014)

[1] TI = transient infection
[2] PI = persistent infection

Table 6.3. The assumed probability of abortion due to bovine viral diarrhoea virus (BVDV) infection and the corresponding management practices after the abortion, applicable to both the literature- and expertise-based scenario

	Pregnancy stages	Probability of abortion due to BVDV infection	Management practices after the abortion	Source
First half of pregnancy	Conception ~ 214d pre-calving	0.1	Restart heat detection	Viet et al. (2004); Foddai et al. (2014); Gethmann et al. (2019) Expert opinion
	215d ~ 144d pre-calving	0.15		
Second half of pregnancy	145d ~ 164d pre-calving	0.15	80% probability to be culled at the end of this lactation, otherwise restart heat detection	
	165d ~ 104d pre-calving	0.2		
	105d pre-calving ~ calving	0.05		

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It was assumed that only PI cows could die due to BVDV infection, and the mortality in TI cows was assumed not to be affected by BVDV infection. A daily mortality probability for the PI cow was used, adapted from literature describing an annual mortality rate of 50% in PI animals (Duffell and Harkness, 1985; Viet et al., 2004; Foddai et al., 2014)

Economic effects due to BVD. The modelled economic effects of BVDV introduction includes both direct and indirect effects. The direct economic effects were calculated based on the milk production losses due to BVDV infection and the differences in feed costs, culling costs, and insemination costs between the scenarios with and without BVDV introduction. Indirect economic effects occur because of changes in the herd composition (higher parity cows have a higher milk yield) and changes in calving interval (a longer calving interval leads to lower milk production per cow per year). The indirection economic effects were calculated by comparing the annual total milk returns between the scenarios with and without BVDV introduction, excluding the direct milk production economic losses. The precise calculation procedure for each type of loss was described in Edwardes et al. (2021). Economic parameters were adapted to the Chinese situation and were based on expertise (Table 6.4).

Table 6.4. Parameters used to simulate the economic effects, applicable to both the literature- and expertise-based scenario

Parameter	Value	Description	Source
Milk price	0.58 (€/kg)[1]	Average monthly milk price from Sept. 2020 to Sept. 2021	China National Dairy Industry and Technology system (2021)
Supplements costs	0.58 (€/1,000 VEM[2])	Cost of supplements	Expert opinion
Insemination costs	12.33 (€/insemination)	Cost per insemination	Expert opinion
Culling			
Nr. lactations	5	Maximum number of lactations	Expert opinion
Rearing costs	2,939 (€/heifer)	Rearing costs per replacement heifer	Expert opinion
Slaughter price	3.56, 3.84, 4.12 (€/kg)	Three slaughtered cow prices for the random selection of the model	Expert opinion
Disposal costs	41.10 (€/kg)	Disposal cost of a culled cow	Expert opinion

[1] 1 EUR = 7.3 RMB (currency in China).
[2] 1 VEM = 1.65 kcal of NEL, VEM is the feed requirements estimated as energy requirements for lactation, as defined by Van Es (1978), NEL is the net energy for lactation (Vermorel and Coulon, 1998).

6.2.3 Model validation, outputs and simulation

Calibrated parameters were validated internally and externally. The procedures for internal validation included tracking and tracing of the daily outputs of individual cows, checking the model logic during live simulations in the debug mode and assessing face validity. For the external validation, the input-output data were validated through 3 rounds of discussions with experts and comparisons with existing research findings.

To estimate the effects of BVDV introduction, 3 scenarios were modelled: 2 scenarios with BVDV introduction (i.e., literature-based scenario and expertise-based scenario) and 1 scenario without BVDV introduction. That way the effects of BVDV introduction can be calculated by comparing the model outputs of the scenarios with and without BVDV introduction. Model outputs were generated for the purposes of model calibration, checking convergence, determining the burn-in period (i.e., the time to achieve a stable output that matched the demographics of the studied herd), and, ultimately, estimating the effects of BVDV introduction. Herd demographics, infection dynamics, and production and economic effects comprised the model outputs.

Herd demographics. Herd demographics, derived from the simulation results, include the annual milk production, annual culling rate and the parity distribution.

Infection dynamics. Infection dynamics output include the counts of susceptible, TI, PI, and recovered cows over time. The daily counts of these compartments in the infection dynamics module allow for outputs regarding the duration of the presence of the PI cow, the duration of the presence of TI cows (with and without the presence of the PI cow), the duration of BVDV circulation and the peak of BVDV prevalence.

Production effects. The herd performance of the 2 BVDV scenarios and the scenario without BVDV introduction included annual milk yield reduction, abortion rate, culling rate, calving interval and number of inseminations per lactation.

Economic effects. The annual economic losses due to BVDV introduction were calculated by comparing the annual net partial economic results of the scenarios with BVDV introduction with the scenario without BVDV introduction. The annual net partial economic result was calculated as the annual total milk returns minus annual economic outflow. The annual total milk returns are the milk price times the annual total milk yield of the herd if there is no introduction of BVDV. Annual economic outflow is the sum of annual direct milk production losses, annual costs of feed, culling, and insemination for the studied herd.

Model convergence. Convergence was checked by running 500 iterations for 10 years. Visual appraisal of the variance in annual milk production, total numbers of TI cows per year, and annual culling rate showed that the results approached an equilibrium at 300 iterations. As a consequence and to be at the safe side, we chose to run 500 iterations for each simulation. The burn-in period was determined to be 8 years because the output of annual parity distribution and annual culling rate stabilized in year 8. The results presented in this paper were derived from the results from year 8 using 500 iterations.

6.3 Results

6.3.1 Infection dynamics

The percentage of susceptible cows, TI cows, PI cows and recovered cows over 3 years after the introduction of a PI heifer in the 2 scenarios with BVDV introduction is presented in Figure 6.2. In the literature-based scenario (Figure 6.2a), the median percentage of recovered cows (cows that experienced transient BVDV infection) peaked at 52% at day 479 after the introduction of the PI heifer. While in the expertise-based scenario, the median percentage of recovered cows reached the peak at 93% at day 106, followed by a peak of 92% at day 295 (Figure 6.2b). In 50% of the simulations in both scenarios, the PI cow left the herd around 446 days (day 447 in the literature-based scenario, day 445 in the expertise-based scenario). After the PI cow left the herd, the transient infection continued for an additional 29 and 129 days as the median in the literature- and expertise-based scenarios, respectively. In 95% of the simulations, transient infection continued until the end of the study period in both scenarios.

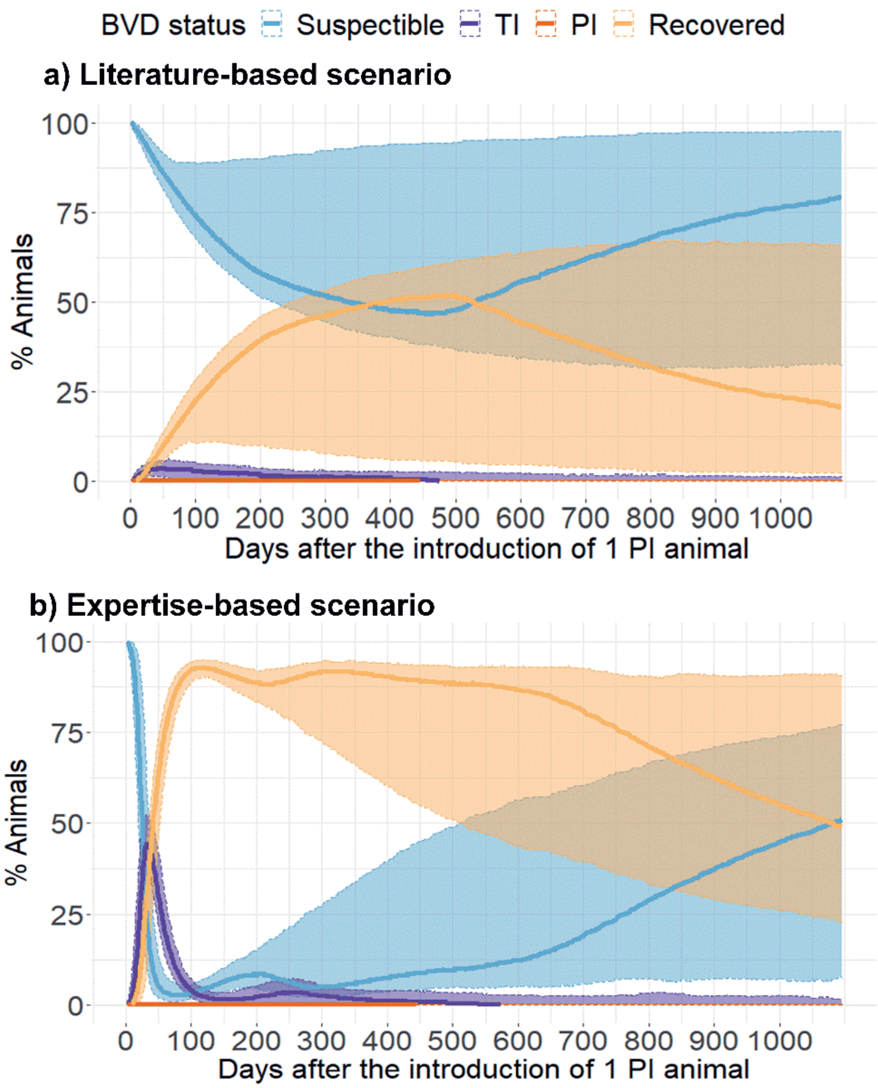

Figure 6.2. Median (with 5th and 95th) percentiles of cows in different infection status of bovine viral diarrhoea virus (BVDV) in a fully susceptible Chinese dairy herd with 300 milking cows after the introduction of 1 persistently infected (PI) heifer.

6.3.2 Production effects

The herd performance of the studied herd is presented in Table 6.5 for the scenario without BVDV introduction, and 2 scenarios with BVDV introduction (literature-based scenario and expertise-based scenarios). In the 2 scenarios with BVDV introduction, the mean milk yield reduction decreased over years, and the studied herd experienced a higher milk production loss (33,548, 8,309, 3,226 kg/herd/year in the 3 years after BVDV introduction, respectively) in the expertise-based scenario compared to the literature-based scenario (11,845, 5,263, 2,926 kg/herd/year in the 3 years after BVDV introduction, respectively). The mean abortion rate induced by BVDV introduction was 39% in the first year after BVDV introduction in the expertise-based scenarios, which was 22% higher than in the literature-based scenarios. Compared to the mean culling rate in the scenario without BVDV introduction (34%), it was 6% and 19% higher in the first year after BVDV introduction in the literature- and expertise-based scenarios, respectively. The mean calving interval did not show a large difference between scenarios, as well as the mean number of inseminations.

Table 6.5. Mean (with 5th and 95th percentiles) simulation results of the production effects of an introduction of a persistently infected (PI) heifer into a large-scale intensive Chinese dairy herd with 300 cows in the scenario without bovine viral diarrhoea (BVD) virus (BVDV) introduction, and scenarios with BVDV introduction (literature-based scenario and expertise-based scenarios). Values are rounded to the nearest whole number

Output	No BVDV introduction			BVDV introduction					
				Literature-based scenario			Expertise-based scenario		
	Year 1[1]	Year 2	Year 3	Year 1[2]	Year 2	Year 3	Year 1[2]	Year 2	Year 3
Milk yield reduction (kg/herd/year)	-	-	-	11,845 (2,627; 16,026)	5,263 (78; 11,512)	2,926 (15; 9,901)	33,548 (27,907; 38,324)	8,309 (707; 14,059)	3,226 (21; 12,791)
BVD induced abortion (%)	-	-	-	17 (4; 24)	9 (1; 15)	7 (1; 13)	39 (34; 45)	4 (0; 7)	5 (1; 9)
Culling rate (%)	34 (29; 38)	33 (29; 38)	33 (29; 38)	40 (35; 45)	38 (31; 44)	34 (29; 41)	53 (47; 59)	33 (28; 38)	33 (29; 39)
Calving interval (days)	401 (365; 465)	402 (365; 465)	402 (365; 465)	402 (365; 465)	404 (365; 468)	401 (365; 465)	405 (365; 468)	404 (365; 469)	401 (365; 463)
Number of inseminations	1.1 (1.0; 1.2)	1.2 (1.1; 1.2)	1.2 (1.1; 1.2)	1.2 (1.1; 1.3)	1.2 (1.1; 1.3)	1.2 (1.1; 1.3)	1.2 (1.2; 1.3)	1.2 (1.0; 1.3)	1.2 (1.1; 1.3)

[1] Same years as the scenarios with BVDV introduction
[2] Years after an introduction of a PI heifer into the dairy herd

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6.3.3 Economic effects

The annual economic effects of BVDV introduction are presented in Table 6.6. In the literature-based scenario, at the herd level, the mean annual economic losses in the 3 years after BVDV introduction were 16, 30, 16 k€/herd/year in the literature-based scenario, respectively. At the cow-level, the mean economic losses in the 3 years after BVDV introduction were 52, 98, and 54 €/cow/year in the literature-based scenario, respectively. Interestingly, the mean annual culling costs in the literature-based scenario were higher in the second year after BVDV introduction, compared to the previous year.

In the expertise-based scenario the mean annual economic losses decreased over years, and were 77, 27, 14 k€/herd/year in the 3 years after BVDV introduction, respectively. Losses at the cow level were averaged over the herd size of 300 milking cows. Annually, the cow-level mean economic losses in the 3 years after BVDV introduction were 255, 89, 45 €/cow/year in the expertise-based scenarios, respectively.

Table 6.6. Mean (with 5th and 95th percentiles) annual economic effects of an introduction of a persistently infected (PI) heifer into a large-scale intensive Chinese dairy herd with 300 cows in the scenario without bovine viral diarrhoea (BVD) virus (BVDV) introduction, and scenarios with BVDV introduction (literature-based scenario and expertise-based scenarios). Values are rounded to the nearest whole number

Output	No BVDV introduction			BVDV introduction					
				Literature-based scenario			Expertise-based scenario		
	Year 1[1]	Year 2	Year 3	Year 1[2]	Year 2	Year 3	Year 1[2]	Year 2	Year 3
Annual milk returns[3] (k€/herd)	1,619 (1,602; 1,636)	1,619 (1,602; 1,635)	1,618 (1,601; 1,635)	1,624 (1,608; 1,641)	1,610 (1,593; 1,628)	1,615 (1,596; 1,633)	1,604 (1,586; 1,621)	1,619 (1,601; 1,637)	1,622 (1,605; 1,641)
Direct milk production losses (k€/herd)	-	-	-	7 (2; 9)	3 (0; 7)	1 (0; 5)	19 (16; 22)	5 (0; 8)	2 (0; 7)
Feed costs (k€/herd)	631 (628; 633)	631 (628; 633)	630 (628; 633)	628 (625; 631)	628 (624; 632)	630 (627; 633)	619 (617; 622)	631 (628; 633)	632 (629; 635)
Culling costs (k€/herd)	71 (59; 83)	69 (56; 83)	69 (57; 82)	87 (71; 106)	90 (67; 111)	82 (63; 105)	124 (104; 150)	91 (74; 109)	84 (70; 99)
Insemination costs (k€/herd)	4 (4; 5)	4 (4; 5)	4 (4; 5)	5 (4; 5)	4 (4; 5)	4 (4; 5)	5 (4; 5)	5 (4; 5)	5 (4; 5)
Net partial economic result[4] (k€/herd)	913 (896; 932)	914 (896; 935)	914 (894; 931)	897 (871; 919)	885 (854; 919)	897 (864; 924)	836 (803, 861)	888 (864; 914)	900 (876; 924)
Economic losses due to BVD[5] (k€/herd)	-	-	-	16 (12; 25)	30 (15;42)	16 (7; 30)	77 (71; 94)	27 (21; 32)	14 (7; 18)
Economic losses due to BVD[6] (€/cow)	-	-	-	52 (41; 82)	98 (51; 140)	54 (24; 100)	255 (236; 312)	89 (68; 106)	45 (22; 60)

[1] Same years as the scenarios with BVDV introduction.
[2] Years after an introduction of a PI heifer into the dairy herd.
[3] Total milk returns for the studied herd, without subtracting the direct milk production losses due to BVD.
[4] Net partial economic result = total milk returns – direct milk production losses – culling costs – feed costs – insemination costs.
[5] Economic losses due to BVDV introduction per herd = net partial economic results of the scenario without BVDV introduction - net partial economic results of the scenario with BVDV introduction.
[6] Economic losses due to BVDV introduction per cow = economic losses due to BVDV introduction per herd/300

6.4 Discussion

To our knowledge this is the first study attempting to quantify the economic impact of BVDV for large-scale intensive Chinese dairy herds. This study showed that average economic losses over 3 years were between 52 and 98 €/cow/year in the literature-based scenario, and between 45 and 255 €/cow/year in the expertise-based scenario. Our estimates provide evidence that BVDV introduction causes significant losses in large-scale intensive dairy herds in China. These new insights are of interest to Chinese policy makers to take action against BVD.

The simulated economic losses associated with BVDV infection in this study are comparable to previous studies in countries in Europe and North America. Yarnall and Thrusfield (2017) reviewed the economic impact of BVD and reported economic losses ranging between 0 to 654 €/cow/year, with an average of 55 €/cow/year. Different outcomes among studies can be caused by different assumptions. For instance, we simulated the losses in a fully susceptible herd where cows will suffer more losses. Likewise, Richter et al. (2017) presented an average loss for a naïve cow of 178€/cow/year. In our results, especially culling resulted in economic losses. This is comparable to previous studies (Chi et al., 2002; Compton, 2006). For instance, we found that culling contributed 69% to the total losses in the first year after BVDV introduction in the expertise-based scenario, while Chi et al (2002) reported that premature culling accounted for 43% of the direct losses due to BVD, which accounted for the largest proportion. Compared to the culling costs, losses due to reduced milk production were relatively low in our results, contributing 7-44% to the total losses. This range is consistent with previous studies reporting 3-44% of the losses associated with BVD came from milk production reduction (Compton, 2006; Reichel et al., 2008; Hasler et al., 2012). Nevertheless, other studies demonstrated high direct losses due to other types of effects such as mortality of adult animals (Ózsvári et al., 2001; Hasler et al., 2012b; Szabára and Ózsvári, 2013), abortion (Dufour et al., 1999; Reichel et al., 2008), and reproductive losses (Valle et al., 2005). Notably, the classification of losses varies across studies, which partly explains the different contributions of different types of effects to the total losses. Additionally, in the literature-based scenario, the mean annual culling costs in the second year after BVDV introduction were higher compared to the previous year, this is largely attributable to additional milk returns and reduced direct milk production losses.

The overall presented economic effects for the simulated herd may have been under- or over-estimated. Underestimation may be due to the fact that not all effects of BVDV introduction were included in our study. BVDV infection has been found associated with higher incidence of clinical mastitis, poorer milk quality, and increased susceptibility to secondary infections, etc. (Potgieter, 1988; Waage, 2000). These effects were discarded in our model due to a lack of "solid scientific evidence" (Chi et al., 2002). In addition, treatment costs were not included which may results in an underestimation of the economic effects. We assumed no treatment based on field experience in China, where due to the subclinical nature for most BVDV infections no treatment is carried out. Finally, underestimation may have occurred because we modelled only 1 PI cow, while in practice there are often more PI cows present (Liu et al., 2010; Zhiyong, 2014; Deng et al., 2015; Ran et al., 2019). PI animals are the "workhorses" for BVDV transmission and suffer much more severe losses, while in our model we only assumed 1 PI animal with the associated losses. On the other hand, we may also have overestimated the economic effects of BVD, possibly because we did not set an upper limit on the culling rate and maintained a set of strict culling rules, resulting in a potential overestimation of the culling costs. Culling rules, in practice, may be more flexible. This means that when farmers realize that the culling rate is too high, they may choose to keep raising lower-performing cows (such as those who aborted and did not conceive before LDC) and suffer losses from reproduction loss instead of culling costs. In such a situation, we would see longer calving intervals in the results, which in the current results was almost indistinguishable between the scenarios with and without BVDV introduction.

Two scenarios were developed to simulate infection dynamics in the studied herd with the purpose of providing decision makers with more comprehensive information. In the parameterization process, we first selected the most commonly known values for the transmission parameters (the literature-based scenario). Considering the observed high antibody prevalence in a field study (Yue et al., submitted), we decided however that a second scenarios was necessary. In the expertise-based scenario the infection dynamics were calibrated towards the observed high prevalence). Notably, in the expertise-based scenario, infections in the first year occurred very quickly, potentially too quickly. In modelling the transmission, we made therefore some assumptions, for instance in the distribution of contacts between cows. The social hierarchy that exists in a dairy herd may affect contacts between animals and, therefore, dynamics. The age of individuals is positively correlated with their social ranks (O'Connell et al., 1989; Sołtysiak and Nogalski, 2010). The introduced PI heifer, as one of the youngest cows in the herd, is most likely in a lower social rank and subordinate to other cows, making room for higher-ranking cows and avoiding conflicts (Sołtysiak and Nogalski, 2010). In this way, even though the introduced PI cow shed a large amount of virus, less direct contact with other cows may restrict the transmission in an early stage after the PI heifer entered the herd. Additionally, there are many risk factors associated with BVDV introduction and transmission in large-scale intensive dairy herd, which contribute to more complex infection dynamics. However, transmission of BVDV in relation to risk factors and contact structure of cows has not been studied in enough detail to be modelled in a simulation model such as ours.

The simulated between-pen transmission is different from, and more efficient than, between-group transmission defined in other studies. Between-group transmission modelled in other studies occurred between animal groups such as calves, heifers, and dairy cows (Viet et al., 2004; Smith et al., 2009; Foddai et al., 2014). Whereas in our study, between-pen transmission occurred between lactating cows from the same animal group in different pens, which had more opportunities for daily contact. The between-pen contact was largely determined by herd characteristics including location, herd size, herd structure, land use and management practices (e.g., grazing) (Lindberg and Alenius, 1999; Ståhl et al., 2002; Viet et al., 2004; Stott et al., 2010; Viet and Krebs, 2010). Directly, cows between pens could have nose-to-nose contact twice a day through the barrier in the cow lane before milking. Indirectly, between-pen transmission can happen through contaminated clothing, environment (e.g., discharges from infected cows in the alleyway) and equipment, or through short-range (less than 40m) airborne transmission (Mars et al., 1999; Bitsch et al., 2000; Niskanen and Lindberg, 2003). These routes of transmission are specifically based on the characteristics of the studied herd and have not been included in other studies on large-scale herds (Smith et al., 2010; Nickell et al., 2011; Foddai et al., 2014), or smaller herds (Innocent et al., 1997; Cherry et al., 1998; Stott et al., 2003; Viet et al., 2004). This confirms the necessity of modelling the infection dynamics and associated economic consequence based on the herd characteristics of specific farming system.

The estimates from this simulation model may also be applicable to other countries with comparable herd characteristics (e.g., approximately 300 milking cows, housed indoors all year round, cows from different pens passing through the same cow lane, with no treatment and control measures for BVD, etc.). The different initial within-herd prevalence can be achieved by modifying the proportion/number of susceptible animals prior to the introduction of PI/TI animal(s). A further application of this novel BVDV simulation model is on decision support. By developing a module of BVDV control measures and combining these with the current infection dynamics section, the efficacy of different control strategies can be compared. While with the developed net partial economic results calculation section, the associated economic consequence can be calculated.

As a simplified representation of a real-world situation, the simulation model developed in the current study has certain strengths and limitations. The main strength is the flexibility of the simulation model. With great flexibility, the conditions of the simulated herd can be changed, corresponding results can be investigated, and the study period can be adjusted. The main limitation is the lack of precise data on BVD status and herd performance, which may lead to lack of precision in the results of the simulation model. Better data on infection (antibody prevalence, antigen prevalence, individual infection status) and performance (milk yield, milk quality, reproduction, incidence of other diseases, culling, etc.) could help improve the precision of validation process in the simulation model.

Although we did lack accurate data on BVDV infection and herd performance for large Chinese dairy herds, by using existing literature, expert opinion, and field experience we did develop a simulation model that is as accurate as possible. Previous studies have shown that the value of parameters also affects the estimates from simulation model to varying degrees. In addition to the presented different infection dynamics driven by $\beta_{TIin,} \beta_{TIbtw}, \gamma$ in the two scenarios (Table 6.1, Figure 6.2), other key parameters include mortality of PI animals, initial herd immunity, the abortion risk following foetal infection, culling rate, etc. (Houe et al., 1993b; Houe, 1999; Ezanno et al., 2007). It was assumed that all cows at the beginning of the simulation and all heifers that entered the herd during the simulation were susceptible to BVDV. This has been reported to exist in China (unpublished initial data from personal communication), but it is rare. Future studies could set different initial prevalence and assume that (part of) the heifers are already immune to BVDV based on the actual situation. Additionally, in this study, we focused on the losses associated with BVDV introduction on the milking cow herd and did not include other animal groups such as calves, heifers, etc. Although these animal groups in the studied herds are often separated from the milking cow herd making airborne transmission nearly impossible, it is still possible that BVDV could be indirectly transmitted (e.g., through farm managers, veterinarians, vehicles, etc.). Future studies are required to establish other animal groups, including vertical transmission and movement between groups. Subsequently, the effects of BVDV introduction on calf mortality, growth retardation, immunosuppression of calves, etc. can be estimated. Based on such more complete production and infection dynamics, decision makers can be provided with more complete information on losses caused by BVD.

All in all, we did develop a simulation model for large Chinese dairy farms while lacking precise input data. However, also when input data are not very precise and uncertain, simulation modelling studies can be useful. Simulation models, for instance, can be used to study the sensitivity of BVDV transmission and BVDV control measures for variables that are not known. That way, hypotheses of the importance of BVDV factors can be determined shaping future epidemiological field research. That way, resources can be saved because expensive field research can be focused on those aspects that are shown to be important in simulation studies.

6.5 Conclusion

In this study we determined the production and economic losses associated with BVDV infection in large-scale intensive dairy herds in China. Using a novel bio-economic simulation model we estimated the average economic losses of a BVDV introduction over 3 years. Direct and indirect losses due to BVDV infection were calculated based on daily production and infection dynamics of each cow. The losses ranged between 45 and 255 €/cow/year after the introduction of a PI heifer into a fully susceptible dairy herd with 300 milking cows. Our estimates provide evidence that BVDV introduction causes significant losses in large-scale intensive dairy herds in China.

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Supplementary material

Table 6.S1. Input values (derived from Jia et al., 2016 and Sun et al., 2018) used for fitting individual lactation curves with the Wilmink function (Wilmink, 1987; Edwardes et al., 2021) and calculating fat-protein corrected milk production (FPCM)

Parity	a	b	c	k	Fat	Protein
1	33.6962	-0.03232	-15.075	0.05	3.81	3.05
2	41.9446	-0.0678	-15.075	0.05	3.77	3.14
>=3	42.8556	-0.0742	-15.075	0.05	3.78	3.11

7

CHAPTER 7

General Discussion

7.1 BVDV control

Bovine viral diarrhoea virus (**BVDV**) introduction in dairy herds results in reduced milk yield, decreased udder health, premature culling, prolonged calving interval and increased mortality among cattle. Consequently, BVDV negatively affects the productivity and economic performance of dairy herds, leading to inefficiency in dairy production. To reduce this inefficiency, BVDV control programmes can be carried out at herd, regional or country level.

Different countries are at different stages of BVDV control. Dependent on the stage of BVDV control, farmers and/or animal health authorities have to decide on going to the next step in BVDV control or not. In order to make good decisions, information is important. Information, needed to support decisions, differs between various BVDV control situations. Figure 7.1 provides stages of BVDV control in combination with potential information that is useful for decision making at those different stages. The figure also shows the contribution of this thesis to existing scientific research on BVDV. In the stage of no control, information on the current BVDV infection situation as well as the corresponding effects of Bovine viral diarrhoea (**BVD**) is useful before any further decisions on BVD control are taken. In the stage of non-systematic control, BVDV control is implemented without clear objectives and monitoring. Therefore, information as expected efficiencies of systematic control programmes and experience of other countries are needed to help decision makers to design systematic BVDV control programmes. Within a systematic BVDV control programme there are three stages: biosecurity, elimination of persistently infected (**PI**) animals and surveillance (Lindberg et al., 2006; Moennig et al., 2007). Biosecurity includes all measures to prevent transmission between herds (Lindberg et al., 2006). Useful information for decision-making at that stage includes knowledge on the efficacy of the BVDV control programme options, farmers' perspectives on control programme options. Vaccination may be part of the control options. In the stage of elimination of PI animals, all animals in a herd with BVDV should be tested to identify PI animals, available diagnostic strategies will aid in related decision making. During the stage of surveillance, it is the objective to monitor the progress of the interventions as well as to rapidly detect new infections. Information required for decision-making in the stage of surveillance includes knowledge on the effects of new introductions on herd performance within the current programmes and the efficacy of other available control strategies. As indicated in Figure 7.1, for each stage of BVDV control, different types of studies can be carried out. Over the past decades, in countries that have been implementing and discussing the implementation of BVDV control programmes, numerous studies providing information for decision making in the various stages of BVDV control have been carried out.

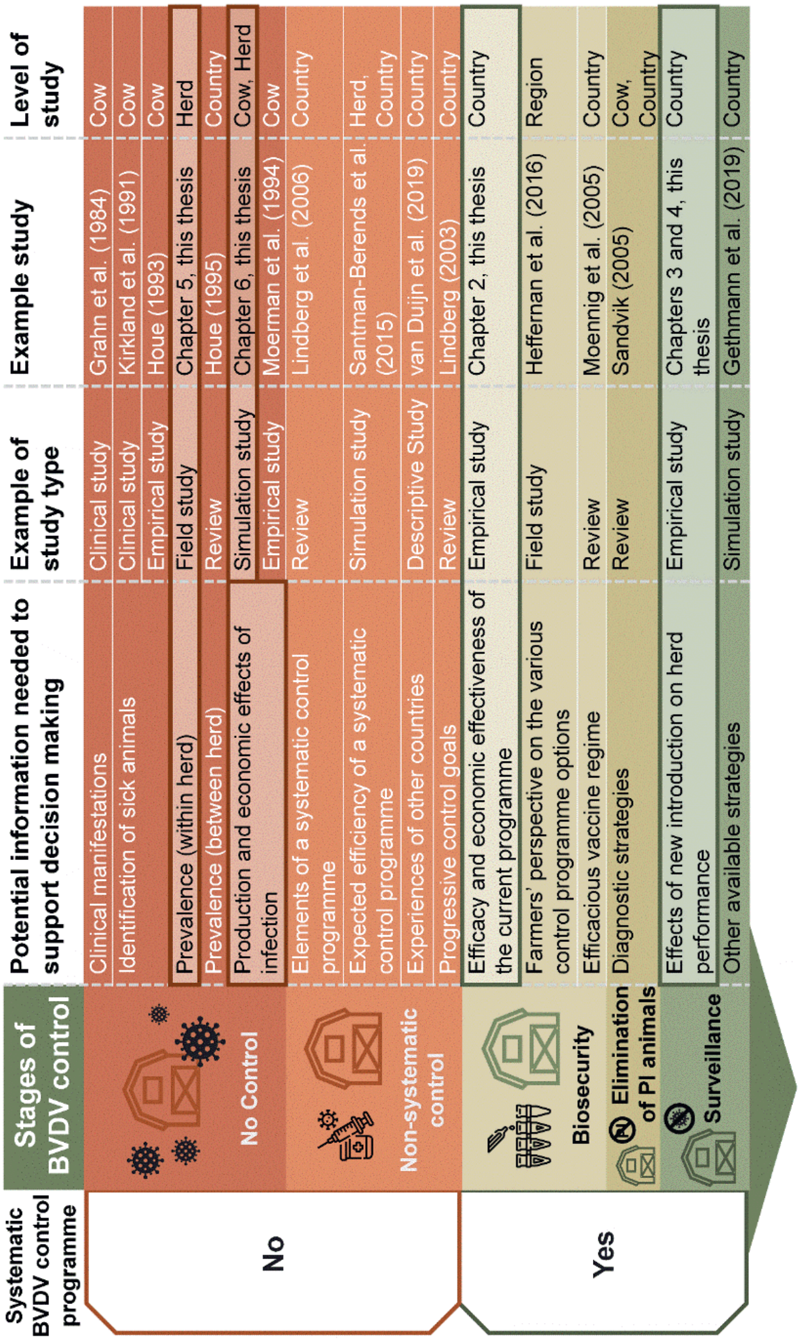

Figure 7.1 Bovine viral diarrhoea virus (BVDV) control stages and associated potential information with examples of research to support decision making. The highlighted boxes indicate the content of research chapters in this thesis. PI = persistently infected.

This thesis has been focussed on providing information for various stages in the implementation of BVDV control programmes. The focus of this thesis is highlighted with boxes in Figure 7.1. The overall objective of this thesis was to determine the effects of BVDV infection on the production and economic performance of dairy herds in order to support decision making in countries with and without a systematic BVDV control programme. For this purpose, The Netherlands and China were studied as countries with and without a systematic BVDV control programme, respectively.

Specifically, Chapter 2 estimated the effects of the Dutch BVDV-free programme on the production and economic performance of dairy herds that became certified BVDV free. Results showed that there were no changes in milk yield, somatic cell count, calving interval, and gross margin upon BVDV-free certification. Chapters 3 and 4 determined the effects of new BVDV introduction based on unique longitudinal datasets and found that a new introduction of BVDV had a negative but on average relatively small effect on herd performance in herds participating in the Dutch BVDV-free programme. Chapter 5 investigated the seroprevalence of BVDV in 3 large dairy herds in North China and presented a very high within-herd prevalence. Chapter 6 estimated the production and economic effects of BVDV introduction in Chinese dairy herds and quantified for the first time the specific losses caused by BVD in Chinese dairy herds.

In this chapter, important information related to decision making in BVDV control will be discussed. First, the contribution of this thesis to a better understanding of the effects of BVDV with and without systematic control programmes is discussed in the section “synthesis of the results”. Secondly, data and methodological approaches used are discussed. Thirdly, possible implications for decision-makers and future research are explored. Finally, the main conclusions of this thesis are provided.

7.2 Synthesis of the results

The main contributions of this thesis consist of an improved knowledge on the efficacy of the Dutch BVDV-free programme, and knowledge on the BVDV infection situation and associated production and economic effects in Chinese dairy herds. In this section a synthesis of the results is given.

7.2.1 The effects of BVDV in systematic BVDV control programmes

Three empirical studies were conducted in this thesis to investigate the effects of the BVDV-free control programme in the Netherlands (Chapters 2, 3 and 4).

Chapter 2 is an empirical study to assess the effects of the Dutch BVDV-free programme based on longitudinal data on herd BVDV status, herd performance and accounting. This study was designed as a case-control study: case herds were defined as herds where the BVDV status changed from unknown to BVDV-free during the study period, while control herds were BVDV-free during the entire study period. The results showed that the BVDV-free programme had no effects on the gross margin and other production performance of the studied dairy herds. This result was unexpected, as previous observational studies found an increase in somatic cell count (**SCC**, Lindberg and Emanuelson, 1997; Tschopp et al., 2017) and calving interval (Niskanen et al., 1995; Burgstaller et al., 2016a) and a decrease in milk yield (Lindberg and Emanuelson, 1997; Beaudeau et al., 2004) in BVDV-infected herds. The unexpected findings in Chapter 2 may be attributed to the unknown status of case herds prior to participating in the BVDV-free programme. The case herds, studied in Chapter 2 reflect the overall low number of herds with BVD-related issues after more than two decades of BVDV control in the Netherlands. The herds were selected from a group of herds that were enrolled in study groups and it can be assumed that those herds are well-managed. As a consequence, it could very well be the case that the studied case-herds did not have any BVD-related problems. Therefore, the results of Chapter 2 are consistent with previous studies evaluating the effects of BVDV on herd performance in countries that have had systematic BVDV control programmes for many years and also did not find significant differences between case and control herds Chapter 2 provides insights that for farms that do not have many or any BVD related problems and may only participate in a certification trajectory when it becomes a mandatory programme. The motivation to comply with a BVDV control programme cannot be derived from future production and economic improvements. Most likely, these farms would not have jointed the BVDV-free programme if the programme would not have been compulsory.

Chapters 3 and 4 determined the effects of a new introduction on Dutch dairy herds in the BVDV-free programme using unique datasets combining longitudinal herd-level surveillance data and herd information data (milk production, SCC, calving interval, culling and calf mortality). Some negative effects were determined, but on average these were relatively small compared to previous studies using longitudinal datasets (e.g., Niskanen et al,. 1995; Beaudeau et al., 2004; Gates et al.,2013). The datasets included herds where BVDV was introduced while the herds were enrolled in the BVDV control programme. With the quick detection and clearance of the PI animals within such programme, it is therefore plausible that the effects we found were much smaller than in previous studies, where herds did not participate in a systematic control programme (e.g., Beaudeau et al., 2005; Laureyns et al., 2013; Tiwari et al. 2005). Chapters 3 and 4 provide the decision makers with information on the success of the BVDV-free programme and show that implementation of the BVDV control programme is expected to substantially reduce the negative effects of BVDV introduction at the herd level.

An important challenge encountered in Chapters 3 and 4 was to determine the true period of BVDV infection because with semi-annual herd-level BVDV status data, new BVDV introductions are likely to occur before the reported breakdown date (i.e., the date when the herd lost its BVDV-free status). Therefore, in this research a timeline was developed representing multiple possible BVDV-introduction dates (i.e., BVDV was introduced 0, 4, 6, and 9 months prior reported breakdown date). Using this timeline, we concluded that, on average, the true period of BVDV infection was closest to the period after the reported breakdown date. This thesis demonstrates the rationality and effectiveness of biannual monitoring and provide a solution to determine the true period of BVDV infection.

Given the very small effects found in Chapters 3 and 4, the economic effect of a new introduction in the BVDV-free programme was not investigated anymore in this thesis. In fact, an accounting dataset with annual records of 2,809 herds was available for such an economic evaluation. However, given the small herd performance effects found in Chapters 3 and 4, it was believed that the economic performance will likely not change significantly after a BVDV introduction within the BVDV-free programme, especially when the analysis would be based on annual records.(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)(Vredenberg et al., 2021)

7.2.2 The effects of BVDV without systematic BVDV control programmes

In dairy systems without systematic BVDV control programmes, especially those without any control attempts (e.g., China), we aimed at providing information to support the decision making on whether to develop a control programme or not. For this purpose, we investigated the prevalence of BVDV infections in dairy systems without systematic BVDV control programmes in Chapter 5, and subsequently estimated the production and economic consequences of BVDV introduction in such dairy systems in Chapter 6.

Chapter 5 showed a very high within-herd prevalence (96%-100%) in 3 large dairy herds with no obvious signs of BVDV infection in North China. The within-herd prevalence found in our study is comparable to other studies conducted in North China recently, which also reported high prevalence ranging from 71% to 95% (Zhang et al., 2010; Li et al., 2014; Wang et al., 2014). Together with previous studies, our findings contribute to a more complete view on the BVDV infection situation in China. Notably, the very high within-herd prevalence found was a surprise for the involved dairy farmers. This is partly due to the inconspicuous clinical appearance of BVDV infections. The study showed a serious underestimation of the occurrence of BVDV infections in the studied herds and called for urgent attention by dairy farmers and their advisors to ongoing BVDV infections on their farms.

The fieldwork described in Chapter 5 was designed as a pilot study, preceding an extensive cross-sectional study. The cross-sectional study was designed to estimate the production differences between cows that were infected and were not infected with BVDV in large-scale Chinese dairy herds. The very high within-herd prevalence in the pre-sampling suggested that there would not be sufficient number of cows not infected with BVDV to study the assumed differences in production. Therefore, the planned extensive cross-sectional data collection was expected to not lead to useful results and was therefore cancelled. Nevertheless, the results are still informative, especially as a basis for the simulated herd in Chapter 6.

In Chapter 6 the production and economic effects of BVDV introduction in a large dairy herd in China were estimated by using a bio-economic simulation model. The vast majority of the previously published simulation models were aimed at European farming systems, which may differ from large-scale intensive dairy herds in China. Therefore, we developed a stochastic bio-economic simulation model based on the situation in Chinese dairy herds. The economic losses estimated in our study ranged between 45-255 €/cow/year, which is comparable to earlier reported economic losses (Yarnall and Thrusfield, 2017). For Chinese dairy farmers facing BVDV infection problems, such as those in Chapter 5, the results of Chapter 6 can inform them on the production and economic losses of BVDV introduction. Further, this study showed continuous losses over 3 years after BVDV introduction. If dairy farmers do not act on BVDV infections, they will suffer losses for a long time. In general, our study may increase the perceived severity of BVDV among Chinese dairy farmers, and may be a motivation for farmers to start with BVDV control (Champion and Skinner, 2008).

7.3 Data and methodological approaches

In this section, reflections on data and methodological approaches are presented. Figure 7.2 provides an overview of the data and methodological approaches used in different chapters of this thesis.

Several interesting data collection approaches were applied in this work. First, field data collection was conducted in Chinese dairy herds (Chapter 5). Secondly, we collaborated with Dutch institutions including DMS (Dirksen Management Support, Beusichem, the Netherlands), Royal GD (Deventer, the Netherlands), CRV (Cattle Improvement Cooperative , Arnhem, the Netherlands), and I&R (Identification and registration system, Assen, the Netherlands) to collect secondary data, and used it in Chapters 2, 3, and 4. Finally, secondary data was also derived from literature and interviews with European and Chinese experts, to be used in Chapter 6.

The collection of field data in Chapter 5 reflects the advantages and disadvantages of such collecting. The advantages of collecting field data compared to collecting secondary data are the high level of control on the data collection process as well as the high quality and reliability of the collected data. Another advantage is that communicating with dairy farmers, their advisors, and veterinarians can help to obtain more information and understanding (e.g., farmers' perspective on BVDV control). On the other hand, collecting field data is resource-intensive and is associated with high costs (money, time, labour, etc.), uncertainty (e.g., risk of not having enough samples in both case and control groups), unavoidable selection bias (e.g., the available farms were through personal communication, randomness cannot be guaranteed), dependence (e.g., requires external resources for experiment, farmers unwilling or unable to cooperate due to concerns about animal health/welfare) and inconvenience of communication (e.g., language, time difference). A more effective way to collect primary data is to cooperate with dairy farms with a good registration system in place. Subsequently, based on their available data, it will be possible to determine whether they meet the requirements before the data collection actually starts. Although we tried to find such farms through different channels, farms with sufficient disease and/or (re)production data were unavailable.

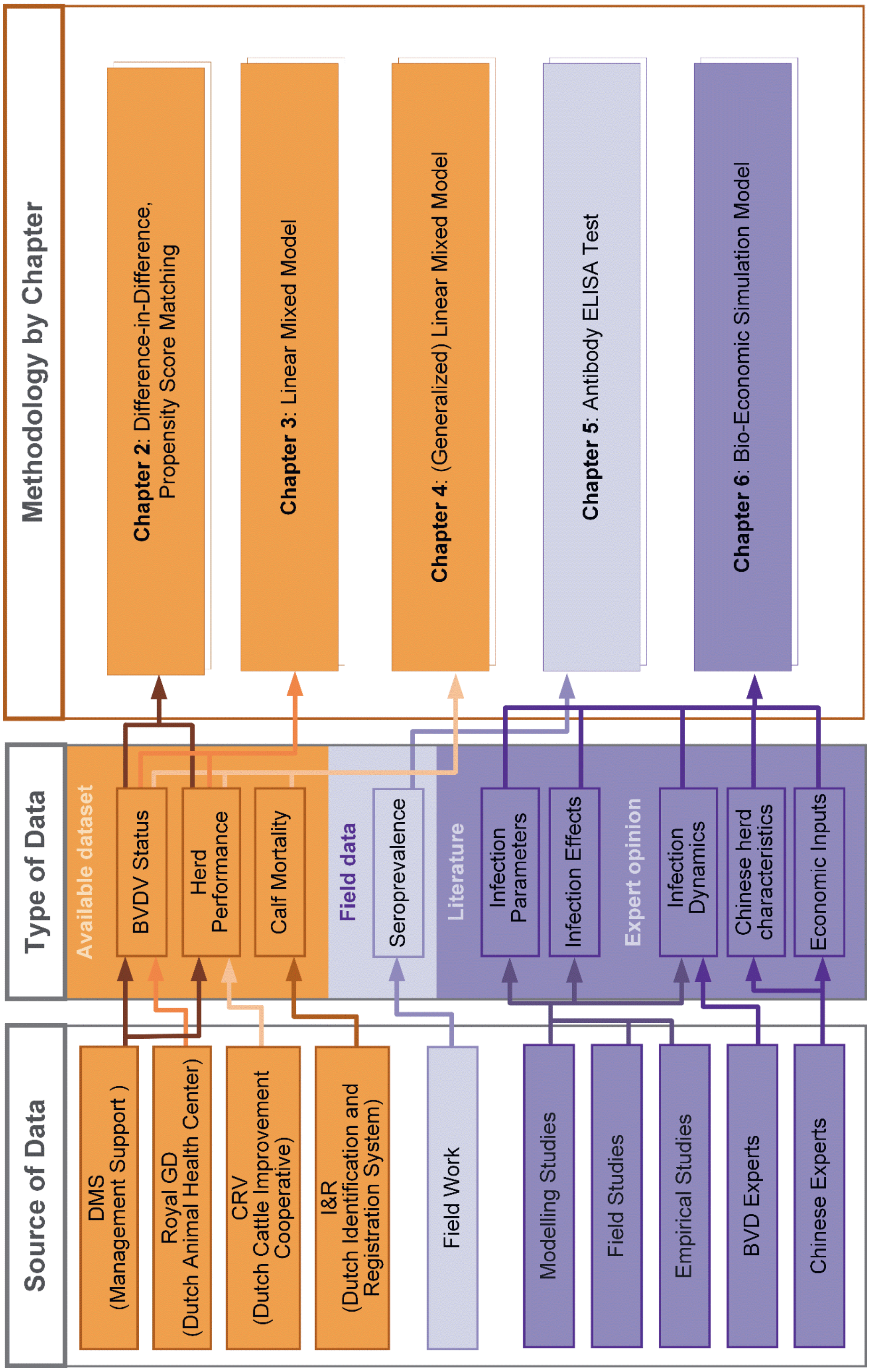

Figure 7.2 Overview of the data and methodologies used in different chapters of this thesis.

Based on the collected data by the Dutch institutions, we propose two suggestions for future data collection related to ex-ante data collection and the frequency of data collection. Ex-ante data (i.e., BVDV status and herd performance data prior to intervention) play a key role in assessing the effects of BVDV control measures. This was demonstrated in Chapter 2, where the actual BVDV status of the case herds before becoming BVDV-free, is unknown. With more precise ex-ante data (e.g., number of infected and/or PI animals), the case herds can be determined in a more precise way, and herds without clear BVDV-related issues can therefore be excluded from case herds. The frequency of the data also determines the precision of the analysis. In this thesis, the frequency of available data is monthly (milk production, SCC), quarterly (calf mortality), semi-annual (BVDV status in Chapters 3 and 4) and annual (BVDV status in Chapter 2, calving interval, culling risk, gross margin). With a higher data collection frequency, it is possible to detect more precise effects of the BVDV introduction/control programme. The above two suggestions for data collection apply to both countries with and without systematic BVDV control programmes. In particular, in countries without systematic BVDV control programmes such as China, it is very interesting to collect data through the collaboration with farms, companies, and universities to support the development of BVDV control programmes on pilot farms. Implementation of BVDV control programmes on pilot farms are also a reasonable first attempt to control BVDV in these countries and can be seen as a test phase of such programs.

Information can be retrieved through literature and expert interviews when field data are not available. In Chapter 6, BVDV data on Chinese dairy farms were not available and thus, these were collected from different sources. First, the BVDV transmission model and effects related to BVDV introduction were based on literature from Europe and North America (e.g., Viet et al., 2004, Moen et al., 2005, Smith et al., 2009). Second, infection dynamics were calibrated based on expert opinion and the results of Chapter 5. Third, herd characteristic and economic inputs were obtained from Chinese experts to ensure the simulation of a typical herd. This thesis further calls for field data storage on BVDV status and other herd performances of Chinese dairy herds. In general, this thesis demonstrates the importance of routine (long-term) data collection supported by farmers, companies, universities and other organizations. These data allow for a more profound knowledge of BVDV prevalence, transmission, and its effects on cow and herd performance, to support control decisions.

The uniqueness of this thesis is that methodologies from different scientific disciplines were combined. From the field of veterinary epidemiology, this thesis covers disease frequency measurement (sampling, seroprevalence investigation, Chapter 5), and statistical modelling (mixed models, Chapters 3, 4). From the field of economics, a quasi-experimental method (difference-in-difference in combination with propensity score matching, Chapter 2) was used. At last we used a normative bio-economic simulation model integrating biophysical and economic models in Chapter 6.

Two matching methods have been used in this thesis to match the BVDV infected and non-infected herds: propensity score matching (**PSM**) and matching based on BVDV-introduction date. Propensity score matching is an increasingly popular approach in econometric research to estimate causal treatment effects (Caliendo and Kopeinig, 2008) and was used in Chapter 2. The case herds in our study were certified as BVDV-free in different years, thus the matching process was performed in sub-data sets categorised by the year of BVDV-free certification. In each sub-data set, most suitable matching algorithm were selected. This process ensures the accuracy of matching. Matching based on BVDV-introduction date was used in Chapters 3 and 4. Free-herds, to be used controls, were generated based upon a random artificial BVDV-introduction date, which was used to match breakdown-herds with the same BVDV-introduction date. The generation of random artificial BVDV-introduction date was performed with 200 iterations to include the uncertainty. This matching process ensures that the free-herds can correct for fluctuations in the variables over time. The two matching methods used in this thesis described above can be applied to future research dealing with the same matching situations.

Uniquely, we modelled the between-pen transmission within large-scale intensive Chinese dairy herds (Chapter 6). To date, many studies have established a relatively complete framework for modelling the spread of BVDV and associated losses (Pasman et al., 1994; Sørensen et al., 1995; Innocent et al., 1997; Stott et al., 2003; Gunn et al., 2005; Viet et al., 2007; Hasler et al., 2012a; Knific and Zgajnar, 2014). However, previous studies only considered transmissions between different animal groups (Smith et al., 2010; Foddai et al., 2014), and did not include transmissions between lactating cow housed in different pens. In large-scale dairy farms, different animal groups are housed in different areas and contact occurs more within than between animal groups (Ezanno et al., 2008). In the current model in Chapter 6, the between-pen transmission within the milking cow herd was involved, taking into account the daily activities of milking cows based on typical Chinese housing structures. This between-pen transmission is a logical method to incorporate in future BVDV simulation models, especially for large-scale dairy farms.

7.4 Implications

In the Netherlands, BVDV control has come to the tail end of the control programme. It was reported that 86% of dairy farms in the 4th quarter of 2021 were with BVDV-free or BVDV-unsuspected status . Almost all farms are certified BVDV-free. Our results show that production effects of new introductions are small within the BVDV control programmes (Chapters 3, 4). Moreover, when more farms are free of BVDV, the probability of (re)introduction also decreases, leading to a lower risk of BVDV infection. As a consequence, the surveillance intensity may be reduced. An optimal intensity of surveillance can be assessed and determined using our presented bio-economic model. Of course, the model should be adjusted towards different surveillance scenarios, BVDV introduction risk factors, and adjusted for herd characteristics and initial BVDV situation.

For China, this thesis shows the severity of BVDV infection by presenting a very high BVDV seroprevalence (Chapter 5) and large production and economic losses due to BVDV introduction (Chapter 6). This work calls on decision makers of Chinese dairy herds, dairy sector and government to take actions. For instance, develop and implement BVDV control programmes on pilot farms while collecting routine data on BVDV status and herd performance. Our presented bio-economic model can also be applied to this process. For example, predict the efficacy of the implemented programmes by adding the specific measures and data collected in the programmes.

7.5 Main Conclusions

This thesis determined the effects of BVDV infection on the production and economic performance of dairy herds to support decision making in countries with and without a systematic BVDV control programme. Based on the main results of the research presented in this thesis, the following conclusion are drawn:

- The milk yield, SCC, CIV and gross margin did not change when the dairy herds changed from an unknown BVDV status to a BVDV-free status (Chapter 2).
- The new introduction of BVDV had a negative, but on average a relatively small, effect on milk production in BVDV-free herds participating in the Dutch BVDV-free programme (Chapter 3).
- The new introduction of BVDV had a negative, but on average a relatively small, effect on herd performance (mainly on SCC and CMR) in BVDV-free herds participating in the Dutch BVDV-free programme (Chapter 4).

- The within-herd seroprevalence of BVDV in 3 large commercial dairy herds in North China was very high, ranging between 96.3% and 100.0% (Chapter 5).
- BVDV introduction in a large-scale Chinese dairy herd caused large production and economic losses (Chapter 6).

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Summary

Bovine viral diarrhoea (**BVD**) is a viral cattle disease that presents in most cattle-raising countries worldwide and is listed by the World Organisation for Animal Health as a notifiable disease (Houe, 1995; Richter et al., 2019; OIE, 2021) Infection of bovine viral diarrhoea virus (**BVDV**) negatively effects the production and economic performance of the dairy herds. Many countries and regions developed BVDV control or eradication programmes and are at different stages of BVDV control. Therefore, information required for decision making in these countries is different. The overall objective of this thesis was to determine the effects of BVDV infection on the production and economic performance of dairy herds in order to support decision making in countries with and without a systematic BVDV control programme. A systematic BVDV control programme is identified by three central elements: biosecurity, elimination of PI animals and surveillance, as opposed to control attempts without clear objectives and monitoring to assess progress (Lindberg et al., 2006). The Netherlands and China were studied as countries with and without a systematic BVDV control programme, respectively.

The overall objective of this thesis was divided into the following five sub-objectives:

i. Investigate the economic and production effects of BVDV-free certification in Dutch dairy herds.
ii. Determine the effects of a new BVDV introduction on milk yield in BVDV-free herds participating in the Dutch BVDV-free programme.
iii. Determine the effects of a new BVDV introduction on herd performance (i.e., somatic cell count (**SCC**), calving interval (**CIV**), culling risk (**CR**), and calf mortality rate (**CMR**)) in BVDV-free herds participating in the Dutch BVDV-free programme.
iv. Investigate the within-herd seroprevalence of BVDV in large dairy herds in North China.
v. Simulate the dynamics of BVDV infection and the associated production and economic losses in a large-scale Chinese dairy herd using a bio-economic simulation model.

In **Chapter 2**, the economic (gross margin) and production effects (milk yield, SCC), and CIV) of BVDV-free certification were determined based on longitudinal annual accounting and herd performance data from Dutch dairy herds between 2014 and 2019. The study was designed as a case-control study: case herds were defined as herds where the BVDV status changed from unknown to BVDV-free during the study period, while control herds were BVDV-free during the entire study period. Potential bias between the covariates of the two herd groups was reduced by matching case and control herds using the propensity score matching (**PSM**) method. To compare the differences between case and control herds before and after BVDV-free

certification, time-varying Difference-in-Differences estimation (**DID**) methodology was used. The results indicate that there were no significant changes in milk yield, SCC, CIV, and gross margin upon BVDV-free certification. There are several possible explanations for the non-significant effects, such as the unknown status for case herds, not knowing the true BVDV infection situation in case herds and not knowing if control measures were implemented in case hers prior to participating in the BVDV-free programme. The effects of BVDV-free certification might have been underestimated, given that the Dutch BVDV control programme became mandatory during the study period, and some of the case herds might have never experienced any BVDV infection.

In **Chapter 3 and 4**, the effects of a new BVDV introduction in BVDV-free herds participating in the Dutch BVDV-free programme on herd performance (average daily milk yield (**ADMY**) (Chapter 3); SCC, CIV, CR, CMR (Chapter 4)) were determined. Longitudinal herd-level surveillance data were combined with herd information data to create 5 unique datasets for the 5 indicators of herd performance. Each database contained 2 types of herds: herds that remained BVDV free during the whole study period (defined as free-herds), and herds that lost their BVDV-free status during the study period (defined as breakdown-herds). The date of losing the BVDV-free status was defined as breakdown date. To define the possible BVDV-introduction dates, 4 scenarios were developed. In the default scenario, the breakdown date was assumed as the BVDV-introduction date. For the other 3 scenarios, the BVDV-introduction dates were set at 4, 6, and 9 months before the breakdown date, based on the estimated birth date of a persistently infected calf. To compare breakdown-herds with free herds, a random breakdown date was artificially generated for free herds by simple random sampling from the distribution of the breakdown month of the breakdown-herds. The ADMY, SCC and CIV before and after a new introduction of BVDV were compared through linear mixed-effects models with a Gaussian distribution, and the CR and CMR were modelled using a negative binomial distribution in generalized linear mixed-effects models. Of the 4 scenarios developed, the default scenario on average appeared to be most closely aligned with the true period of BVDV infection. Specifically, free herds have lower SCC, CR, CMR, and shorter CIV than the breakdown-herds. Within the breakdown-herds, the new BVDV introduction affected the ADMY, SCC and CMR. The loss in ADMY occurred mainly in the first year after breakdown, with a reduction in yield of 0.08 kg/cow per day compared with the last year before breakdown. Similarly, the SCC was higher in the first year after breakdown than that in the last year before breakdown, with a factor of 1.011. Compared with the last year before breakdown, the CMR in

the year of breakdown and the year after breakdown was higher, with factors of 1.170 and 1.096, respectively. Chapters 3 and 4 revealed that a new introduction of BVDV had a negative but on average relatively small effect on herd performance in herds participating in a BVDV control programme.

In **Chapter 5**, a study survey on the seroprevalence of BVDV was carried out in 3 large commercial dairy herds in North China in July 2019. In total 98 blood samples were randomly collected from first and second parity cows. In each pen on the farm and for each parity, an equal number of animals was sampled. Samples were tested for BVDV antibodies by blocking antibody enzyme-linked immunosorbent assay. The results showed that the true BVDV seroprevalence was 96.3% in one herd and 100.0% in the other two herds. The high values indicated a very high within-herd seroprevalence of BVDV and calls on Chinese dairy farmers to increase their awareness of BVDV prevention and control to reduce the associated production and economic losses.

In **Chapter 6** the effects of BVDV introduction on large-scale intensive Chinese dairy herds (300 cows) were simulated, and subsequently the production and economic effects of BVDV introduction were estimated. An individual cow-based dynamic, stochastic bio-economic simulation model with daily time steps was used. The model simulated the average production and economic losses over 3 years after a PI heifer entered into a fully susceptible herd. Production effects due to BVDV introduction consisted of a reduced milk production, reduced feed intake, increased probability of abortion, and a mortality probability of the PI animal. Subsequently, associated economic effects were calculated. Three scenarios were modelled: 1 scenario without BVDV introduction and 2 scenarios with BVDV introduction (i.e., literature-based scenario and expertise-based scenario). In the literature-based scenario, the input values for the BVDV infection dynamics were retrieved from literature, while in the expertise-based scenario, the input values were calibrated based on expert opinion to mimic the situation in large Chinese dairy herds observed in Chapter 5. The effects of BVDV introduction were calculated by comparing the model outputs of the scenarios with and without BVDV introduction. The mean annual economic losses in the 3 years after BVDV introduction were 52, 98, 54 €/cow/year in the literature-based scenario, and 255, 89, 45 €/cow/year in the expertise-based scenario, respectively. Estimates provided evidence that BVDV introduction caused significant losses in large-scale intensive dairy herds in China.

In **Chapter 7** the results, the used data, and methodological approaches in this thesis were synthesized. This chapter also discussed the potential implications. Overall, this thesis

determined the effects of BVDV infection on the production and economic performance of dairy herds to support decision making in countries with and without a systematic BVDV control programme. Based on the main results of the research presented in this thesis, the main conclusions are drawn:

- The milk yield, SCC, CIV and gross margin did not change when the dairy herds changed from an unknown BVDV status to a BVDV-free status (Chapter 2).
- The new introduction of BVDV had a negative, but on average a relatively small, effect on milk production in BVDV-free herds participating in the Dutch BVDV-free programme (Chapter 3).
- The new introduction of BVDV had a negative, but on average a relatively small, effect on herd performance (mainly on SCC and CMR) in BVDV-free herds participating in the Dutch BVDV-free programme (Chapter 4).
- The within-herd seroprevalence of BVDV in 3 large commercial dairy herds in North China was very high, ranging between 96.3% and 100.0% (Chapter 5).
- BVDV introduction in a large-scale Chinese dairy herd caused large production and economic losses (Chapter 6).

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"To what can human life be likened?

Perhaps to a wild gooses foot print on snow."

~ Su shi (苏轼), Nostalgia--In Response to Ziyou (和子由渑池怀旧)

So this is the end of my PhD story.

人生到处知何似？应似飞鸿踏雪泥。就以此作结吧。

About the author

About the author

Xiaomei Yue was born in Zibo, China, on the 2nd of March 1993. After graduating from high school, she started studying Marketing at Ocean University of China in 2011 and graduated in 2015. She received her MSc degree of accounting in 2017 from China Agricultural University with a thesis entitled “The effect of the integration of feed planting and dairy farming on the cost-effectiveness of dairy farms”. During her MSc, she performed an internship in the project “Dairy farming and land use” funded by Sino-Dutch Dairy Development Centre (SDDDC). During the internship, she developed a keen interest in the dairy industry and decided to explore further in this field. In October 2017, funded by China Scholarship Council and SDDDC, she started her PhD studies in Business Economics Group of Wageningen University & Research. During her PhD studies, she specialized in animal health economics and worked on estimating the economic and production effects of bovine viral diarrhoea in Dutch and Chinese dairy systems.

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List of publications

Xiaomei Yue*, Wilma Steeneveld, Mariska van der Voort, Gerdien van Schaik, J. C. M. Vernooij, Linda van Duijn, Anouk M. Veldhuis, Henk Hogeveen. The effect of bovine viral diarrhea virus introduction on milk production of Dutch dairy herds, *Journal of Dairy Science*, 2021, 104(2): 2074-2086.

Xiaomei Yue*, Mariska van der Voort, Wilma Steeneveld, Gerdien van Schaik, J. C. M. Vernooij, Linda van Duijn, Henk Hogeveen. The effect of new bovine viral diarrhea virus introduction on somatic cell count, calving interval, culling, and calf mortality of dairy herds in the Dutch bovine viral diarrhea virus–free program, *Journal of Dairy Science*, 2021, 104(9): 10217-10231.

Xiaomei Yue*, Wilma Steeneveld, Mariska van der Voort, Gerdien van Schaik, J. C. M. Vernooij, Linda van Duijn, Henk Hogeveen. The effect of a new introduction of bovine viral diarrhoea virus on somatic cell count and calf mortality based on 10 years of Dutch field data. *In Proceedings of the 2021 Society of Veterinary Epidemiology and Preventive Medicine*, online.

Xiaomei Yue*, Jingyi Wu, Mariska van der Voort, Wilma Steeneveld, Henk Hogeveen. Estimating the Effect of a Bovine Viral Diarrhea Virus Control Program: An Empirical Study on the Performance of Dutch Dairy Herds. (submitted)

Xiaomei Yue*, Mariska van der Voort, Wilma Steeneveld, Shenghua Wang, Henk Hogeveen. Seroprevalence of bovine viral diarrhea virus in 3 large dairy herds in North China. (submitted)

Xiaoge Sun, Yitong Su, Yangyi Hao, Jun Zhang, **Xiaomei Yue**, Wei Wang, Zhu Ma, Kangkang Chu, Shuang Wang, Yajing Wang, Shengli Li. Novel Process Methods for the Whole Cottonseed: Effect on the Digestibility, Productivity, Fat Profile, and Milk Gossypol Levels in Lactating Dairy Cows. *Frontiers in Nutrition*, 2022, 9.

Yale Deng, Fan Zhou, Yunjie Ruan*, Bin Ma, Xueyan Ding, **Xiaomei Yue**, Wenjun Ma, Xuwang Yin. Feed Types Driven Differentiation of Microbial Community and Functionality in Marine Integrated Multitrophic Aquaculture System. *Water*, 2020, 12(1): 95-110.

Xiaomei Yue

Wageningen School of Social Sciences (WASS)

Completed Training and Supervision Plan

Name of the learning activity	Department/Institute	Year	ECTS*
A) Project related competences			
A1 Managing a research project			
WASS Introduction Course	WASS	2017	1
Writing PhD Research Proposal	WUR	2017-2018	6
PhD Meetings BEC	WUR	2017-2022	2
'Milk production losses due to BVD'	Boehringer Ingelheim Infectieziekten expert panel, Leuvenum, the Netherlands	2019	1
'Economic impact of Bovine Viral Diarrhoea on dairy farms'	Sino-Dutch Dairy Development Centre (SDDDC) webinar, Online	2020	1
'Modelling the dynamics of herd performance associated with new introduction of bovine viral diarrhoea virus based on 10 years of Dutch field data'	Society for Veterinary Epidemiology and Preventive Medicine (SVEPM) 2021 Annual Conference, Online	2021	1
'The effects of bovine viral diarrhoea virus-free program on the gross margin of Dutch dairy herds'	International Society for Economics and Social Sciences of Animal Health (ISESSAH), Online	2021	1
Project and Time Management	WGS	2018	1.5
Information Literacy for PhD including EndNote introduction	WUR Library	2018	0.6
Scientific Writing	Wageningen In'to Language	2019	1.8
A2 Integrating research in the corresponding discipline			
Economics of Animal Health and Food Safety: BEC-52806	WUR	2017	6
Theories for Business Decisions: BEC-54806	WUR	2018	6
B) General research related competences			
B1 Placing research in a broader scientific context			
Quantitative Veterinary Epidemiology: QVE-30306	WUR	2018	6
SDDDC Deep Training Course	SDDDC	2018	1
Tidy Data Transformation and Visualization with R tidy versus and ggplot	SDDDC	2020	0.9
Winter School From Farm to Fork: Trend and Technologies (online)	WUR	2022	1

B2 Placing research in a societal context			
SDDDC Blog 1	SDDDC	2020	0.1
SDDDC Blog 2	SDDDC	2021	0.1
C) Career related competences/personal development			
C1 Employing transferable skills in different domains/careers			
Career Perspectives	WGS	2021	1.6
Total			**39.6**

*One credit according to ECTS is on average equivalent to 28 hours of study load

Colophon

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