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The effect of bovine viral diarrhea 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 diarrhea 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 Existing literature on potential milk production losses is based on relatively outdated data and hardly evaluates milk production loss in relation to a new BVDV infection in a surveillance system.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 program 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 diarrhea 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 mo 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 program. 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 program.

Key words: bovine viral diarrhea virus, bovine viral diarrhea virus introduction, control program, milk production

INTRODUCTION

Bovine viral diarrhea (**BVD**) is an endemic bovine disease in many countries across the world and is caused by BVD virus (**BVDV**; Houe, 2003; Lindberg et al., 2006). Bovine viral diarrhea can have major effects on cattle health. In addition to diarrhea, BVD can lead to fever, pneumonia, growth retardation, immunosuppression, and reproductive disorders. These symptoms 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/cow per year (Sørensen et al., 1995; Stelwagen and Dijkhuizen, 1998).

To reduce BVDV infection and its negative effects, some European countries and regions, such as Switzerland, Austria, Denmark, Germany, Ireland, and Scandinavia, have successfully implemented eradication or control programs 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

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BVDV control program (i.e., BVDV-free program) in 1997 (Mars and Van Maanen, 2005). Herds participating in this control program are certified as BVDV-free if they succeed in identifying and removing persistently infected (**PI**) animals, and if they follow up with a monitoring phase surveilling BVDV status at the herd level. When monitoring indicates BVDV has circulated (i.e., BVDV was introduced or reintroduced in previously BVDV-free herds), the herd loses its BVDV-free status. In 2007 and 2008, 7% of the herds certified as BVDV-free in the program lost their BVDV-free status (i.e., experienced a breakdown), while in 2015 and 2016, this was only true for 4% of the certified herds (Veldhuis, et al., 2018). Overall, the implementation of the BVDV-free control program 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 Animal Health, 2016, 2017). Although some research has been carried out on the BVDV-free program 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. Bovine viral diarrhea virus 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 fetus is infected in early gestation and a PI calf is born (Pasman et al., 1994; Peterhans et al., 2010; Foddai et al., 2014). The 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, but the amount of virus 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 the cow and herd levels. For individual cows, studies show a dramatic reduction in milk production: milk production of PI cows is 48 to 76% lower compared with non-PI cows (Voges et al., 2006; Knific and Zgajnar, 2014). A 50-d 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 d after seroconversion. At the level of the herd, milk production of herds positive for BVDV antibodies is 0 to 1.7 kg lower per cow per day, and 368 to 394 kg lower per cow per 305 d, compared with herds negative for BVDV antibodies (Tiwari et al., 2005; Tiwari et al., 2007). Beaudeau et al. (2004) identified a milk yield reduction of 0.58 kg/cow per 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 rely on relatively outdated data obtained before the introduction of BVDV control programs. As such, it is unclear what the effect of new BVDV infection on milk production has been from BVDV control programs, such as the Dutch BVDV-free program. 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 program between 2007 and 2017.

MATERIALS AND METHODS

Data Collection

Dairy farms participating in the Dutch BVDV-free program 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 program were tested, and PI animals (if any) were removed, followed by a 10-mo period of virus testing of all newborn calves. If no PI calf was detected during this 10-mo period, the herd was certified as BVDV-free and entered the monitoring phase. In the monitoring phase, 5 calves were tested every 6 mo for BVDV antibodies, or all newborn calves in the herd were tested for BVDV (explained below). When the monitoring indicated BVDV had been introduced, the herd would lose 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 percentages, 305-d milk yield, 305-d 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.

Data Editing

Data from the farms in the BVDV-free program (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 data set contained 472,523 test days of 4,211 dairy herds, as not all herds in the data set of BVDV-free program participated in CRV test-day sampling. Subsequently, another 1,085 herds were excluded for the following reasons: 507 herds left the BVDV-free program for different reasons (e.g., stopped dairy farming), 429 herds had incomplete milk production records, 37 herds had a herd size with fewer than 20 cows (a herd with less than 20 lactating cows is not considered a commercial dairy farm), 26 herds had ADMY out of the range of 0.1th and 99.9th percentile of the total, and 86 herds lacked (sufficient) pre- or postbreakdown-date test-day records because the breakdown occurred before January 1, 2008, or after December 31, 2014. Because herds had to undergo a 10-mo virus test on all newborn calves before obtaining the BVDV-free status, test-day milk production data earlier than 10 mo before the free-date were removed to ensure that the study herds were indeed free of BVDV before its defined introduction. Therefore, data for 85,363 test days were removed. The final data set included 3,126 Dutch dairy herds with information on 244,701 monthly test days from January 1, 2007 to December 31, 2017, comprising 41,650 test days for 640 breakdown-herds and 203,051 test days for 2,486 free-herds.

Scenarios of BVDV Introduction

Because 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 1) based on the Dutch BVDV-free program (van Duijn et al., 2019) and existing BVD epidemiological knowledge and expert opinion. In the monitoring phase of the BVDV-free program, blood samples were collected every 6 mo from 5 randomly selected 8- to-12-mo-old calves and tested for BVDV antibodies. Alternatively, all newborn calves in the herd were tested for the presence of BVDV [for more detail see van Duijn et al. (2019)]. The monitoring results determined if the herd would lose 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 defined from which point in time milk production was 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 lost 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 herds, PI calves are born within the last 4 mo before

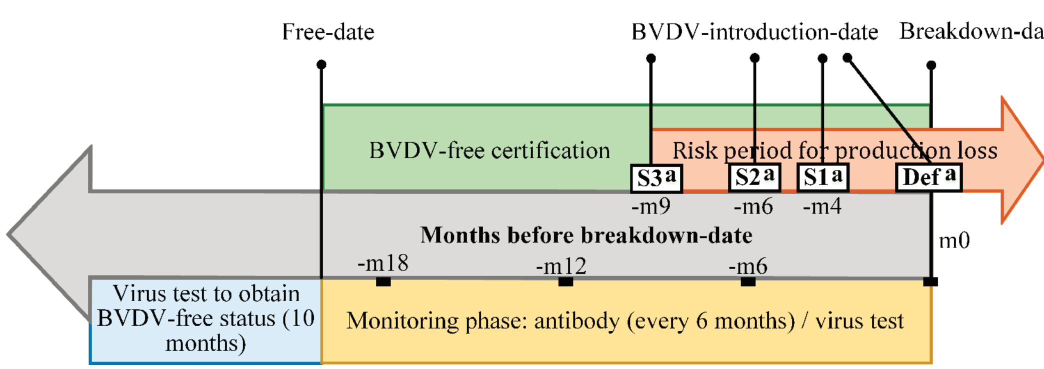

Figure 1. The timeline of bovine viral diarrhea virus (BVDV) introduction in dairy herds participating in the BVDV-free program. Def [a] (default scenario) = the risk period for production loss starts from the BVDV breakdown-date. S1[a], S2[a], and S3[a] = the risk period for production loss starts from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

the breakdown-date; in 50% of herds, PI calves are born within the last 6 mo before the breakdown-date; in 75% of herds, they are born within 9 mo before the breakdown-date. Thus, to account for this distribution, the BVDV-introduction date was set 4 mo (scenario 1), 6 mo (scenario 2), and 9 mo (scenario 3) before the breakdown-date.

Statistical Analysis

To estimate the effect 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, considering 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, 2018).

Annual Effect of BVD. For the annual effect of BVD on milk production, the 2 yr prior and 3 yr after introduction were considered. 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:

$$\begin{aligned} ADMY_{ij} = \beta_0 + \beta_1 BH\_FH_i + \beta_2 BVDstatus_{ij} \\ + \beta_3(BH\_FH_i \times BVDstatus_{ij}) + \beta_4 Year_{ij} \\ + \beta_5 Season_{ij} + \mu_{herd(i)} + \varepsilon_{ij}, \end{aligned} \quad [1]$$

for herd $i \in \{1, \ldots, 3{,}126\}$ and test-day $j \in \{01/01/2007, \ldots, 12/31/2017\}$, where $ADMY_{ij}$ is the average daily milk production in kilograms on test-day j of herd i. Estimate for the intercept β_0 is the ADMY for the reference level of each of the explanatory or fixed variables, β_i (i = 1–5) is the difference between the mean ADMY of a specified class of the fixed factor compared to the mean ADMY in the reference class. BH_FH_i is a dummy variable that represents herd type (breakdown-herd versus free-herd). $BVDstatus_{ij}$ is a defined categorical variable, which indicates the BVDV infection status of herd i on test-day j. $BVDstatus_{ij}$ was defined based on the BVDV-introduction date (real and artificial), and consisted of 5 categories: second to last year before BVD, last year before BVD, first year after BVD, second year after BVD, and third year after BVD. The category "last year before BVD" was used as the reference category. The effect of BVD on milk production within the breakdown-herd can be explained by the coefficients of the interaction term $BH\_FH \times BVDstatus$ 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 ith herd that takes into account repeated measures within 1 herd (Dohoo et al., 2003). Further, the errors $\varepsilon_{1j}, \ldots, \varepsilon_{3,126j}$ are assumed to be independent with $\sim N(0, \sigma^2)$. 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., 2015). 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 modeling 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 95th percentile interval was considered as the range of estimated coefficients that could be used to judge 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 performace (Lüdecke et al., 2019). The independent variable $BVDstatus_{ij}$ 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 $BVDstatus_{ij}$ 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 the performance package in R (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. Similar to the annual effect of BVD, the presence of quarterly effects was also analyzed for the first year after BVDV introduction. The BVD status variable for the quarterly analysis consisted of 5 categories representing the first 4 quarters (**Q**; 1–4) of the first year after the BVDV-introduction date, and the last year before the BVDV-introduction date as 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. To understand how initial prevalence in the herd affected 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 were. In the sensitivity analysis, therefore, only herds which had been BVDV-free for more than 3 yr 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.

RESULTS

Descriptive Analysis

Table 1 presents herd size and milk production performance by BVD 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-d milk production. Within the breakdown-herds, the mean ADMY is 0.1 kg/cow lower in the

Table 1. Average herd size and milk production performance [mean (SD)] for the 3,126 Dutch dairy herds participating in the bovine viral diarrhea virus (BVDV)-free program for the years 2007 to 2017 in the default scenario[1]

		BVDV breakdown-herds[2] (n = 640)						Free-herds[3] (n = 2,486)
Variable	Unit	Second to last year before breakdown	Last year before breakdown	First year after breakdown	Second year after breakdown	Third year after breakdown	Overall	Overall
Herd size	Number	78 (35)	79 (36)	81 (38)	84 (40)	87 (44)	82 (39)	80 (38)
ADMY[4]	kg/cow per 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)
305-d milk	kg/cow per 305 d	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]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.

[2]BVDV breakdown-herds = herds that lost the BVDV-free status during the study period.

[3]Free-herds = herds that did not lose the BVDV-free status during the study period.

[4]ADMY = average daily milk yield per cow.

Table 2. Estimated coefficients of the linear mixed model for the annual effect of bovine viral diarrhea virus (BVDV) introduction on average daily milk yield (kg) per cow with 200 iterations in the default scenario[1]

		Estimated coefficients				
Effect	Category	Mean	SD	Minimum	95% PI[2]	Maximum
Intercept		26.20	0.07	26.10	26.10; 26.40	26.50
BH_FH[3]	Free-herd	Referent				
	BVDV Breakdown-herd	0.05	0.03	−0.04	−0.01; 0.11	0.13
Bovine viral diarrhea (BVD) status	Last year before BVD	Referent				
	Second to last year before BVD	0.23	0.04	0.13	0.15; 0.30	0.34
	First year after BVD	−0.21	0.03	−0.31	−0.28; −0.15	−0.11
	Second year after BVD	−0.46	0.05	−0.59	−0.55; −0.36	−0.32
	Third 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	Referent				
	BH_FH × second to last year before BVD	0.02	0.04	−0.10	−0.05; 0.09	0.10
	BH_FH × first year after BVD	−0.08	0.03	−0.17	−0.15; −0.02	0.00
	BH_FH × second year after BVD	−0.05	0.04	−0.15	−0.12; 0.03	0.05
	BH_FH × third year after BVD	−0.03	0.04	−0.14	−0.10; 0.04	0.08
Year	2007	Referent				
	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[4]	Summer	Referent				
	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]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.

[2]95% PI = 2.5th percentiles to 97.5th percentiles of the parameter estimate; the significance of the model results was indicated by this interval. PI = persistently infected animal.

[3]BH_FH = a dummy variable indicating BVDV breakdown-herd and free-herd.

[4]Season = spring (March–May), summer (June–August), autumn (September–November), winter (December to next February).

first year after breakdown compared with the last year before breakdown.

Annual Effect of BVD on Milk Production

Table 2 shows the annual modeling results of 200 iterations for the default scenario, and Figure 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 with 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 yr. The results for scenario 1, 2, and 3 (i.e., setting the BVDV-introduction date at 4, 6, or 9 mo before the breakdown-date) are presented in Supplemental Table S1 (https://doi.org/10.17026/dans-zq3-x2ck). In scenario 1, 2, and 3, the mean ADMY in the first year after introduction was respectively 0.04, 0.02, and 0.04 kg/cow per day lower compared with 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 per day, respectively.

Quarterly Effect of BVD on Milk Production

Table 3 presents the results of the quarterly linear mixed model for the default scenario, and Figure 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 Q1 after breakdown, compared with the last year before breakdown. Further, for Q2, Q3, and Q4 after breakdown, the mean ADMY was 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 Supplemental Table S2 (https://doi.org/10.17026/dans-zq3-x2ck). Although the quarterly effects of BVD differed in scenario 1, 2, and 3, the milk production of the breakdown-herds declined after BVDV introduction in all 3 scenarios.

Sensitivity Analysis

The sensitivity analysis modeled that herds had been BVDV-free for more than 3 yr. Figure 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 Supplemental Table S3 (https://doi.org/10.17026/dans-zq3-x2ck). 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 was 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 yr were 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 was 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 were 0.02, 0.05, 0.08 kg/cow per day greater than the overall quarterly effect analysis results (i.e., 0.14, 0.09, 0.02 kg/cow per day reduction in milk yield). Overall, the trends found in the annual sensitivity analysis were comparable to the annual linear mixed model results, whereas there was

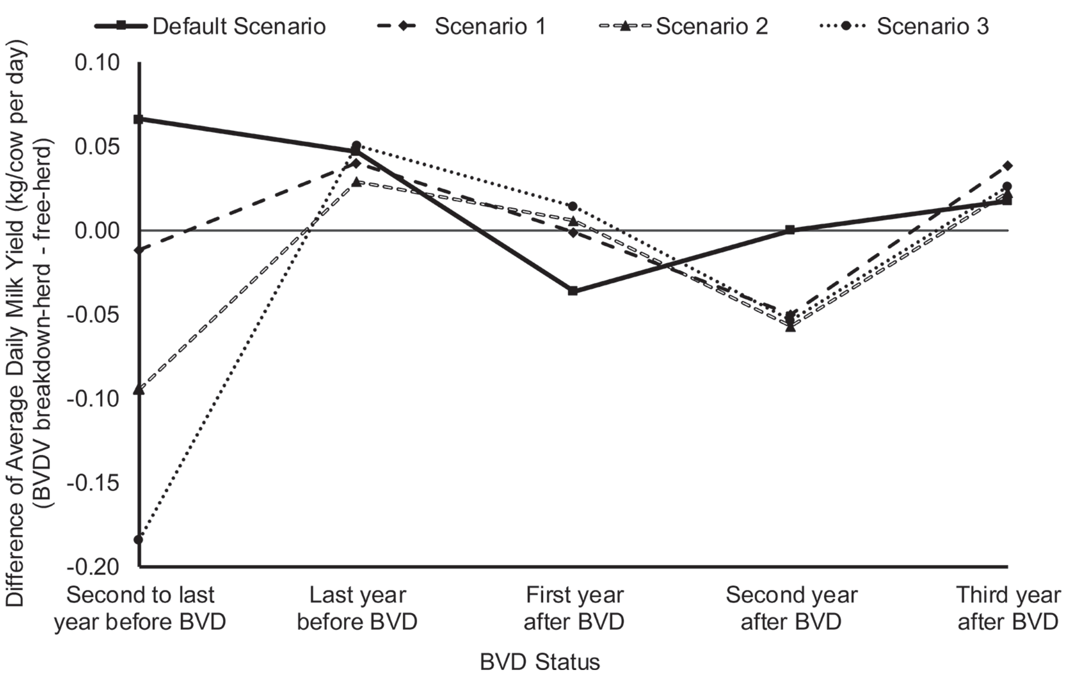

Figure 2. The estimates of mean average daily milk yield (AMDY; kg/cow) of bovine viral diarrhea virus (BVDV) breakdown-herds in the years before and after BVDV introduction. The ordinate 0 is the reference level of free-herds; there is no difference in ADMY of free-herds. A BVDV breakdown-herd is a dairy herd that obtained and subsequently lost the BVDV-free status, and a free-herd is a dairy herd that did not breakdown during the study period. Four 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 mo before the breakdown-date. BVD = bovine viral diarrhea.

a clear divergence between the quarterly sensitivity analysis and the quarterly linear mixed model results in Q4 after breakdown.

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 to 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 per year (SD = 1,139 kg/herd per year), which was calculated based on the average herd size in this study (mean = 82, SD = 39, Table 1). This demonstrated that BVDV introduction has a negative, but on average a relatively small, effect on milk production in herds involved in the BVDV control program.

The effect of BVDV introduction on milk production in dairy farms in this study was smaller compared with 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 per day, which was 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 per day less milk compared with cows in herds not recently infected. These differences in the findings may be explained by the fact that PI animals were removed quickly from the herds in the BVDV-free program in our study. In the herds that were analyzed by Beaudeau et al. (2004), bulk tank milk was periodically tested for BVDV antibodies, but no intervention measures were taken.

Table 3. Estimated coefficients of the quarterly effect linear mixed model of average daily milk yield (kg) per cow with 200 iterations in the default scenario[1]

		Estimated coefficients				
Effect	Category	Mean	SD	Minimum	95% PI[2]	Maximum
Intercept		26.30	0.10	25.90	26.10; 26.40	26.60
BH_FH[3]	Free-herd	Referent				
	BVDV Breakdown-herd	0.01	0.04	−0.10	−0.06; 0.08	0.12
BVD status[4]	Last year before BVD	Referent				
	Q1 after BVD	−0.12	0.04	−0.23	−0.21; −0.04	−0.02
	Q2 after BVD	−0.17	0.05	−0.30	−0.27; −0.07	−0.04
	Q3 after BVD	−0.18	0.05	−0.30	−0.29; −0.09	−0.07
	Q4 after BVD	−0.27	0.05	−0.39	−0.36; −0.17	−0.14
BH_FH × BVD status	BH_FH × last year before BVD	Referent				
	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	Referent				
	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[5]	Summer	Referent				
	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]In this scenario, the breakdown date [i.e., the date of losing the bovine viral diarrhea virus (BVDV)-free status] was used as the BVDV-introduction date, and signified the start of the period with potential milk production loss.

[2]95% PI = 2.5th percentiles to 97.5th percentiles of the parameter estimate; the significance of the model results was indicated by this interval. PI = persistently infected animal.

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

[4]Q1, Q2, Q3, Q4 = the first, second, third, and fourth quarters after the BVDV-introduction date.

[5]Season = spring (March–May), summer (June–August), autumn (September–November), winter (December to next February).

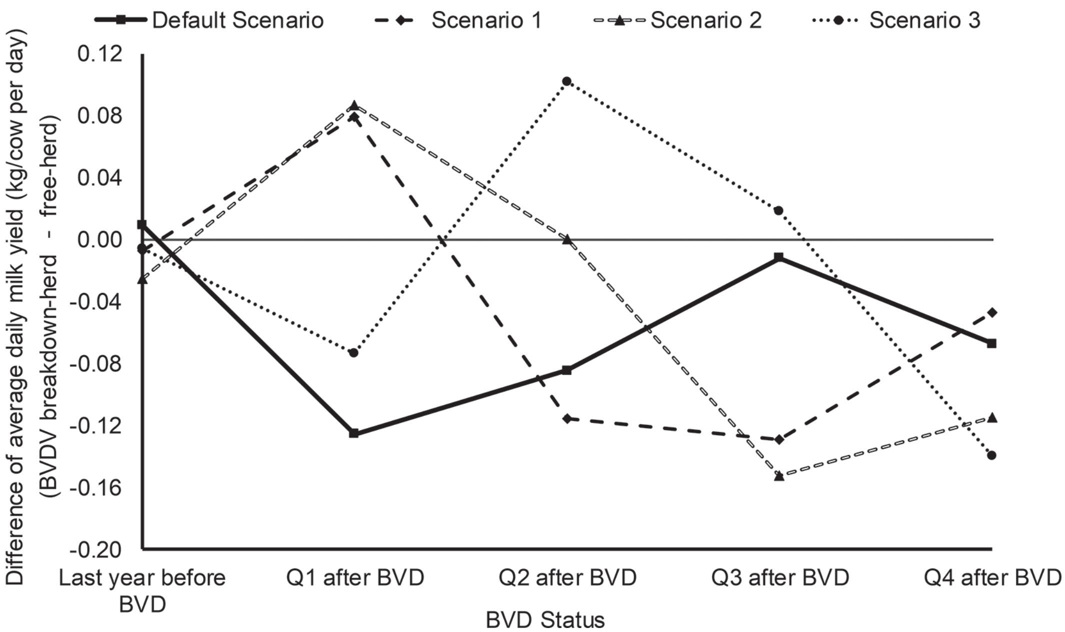

Figure 3. The estimates of mean average daily milk yield (AMDY; kg/cow) of bovine viral diarrhea virus (BVDV) breakdown-herds per quarter for 4 BVDV-introduction scenarios. The ordinate 0 is the reference level of free-herds; there is no difference in ADMY of free-herds. A BVDV breakdown-herd is a dairy herd that obtained and subsequently lost the BVDV-free status, and a free-herd is a dairy herd that did not breakdown during the study period. Four 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 mo before the breakdown-date. Q1, Q2, Q3, and Q4 represent the first, second, third, and fourth quarters after BVDV introduction. BVD = bovine viral diarrhea.

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 per day lower than that of uninfected herds in Styria, Austria. Tschopp et al. (2017) analyzed herds

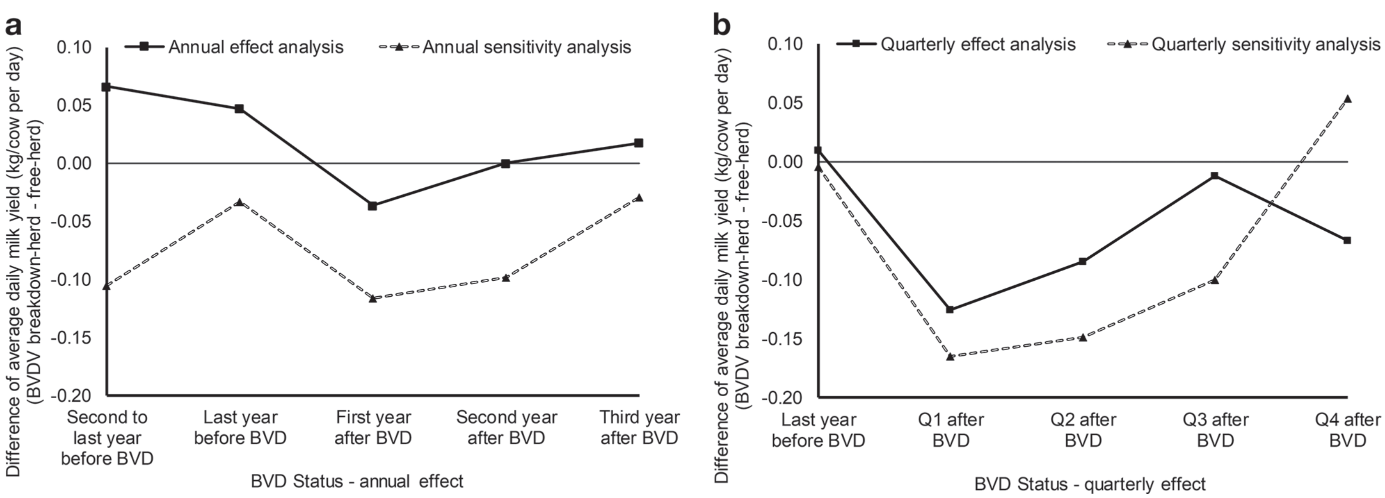

Figure 4. Comparison of the annual (a) and quarterly (b) effect of bovine viral diarrhea virus (BVDV) introduction on the estimates of mean average daily milk yield (AMDY) of all study herds and of herds that remained BVDV-free for at least 3 yr (sensitivity analysis) in the default scenario. The ordinate 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 yr before and 3 yr after 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. BVD = bovine viral diarrhea.

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 herds positive for BVDV antibody produced 368 kg of milk less per 305 d (≈0.21 kg/cow per day), compared with cows in herds negative for BVDV antibody. Differences in research results can partly be explained by variations in BVDV control measures, milk production levels, breed, and study area (Eurostat, 2017), as well as the study design (i.e., inter- vs. intraherd analysis).

The effect 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) indicated 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 effect is of a BVDV introduction on milk production. Second, the duration of BVDV circulation, which depends on when PI animals died or were removed, also influences the effect of BVDV introduction on milk production. In the BVDV-free program, newborn calves of the herd are tested until no BVDV-positive animal is detected for 10 mo (van Duijn et al., 2019). On average, PI animals are removed within 8 wk 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 effects of the introduction of BVDV on milk production may also be underestimated. Generally, dairy farms involved in both CRV milk production registration and a BVDV-free program 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 programs. Therefore, the introduction of BVDV may have a larger effect on milk production of Dutch dairy farms not included in this study.

The BVDV introduction has a greater effect 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 yr 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 d following removal of the last PI animal from the herd. The sensitivity analysis indicated that BVDV introduction indeed had a higher effect 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 per 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 were also greater than the quarterly analysis results of all herds in the Q1, Q2, and Q3 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 when compared with a herd with a low initial antibody prevalence.

The risk period for milk production loss due to BVDV is mostly in the first 2 yr 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 yr after BVDV introduction. These results reflected 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 yr after. It should be noted that the data of these 3 studies are limited to a maximum duration of 5 yr, and thus the longer-term annual effect of BVDV introduction may not be detected due to insufficient data. Our study included surveillance data from 2007 to 2017, and the results of the default scenario showed that in the third year after BVDV introduction, the effect on milk production loss is indeed small (−0.02 kg/cow per day, 95% percentiles interval: −0.10; 0.04 kg/cow per day). While our findings validate previous studies, the long-term effect of BVDV on milk production may be underestimated in our study because all herds participated in the BVDV-free program. This means the presence of BVDV was likely detected before more serious clinical problems, which could cause long-term effects on production, could occur. Furthermore, we analyzed the quarterly effects of BVDV introduction on milk production within the first year after introduction. The results of the default scenario showed that milk production loss is highest (i.e., 0.16 kg/cow per day) in Q1. Previous studies have shown that the effect of BVDV infection on milk production occurs mainly in the first 3 wk after infection (David et al., 1994; Moerman et al., 1994; Bennett et al., 1999). We also found that the annual milk production losses were smaller than the quarterly losses (i.e., milk production decreased significantly in the first few months after infection), but was leveled out in the annual impact analysis. Quarterly analyses may help us to better understand the duration of the effect of BVDV introduction on milk production in a controlled situation.

Of the 4 scenarios developed in this study, the default scenario on average appeared 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 were consistent with this fact. The results of the annual impact analysis in scenarios 1 through 3 were fairly consistent: milk production losses all started from the first year after BVDV introduction, with greater losses in the second year. It may be because scenarios 1, 2, and 3 all assumed that the BVDV introduction started before the breakdown-date, and thus the milk production losses of these scenarios were delayed compared with the default scenario. Given the above, each herd has its own true scenario of (re)introduction and 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 were limitations to the model used in this study. The $Year_{ij}$ variable may not have been 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 effect of the abolition of the European milk quota system in 2015 on dairy farms. Nevertheless, the effects of weather and policy changes can be different on each farm. Therefore, the $Year_{ij}$ variable is a proxy for many unmeasured effects. Another limitation was the multicollinearity between the 2 variables $BVDstatus_{ij}$ and $Year_{ij}$ in the annual analysis model. This is because $BVDstatus_{ij}$ was a categorial variable with year as unit. Both variables were retained in the final linear mixed model because $BVDstatus_{ij}$ is one of the variables of interest in this study, and the $Year_{ij}$ variable was 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 is only a problem for the collinear variables $Year_{ij}$ and $BVDstatus_{ij}$. The coefficient of the interaction term $BH\_FH_i \times BVDstatus_{ij}$ (the main variable of interest) will not be affected, and the performance of the control variables $Year_{ij}$ and $BVDstatus_{ij}$ 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, and feeding systems. These factors will most likely remain stable within the farm over time, and thus the estimates of milk yield changes within the breakdown-herd will not be largely affected by these factors.

The estimated effect of the BVDV introduction on milk production was 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 effects, 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.

CONCLUSIONS

The introduction of BVDV has a negative, but on average a relatively small, effect on milk production for Dutch dairy herds participating in the BVDV-free control program. This effect was mainly observed during the first and second year, especially in Q1, after dairy herds lost their BVDV-free status. Our results provide dairy farmers and policy makers with information on the annual and quarterly loss of milk production due to BVDV introduction in the BVDV-free program, which can be used to develop more effective prevention and control plans.

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