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Title: Evaluation of bovine viral diarrhea virus control strategies in dairy herds in Hokkaido, Japan using stochastic modelling

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Summary

Bovine viral diarrhea virus (BVDV) infection in cattle can result in growth retardation, reduced milk production, reproductive disorders, and death. Persistently infected animals are the primary source of infection. In Hokkaido, Japan all cattle entering shared pastures in summer are vaccinated before movement for disease control. Additionally, these cattle may be tested for BVDV and culled if positive. However, the effectiveness of this control strategy aiming to reduce the number of BVDV infected animals has not been assessed. The aim of this study was to evaluate the effectiveness of various test and cull and/or vaccination strategies on BVDV control in dairy farms in two districts of Hokkaido, Nemuro and Hiyama. A stochastic model was developed to compare the different control strategies over a 10-year period. The model was individual-based and simulated disease dynamics both within and between herds. Parameters included in the model were obtained from the literature, the Hokkaido government and the Japanese Ministry of Agriculture, Forestry and Fisheries. Nine different scenarios were compared: no control, test and cull strategies based on antigen testing of either calves or only cattle entering common pastures, vaccination of all adult cattle or only cattle entering shared pastures, and combinations thereof. The results indicate that current strategies for BVDV control in Hokkaido slightly reduced the number of BVDV infected animals; however, alternative strategies such as testing all calves and culling any positives or vaccinating all susceptible adult animals dramatically reduced those. To our knowledge, this is the first report regarding the comparison of the effectiveness between the current strategies in Hokkaido and the alternative strategies for BVDV control measures.

Keywords: Bovine viral diarrhea virus, Common pasture, Control strategies, Culling, Modelling, Vaccination

Introduction

Acute infection with Bovine viral diarrhea virus (BVDV) in cattle results in temporary fever, respiratory symptoms and diarrhea (Bachofen et al., 2010). Rarely, acutely infected animals may suffer from high fever and internal bleeding due to thrombocytopenia. More importantly, infection during specific stages of pregnancy can result in the birth of immunotolerant calves that are persistently infected (PI) with BVDV (McClurkin et al., 1984). These PI animals, which continuously excrete virus into the environment, are accepted as the main source of transmission regarding the short time span of low-intensity viral excretion by transiently infected animals within a herd. In some cases, clinical signs in PI animals can be differentiated pathogenetically into mucosal disease (Bachofen et al., 2010). Economic losses in dairy and beef industries due to BVDV infection are substantial (Houe, 2003; Weldegebriel et al., 2009). Thus, many countries have implemented BVDV control programs (Greiser-Wilke et al., 2003).

Identification and removal of PI animals is an effective strategy for clearing infected herds from BVDV infection, and a common approach to prevent new herds from becoming infected. BVDV control strategies differ between countries (Lindberg and Houe, 2005; Campen, 2010). In most European countries, BVDV control is aimed at systematic eradication without vaccination. Systematic programs have been implemented in Denmark, Finland, Norway, Sweden, Ireland, Belgium, and Scotland (Bitsch et al., 2000; Lindberg et al., 2006; Graham et al., 2014; Hanon et al., 2014). Based on Scandinavian strategies, which is test and culling only PI cattle but no vaccination, a regional BVDV control program was launched in lower Austria in 1996 and later extended to the entire country (Rossmanith et al., 2005). A national compulsory eradication program has been in place in Switzerland since 2008 (Presi and Heim et al., 2010; Presi et al., 2011). This program is based on identification and culling of PI animals through antigen testing of newborn calves using ear notch samples, a ban on vaccination, and movement restrictions. In contrast, in the United States (US) several voluntary BVDV control programs that include vaccination have been implemented. It has been estimated that approximately 80% of US cattle are vaccinated with either inactivated or modified live virus vaccines to prevent both fetal infections and acute disease (Campen, 2010).

In Japan, BVDV was first reported in 1967 and is currently endemic (Nagai et al., 2008; Kadohira and Tajima, 2010; Abe et al., 2015). According to a pilot survey on PI animals in dairy farms in Japan, the prevalence of PI animals at the herd level and animal level were 7.59% and 0.12%, respectively, in some regions in 2014 (Kameyama et al., 2016). In Hokkaido, which is located in northern Japan between 41°31′ and 45°30′ N latitude and between 139°20′ and 148°53′ E longitude, BVDV has already spread and become an endemic disease in dairy herds; thus, some regional voluntary BVDV control programs have already been implemented (Yasutomi et al., 2004; Kadohira et al., 2007). The current control activities targets pastured animals (Saino et al., 2013). In Japan, a part of cattle are released in a common pasture shared by the multiple herds. All cattle that graze on common pastures during the summer must be vaccinated against BVDV before their movement to common pasture. Both modified live vaccines and killed vaccines are used with the aim to prevent fetal infections and acute disease in most prefectures in Japan including Hokkaido. These cattle are also tested by RT-PCR or virus isolation before entering common pastures, and any positive PI animals are culled. These tests are conducted at Livestock Hygiene Service Center in Hokkaido. Grazing on shared pastures is a major risk factor for BVDV spread between herds (Bitsch et al., 2000; Rossmanith et al., 2005; Valle et al., 1999). However, it is not known whether the current BVDV control strategies are effective for reducing the prevalence of PI animals at the regional level. Therefore, the aim of this study was to evaluate the BVDV control programs in Hokkaido using stochastic modelling. Epidemiological models of BVDV infection are well established (Courcoul and Ezanno, 2010; Gates et al., 2013; Gates et al., 2014; Tinsley et al., 2012). However, common pastures are not included and control strategies concerning common pastures were not tested in previous studies. Here, we developed an individual-based model to describe the dynamics of

BVDV transmission within and between herds and common pastures. Nine different scenarios were assessed with this model: no control, a test-and-cull strategy based on antigen testing of calves or only cattle entering common pastures, vaccination of either adult cattle or only cattle entering common pastures, and combinations thereof. Additionally, we compared the effectiveness of voluntary and compulsory programs.

Materials and methods

Model

To assess the effectiveness of interventions, we constructed a mathematical model describing the transmission process of BVDV at two levels simultaneously, within a dairy herd and between dairy herds. To capture the stochasticity of transmission events, we employed an individual-based stochastic model. Our model is a compartmental SIR-like model; the transition of infection status was previously described (Ezanno et al., 2007). The hosts were classified by the following infection states: *M*: maternal antibodies, *S*: susceptible, *TI*: transiently infected, *PI*: persistently infected, *CP*: recovered cows still carrying *PI* animals, *R*: other recovered animals, or *V*: vaccinated animals (Fig. 1).

The transmission of BVDV occurs by horizontal transmission (from *PI* and *TI* animals to S animals) and vertical transmission (*TI* or *PI* animals carry *PI* offspring). The transmission probability of horizontal transmission differs according to management groups. The animals were stratified by five groups based on the breeding place in a herd: calves, young heifers, pregnant heifers, dry cows, and lactating cows. Age structure of cows is parameterized based on the data of the duration of age group provided by the Hokkaido government. We modeled the heterogeneity of horizontal transmission probability due to the breeding place in herds stratified by age group of cows. The probability of horizontal transmission per a susceptible host, so-called the force of infection at specific time point *t*, $\lambda(t)$, is given by the following formulae:

$$\begin{aligned}
\lambda_{calves,x}(t) &= \beta_{PI}\frac{PI_{calves,x}(t)}{N_{calves,x}(t)} + \beta_{TI}\frac{TI_{calves,x}(t)}{N_{calves,x}(t)} + \beta_{PI,diff}\left(\frac{PI_{heifers,x}(t)}{N_{calves,x}(t)N_{heifers,x}(t)} + \frac{PI_{adults,x}(t)}{N_{calves,x}(t)N_{adults,x}(t)}\right),\\
\lambda_{heifers,x}(t) &= \beta_{PI}\frac{PI_{heifers,x}(t)}{N_{heifers,x}(t)} + \beta_{TI}\frac{TI_{heifers,x}(t)}{N_{heifers,x}} + \beta_{PI,diff}\left(\frac{PI_{calves,x}(t)}{N_{heifers,x}(t)N_{calves,x}(t)} + \frac{PI_{adults,x}(t)}{N_{heifers,x}(t)N_{adults,x}(t)}\right),\\
\lambda_{adults,x}(t) &= \beta_{PI}\frac{PI_{adults,x}(t)}{N_{adults,x}(t)} + \beta_{TI}\frac{TI_{adults,x}(t)}{N_{adults,x}(t)} + \beta_{PI,diff}\left(\frac{PI_{calves,x}(t)}{N_{adults,x}(t)N_{calves,x}(t)} + \frac{PI_{heifers,x}(t)}{N_{adults,x}(t)N_{heifers,x}(t)}\right),
\end{aligned} \tag{1}$$

where $\lambda_{\text{calves,x}}$, $\lambda_{\text{heifers,x}}$, and $\lambda_{\text{adults,x}}$ denote transmission probability for calves (calves and young heifers), heifers (pregnant heifers), and adults (dry cows and lactating cows) in the *x*-th herd, respectively. The stratification of transmission probability, calves, young heifers, dry cows and lactating cows, is based on the place of management in herds. β_{PI} and β_{TI} denote the transmission coefficient of transmission from *PI* and *TI* animals within the same age group and same herd, respectively. $\beta_{\text{PI,diff}}$ denotes the transmission coefficient of transmission from *PI* animals between different age groups in the same herd. We set $\beta_{\text{PI}} = 0.5$, $\beta_{\text{TI}} = 0.03$, and $\beta_{\text{PI,diff}} = 0.1$ per 2 weeks in our simulation runs (Ezanno et al., 2007). *PI*, *TI*, and *N* denote the number of *PI*, *TI*, and total animals, respectively; e.g., $PI_{\text{heifers,x}}$ indicates the number of heifers whose infection status is *PI* in the *x*-th herd. For vertical transmission, only *TI* or *PI* pregnant heifers and lactating cows can carry *PI* offspring in our model. The offspring from *PI* animals are always *PI*. *TI* cows carry *PI* offspring (*TI* becomes *CP*) when the infection timing is early to mid-pregnancy (weeks 7–22) (Brownlie et al., 1987), otherwise *TI* carries *M*. *TI* cows obtain life-long immunity against BVDV (Brownlie et al., 1987; Young et al., 2006; Liebler-Tenorio et al., 2004), we assumed no re-infection for *TI* animals in our model. The infectious period is assumed to be 2 weeks for *TI* and life-long for *PI* animals, similar to the setting in the previous study (Ezanno et al., 2007). We assumed that there was an endemic equilibrium and the BVDV transmission dynamics have reached an endemic equilibrium at the initial time point of the simulations. To this end, we started the simulation runs with the frequency of transiently infected cows = 0.001, the frequency of PI cows = 0.02 and other cows denoted as R for all herds, and discarded the first four years to obtain the initial condition. We set 2 weeks as the unit time. The development of the model and all subsequent analyses were performed using the statistical software R 3.1.3 (R Development Core Team, 2015).

Movement of animals

Parameter values describing the movement patterns of cows were determined based on the current situation in Hiyama and Nemuro, sub-regions of Hokkaido (Table 1 and 2), using data from each sub-region provided by the Hokkaido government. We modeled two movement patterns: i) movement of animals between herds (the common pasture is not included), and ii) movement of animals between the herd and the common pasture. We parameterized the movement of animals between herds based on field data as shown in Table 2. Animals that moved between herds and destination herds were randomly selected. For movement between herds and the common pasture, animals move to the common pasture at the beginning of May and return to their herd at the end of October. The herds using common pastures are fixed over time; constant herds used common pastures. The proportions of herds using common pastures were 0.31 for Nemuro and 0.21 for Hiyama. Based on the situation in Japan, the animals moved to common pastures in the model includes only young heifers. Young heifers moving to the common pasture are determined randomly with probabilities of 0.19 for Nemuro and 0.32 for Hiyama. Both movement patterns were independent of the infection status of animals.

Herd demographics

In addition to the classification according to infection status and herds, cattle were classified into five groups according to age and reproductive status to describe the herd demographics. The duration of each class and the mortality rate in each class are summarized in Table 3. We modeled the birth of calves deterministically; cows over 15 months old (pregnant heifers or dry cows) become pregnant once per year. At birth, newborn calves are PI or M. M describes animals protected against BVDV infection by maternal antibodies. The length of protection by maternal antibodies is parameterized as 84 days by the field data (Palfi et al., 1993). After this period, M animals become S animals and can be infected with BVDV. At the same time, newborn calves become heifers, and the duration before breeding is 280 days. After insemination, all young heifers moved to the pregnant first-calf heifer group for 280 days. Thereafter, a calf was born and the dam moved to the lactating cow group for 304 days and then to the dry cow group for 60 days. At the end of the dry period, a new calf was born and the dam moved to the lactating cow group again. The maximum cow lifespan in this model was assumed to be 7 years because dairy cattle are usually slaughtered at approximately 7 years of age in Japan. We assumed that breeding occurred constantly throughout the year based on the situation in Japan. The mortality rate of PI and non-PI animals were based on the field data of mean mortality rate of the entire cattle population in Japan during five years, which was obtained from the Japanese Ministry of Agriculture, Forestry and Fisheries (Table 3). We included only female cows in the model; males (50% of newborn animals) were assumed to be sold or culled within 14 days after birth.

Intervention

In this study, we assessed the effectiveness of two types of interventions, vaccination and testing and culling. We assumed that all cows in the herd were vaccinated if the herd used the vaccination strategy, and revaccination was repeatedly conducted to maintain protection by the vaccine. Vaccination scenarios assumed that all herds used vaccination. The vaccine efficacy was assumed to be 80% (Newcomer et al., 2015), and the infection probability λ among vaccinated animals was consequently reduced by 80%. For culling, we assumed that animals were tested by RT-PCR for adults or by antigen Enzyme-Linked Immunosorbent Assay (ELISA) testing using ear notch samples for calves, and that positive PI animals were culled. Both tests are set to have the same performance. The sensitivity and specificity of RT-PCR and ELISA were considered to be 99% and 100% for detecting PI animals, respectively (Presi et al., 2010). The timing of culling was dependent on the strategy, as described below.

BVDV control strategies

In Hiyama and Nemuro, all animals that graze on common pastures must be vaccinated. Furthermore, all animals are tested for BVDV before entering common pastures in those regions. RT-PCR and/or virus isolation of BVDV from the blood are considered suitable diagnostic techniques for BVDV infection in Japan, and positive animals cannot enter common pastures. To assess the strategies including the current strategy used in Hiyama and Nemuro, we constructed nine scenarios (Table 4) for simulation using our model. The baseline scenario consisted of no control program (S1). In S2, all animals that moved to common pastures were tested by RT-PCR using blood samples for adult animals before moving to common pastures, and positive animals were culled. In S3, all animals were vaccinated before entering common pastures. In S4, all animals that moved to common pastures were tested before moving to common pastures and positive animals were culled, and all animals were vaccinated before entering common pastures. In S5, all calves were tested by ELISA at the time of birth and positive animals were culled. In S6, all animals over 6 months of age (young heifers, pregnant heifers, lactating cows, and dry cows) were vaccinated with killed vaccine once per year. S7 is the combination of ELISA testing of all calves and vaccinating all animals over 6 months of age. S8 is the combination of antigen ELISA testing of all calves and vaccinating all animals moving to common pastures. In S9, animals moving to common pastures were tested by RT-PCR and animals over 6 months of age were vaccinated.

The effectiveness of interventions was measured by the prevalence of PI animals at the end of the 10-year simulation period. To compare scenarios, 1,000 iterations in each scenario were compared by pairwise Wilcoxon rank sum tests. P values <0.05 were considered statistically significant.

Results

The results of the different BVDV control scenarios were similar in both Hiyama and Nemuro

(Fig. 2). The prevalence of *PI* animals with no control intervention (S1) fluctuated seasonally based on summer pasture use for 10 years in this model (Fig. 2 and 3). In simulation modelling of the current strategies in Hokkaido, the prevalence of *PI* animals gradually decreased by testing and culling (S2), vaccination (S3), or the combination of testing and culling all animals moving to common pastures and vaccinating all animals moving to common pastures (S4), compared to the no control scenario (S1) (Fig. 2A and 2B). However, testing and culling of positive calves (S5) resulted in a dramatic decrease in the prevalence of *PI* animals to almost eradicated levels (Fig. 2C and 2D). Vaccinating all susceptible adult animals (S6) also reduced the number of *PI* animals (Figure 2C and 2D). The combination strategies, i.e., testing and culling all positive calves and vaccinating all susceptible adult animals (S7) and testing and culling all positive calves and vaccinating all animals moving to common pastures (S8), yielded similar results to those obtained from the single strategy of testing and culling all positive calves (Fig. 2E and 2F). The combination strategy of testing all animals moving to common pastures and vaccinating all susceptible adult animals (S9) also showed similar results to the single strategy of vaccinating all susceptible adult animals (Fig. 2E and 2F). At the 10-year time point an important and significant decrease in the prevalence of PI animals in comparison with no control was demonstrated for the following strategies: testing and culling all positive calves (S5), vaccinating all susceptible adult animals (S6), and combinations thereof (S7–S9) (Fig. 4). Although a statistically significant decrease was found also for S2 and S4 after 10 years, the prevalence of PI animals was still at sufficiently high levels to discard these as relevant options for control. We then assessed the sensitivity of the proportion of herds participating in the interventions S5 and S6 in Nemuro. Changes in the proportions of herds participating in S5 and S6 control programs influenced the prevalence of *TI* and *PI* animals at the herd level (Fig. 5). In both scenarios, the prevalence of *TI* and *PI* animals decreased as the proportion of participants increased. When 100% of herds participated, S5 and S6 strategies markedly reduced *TI* and *PI* prevalence at the herd level (Fig. 5A and 5B). We also assessed the effectiveness of the intervention "test and culling all calves" with the varied sensitivity of ELISA (Fig. 6). If the sensitivity of ELISA is not high enough, the intervention cannot eradicate the BVDV epidemic within ten years from the beginning of intervention.

Discussion

Epidemiological models allow investigation of projected dynamics of virus spread and various control strategies (Ezanno et al., 2007; Ezanno et al., 2008; Innocent et al., 1997; Sorensen et al., 1995; Viet et al., 2007; Gunn et al., 2004; Viet et al., 2004). In the current study, we established a stochastic model of within- and between-dairy herd BVDV infection dynamics, including the effects of common pasture use, based on general and epidemiological data from Hokkaido. In general, movement of animals is of most importance for the spread of BVDV infection between herds on a global scale. The use of common pastures is also one of the risk factors for the spread in areas where common pastures are used frequently (Bitsch et al., 2000; Rossmanith et al., 2005; Valle et al., 1999); thus, it is important to consider the use of common pastures in modelling.

If animals are in early pregnancy during pasture and become infected, then their offspring become *PI* calves. Newborn *PI* calves can then spread the virus within their own herd at the end of the summer season. *PI* calves born in the grazing period in common pastures are also important. Trojan *PI* animals are an issue regardless of common pasture use. Movement of animals between herds is another risk factor for BVDV spread. Introduction of infected animals into an uninfected herd results in the spread of BVDV to the previously uninfected herd. In endemic areas for BVDV, the prevalence of *PI* animals in the standing cattle population has been reported to remain approximately 0.5–2% (Houe, 1999). This is considered to be due to the balance between new persistent infections and removal of PI animals. The prevalence of *PI* animals in Japan was 0.12% in the pilot survey performed in other regions in 2014 (Kameyama et al., 2016). The low prevalence of *PI* has been observed in previous studies, but that currently there are no good explanations for this. Further studies might help to understand BVDV situation in Japan.

We evaluated the BVDV control strategies in two sub-regions of Hokkaido, Hiyama and Nemuro, using stochastic modelling. Dairy farming is the main industry in Nemuro, and there are more herds in this region than in Hiyama. However, the results of our simulations were similar between Hiyama and Nemuro. These results indicate that a common BVDV control strategy could be used in both areas. The current strategy of targeting animals moving to pasture with the combination of testing and culling and vaccination (S4) significantly reduced the number of BVDV infected animals in our model, but not too a sufficiently low level to achieve control or eradication. Likewise, the other current strategies of targeting animals moving to pasture, i.e., testing and culling (S2) and vaccination (S3) also significantly, but not sufficiently, reduced the number of BVDV infected animals compared with no control. This is likely because the numbers of tested or vaccinated animals were insufficient to control BVDV transmission. The proportions of animals moving to common pastures were very low in both areas and fewer animals moving to common pastures resulted in fewer animals being tested or vaccinated. Hence, the effect of control strategies targeting only pastured animals on the prevalence of PI animals in Hokkaido is only limited. Certainly the use of common pastures is a risk factor for spreading BVDV between herds; however, farm management situations differ between each farm, area, or country. Therefore, it is important to control risk factors according to individual herd situations. Our results suggest that testing all calves and culling the positive ones (S5) is an effective control method. Elimination of *PI* animals is a rapidly effective means of controlling BVDV within a herd. In Switzerland, a national BVDV eradication program launched in 2008 (Presi and Heim, 2010). All calves must be ear notched and the ear tissue tested using the antigen ELISA test for BVDV within 5 days of birth, and all positive calves are culled. This compulsory eradication program has resulted in a reduction in the prevalence of *PI* animals in Switzerland (Presi et al., 2011). However, combining S5 with the strategies in other scenarios is unlikely to produce a synergistic or additive effect because the test sensitivity is very high. The effectiveness of S5 depends primarily on the participation rate of the herds in this BVDV control program. The Swedish program was voluntary for almost 10 years before it became compulsory (Hult and Lindberg, 2005; Lindberg et al., 2006; Lindberg and Alenius 1999). Compulsory control approaches are biosecurity based and aim to prevent introduction of the infection into uninfected herds, eliminate *PI* animals from infected herds, and rapidly detect new infections (Lindberg et al., 2006). These approaches have been successful in BVDV control (Hult and Lindberg, 2005); however, compulsory testing and culling of all positive calves is costly and requires significant manpower. Therefore, bulk milk testing should be used to establish herd status before individual testing. Then, in infected herds, all animals should be tested using ear notch or blood samples. The results of our model showed that vaccination of all adult animals (S6) could also effectively lead to BVDV control even without culling *PI* animals. Though *PI* animals are not actively removed, they leave the herd by natural means. This suggests that the role of vaccination is to prevent new infection, while testing and culling calves directly decreases the number of *PI* animals. Although the prevalence of *PI* animals decreased slowly in S6 compared with S5, it was sufficient for BVDV control through vaccination.

The optimal vaccine strategy has been greatly debated. A meta-analysis on the efficacy of BVDV vaccination to prevent reproductive disease was conducted, which showed that fetal infection was decreased by over 80% with killed vaccine (Newcomer et al., 2015). Live vaccine was more efficient in fetal infection than killed vaccine. We similarly would not expect a synergistic or additive effect if the control strategy in S6 were combined with other strategies targeting pastured animals (as in S9). Though *PI* animals are not actively removed in S6, 100% of herds participated in the vaccination program, drastically reducing *TI* and *PI* prevalences. This would be effective to control BVDV, which suggests that herd immunity contributes to the effectiveness of this strategy as a BVDV control measure. If a sufficient proportion of the population is vaccinated and immunized, then the potential for contact between infected and susceptible animals decreases and the epidemic fails to spread (Garnett, 2005). However, eradication of BVDV has never been achieved in practice in spite of many decades of vaccinations. The vaccination effectiveness could be reduced by low vaccine coverage, low quality of vaccine and improper use of vaccine. Taking into account these issues is required to evaluate the vaccination effectiveness in practical settings. Because each control strategy has advantages and disadvantages, it is important to find the right balance between testing and culling and vaccination to control or eradicate BVDV. Rapid reduction of *PI* animals may not necessarily be the correct strategy when considering the cost of *PI* animal testing, *PI* animal removal, vaccination, and manpower needed for these strategies. Measures should be selected according to the situation. Furthermore, a compulsory program is necessary for BVDV control/eradication programs to ensure their effectiveness.

Our study has several limitations. In this study, we focused the evaluation of control program on the dairy farms with common pasture since those programs have been implemented on the dairy farms. If non-dairy farms were involved in the programs, it would need to be considered. In addition, other “hot spots” for BVDV transmission, e.g., livestock markets and exhibitions, are also important for the BVDV transmission modelling. The time trend of demographic changes, e.g., the number of dairy herds decrease but the average herd size increases, is also important for the quantitative assessment of BVDV interventions. Our model did not take into account the heterogeneity of the daily herd network with respect to geographical distance, social preferences between herds, and seasonality of animal movement due to the difficulty in obtaining the data. These heterogeneities may affect to our results.

In conclusion, stochastic modelling allows us to predict the extent and duration of infection and evaluate the efficacy of control strategies. The results indicate that the current strategies for BVDV control in Hokkaido slightly reduced the number of BVDV infected animals; however, alternative strategies such as testing all calves and culling any positives or vaccinating all susceptible adult animals drastically reduced those in this region. The proportion of herds participating in the intervention is also a major driver of success for BVDV control. These findings give us the opportunity to reconsider BVDV control strategies and highlight the importance of using control measures that have been proven effective.

Abbreviations

BVDV: bovine viral diarrhea virus
PI: persistently infected
TI: transiently infected
RT-PCR: reverse transcription polymerase chain reaction
ELISA: enzyme-linked immunosorbent assay

Declarations

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

SS, PP, NI, and YS designed the simulation study. PP and RO designed the mathematical model. SS and RO performed the simulations and drafted the manuscript. KS, MS, YY, TU, HN, and YF participated in epidemiological analyses and critically reviewed the paper. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Schematic representation of BVDV transmission dynamics within a dairy herd. Cattle were divided into one of five age categories (calves, heifers, pregnant first-calf heifers, lactating cows, and dry cows). Cattle were also classified into one of six BVDV-related health status groups (*M*: maternal antibody protection; *S*: susceptible animals; *TI*: transiently infected animals; *PI*: persistently infected animals; *CP*: recovered cows still carrying *PI* animals; *R*: other recovered animals; and *V*: vaccinated animals). Dashed line indicates the birth of cows.

Figure 2 Changes in the prevalence of PI animals over a 10-year period. Nine different BVDV control scenarios in Hiyama (left column) and Nemuro (right column) were evaluated. S1: no control. S2: testing all animals moving to common pasture and culling all positives. S3: vaccinating all animals moving to pasture. S4: a combination of testing all animals moving to pasture and culling all positives and vaccinating all animals moving to pasture. S5: testing all calves and culling all positives. S6: vaccinating all adult animals. S7: a combination of testing all calves and culling all positives and vaccinating all adult animals. S8: a combination of testing all calves and culling all positives and vaccinating all animals moving to pasture. S9: a combination of testing all animals moving to pasture and culling all positives and vaccinating all adult animals.

Figure 3 Change in the average prevalence over 10 years of PI and TI animals in Nemuro. The common pasture enhances the prevalence of TI and PI animals during its season when no intervention is conducted.

Figure 4 Boxplot of the prevalence of PI animals at the 10-year time point. Nine different BVDV control scenarios in Hiyama (A) and Nemuro (B) were tested. S1: no control. S2: testing all animals moving to common pasture and culling all positives. S3: vaccinating all animals moving to pasture. S4: a combination of testing all animals moving to pasture and culling all positives and vaccinating all animals moving to pasture. S5: testing all calves and culling all positives. S6: vaccinating all adult animals. S7: a combination of testing all calves and culling all positives and vaccinating all adult animals. S8: a combination of testing all calves and culling all positives and vaccinating all animals moving to pasture. S9: a combination of testing all animals moving to pasture and culling all positives and vaccinating all adult animals.

Figure 5 Changes in the prevalence of PI animals at the herd level in Nemuro. The proportion of herds participating in S5 and S6 changed. A: Prevalence for 0% (black), 25% (green), 50% (brown), 75% (blue), and 100% (gray) of herds participating in a program that tests and culls all calves. B: Prevalence for 0% (black), 25% (green), 50% (brown), 75% (blue), and 100% (gray) of herds participating in a program that vaccinates all adult animals.

Figure 6: The effectiveness of "test and culling all calves" with varying the sensitivity of ELISA. The effectiveness was measured by the prevalence of TI and PI animals in the Nemuro setting. Prevalence for 60% (black), 70% (green), 80% (brown), 90% (blue), and 99% (gray) of sensitivity in a program that tests and culls all calves.

Table 1 Farm structure in Nemuro and Hiyama. The herd size and the number of animals in each age group per herd indicates its average in Nemuro and Hiyama. All values are derived from statistics data of Hokkaido government.

		Nemuro	Hiyama	Reference
Total herds		1500	62	Hokkaido government
Total animals (heads)		189000	3472	
Average herd size (animals/farm)		126	56	
Number of animals in each age group per herd (heads)	Calves	23	5	
	Young heifers	11	3	
	Pregnant heifers	8	8	
	Dry cows	28	8	
	Lactating cows	56	32	

Table 2 Parameters regarding the movement of cows in Nemuro and Hiyama. The proportion of animals moving between herds and those in each category per year indicate average in Hokkaido. Only young heifers are sent to common pasture for 6 months in Japanese farming system. All values are derived from statistics data of Hokkaido government.

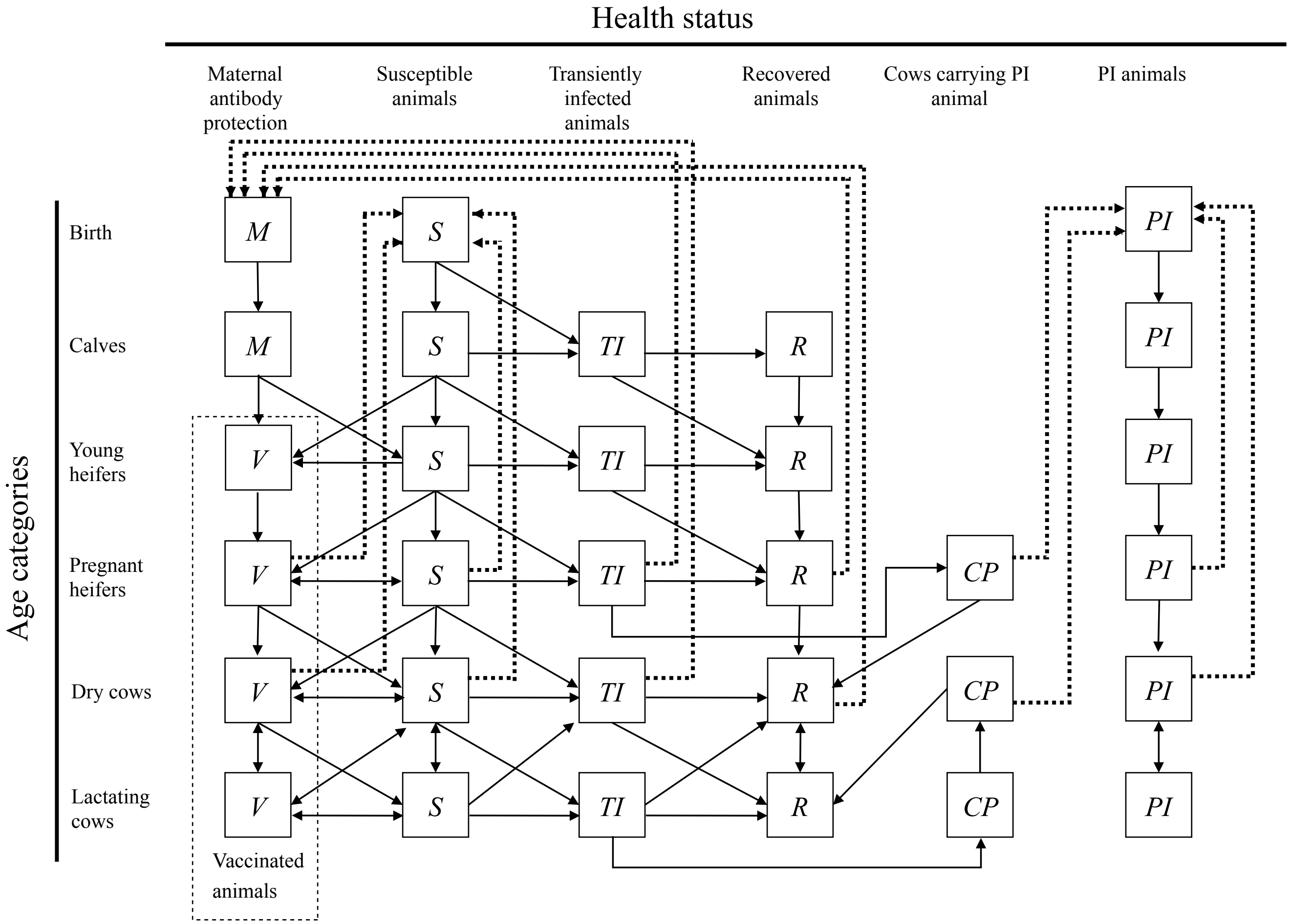
		Nemuro	Hiyama	Reference
The proportion of animals moving between herds per year		0.2	0.2	Hokkaido government
The proportion of animals moving between herds in each age category per year	Calves	0.19	0.19	
	Young heifers	0.08	0.08	
	Pregnant heifers	0.16	0.16	
	Lactating and dry cows	0.57	0.57	
Period of time for the common pasture per year (months)		6	6	
Number of common pasture		11	1	
Number of farms using one pasture (herds/pasture)		42	13	
The proportions of herds using common pastures		0.31	0.21	
Proportion of animals going to pasture per farm		0.19	0.32	
Age group of the animals in common pasture		Young heifers	Young heifers	

Table 3 Mortality rate (including slaughter per 2 weeks) and duration in each class of cows. The mortality rate of non-PI or PI per 2 weeks are derived from statistics data of Japanese Ministry of Agriculture, Forestry and Fisheries.

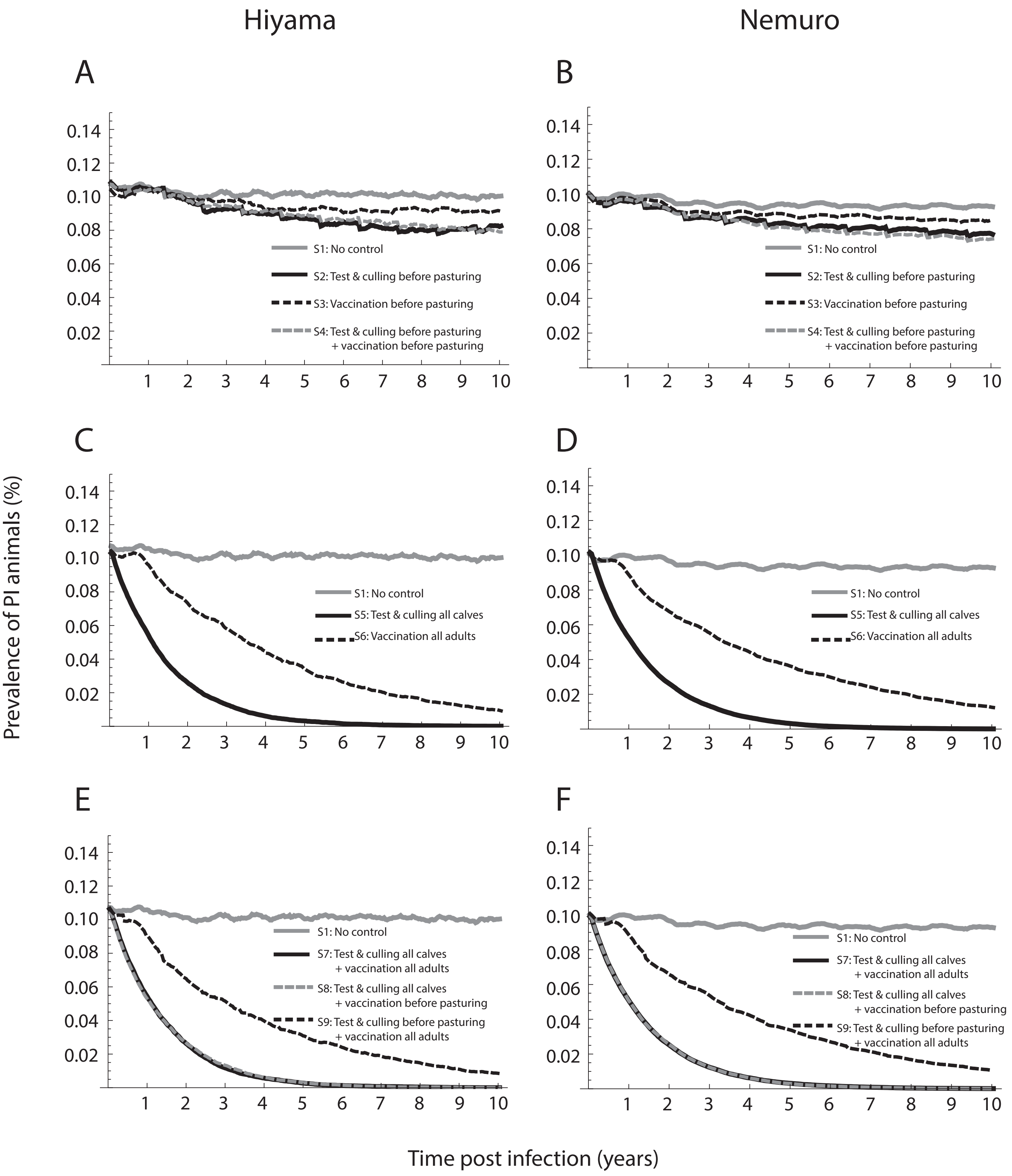
Class	Duration	Mortality rate of non-PI per 2 weeks	Mortality rate of PI per 2 weeks	Reference
Birth	14 days	0.0012	0.0273	Japanese Ministry of Agriculture, Forestry and Fisheries
Calves	182 days	0.012	0.0273	
Young heifers	280 days	0.0057	0.0273	
Pregnant heifers	280 days	0.002	0.0273	
Dry cows	60 days	0.004	0.0273	
Lactating cows	304 days	0.004	0.0273	

Table 4 BVDV control scenarios. Nine different scenarios were evaluated. +: selected; -: not selected. S1: no control; S2: all animals that moved to common pastures were tested by RT-PCR before moving to common pastures, and positive animals were culled; S3: all animals were vaccinated before entering common pastures; S4: all animals that moved to common pastures were tested before moving to common pastures and positive animals were culled, and all animals were vaccinated before entering common pastures; S5: all calves were tested by ELISA at the time of birth and positive animals were culled; S6: all animals over 6 months of age were vaccinated with killed vaccine once per year; S7: the combination of ELISA testing of all calves and vaccinating all animals over 6 months of age; S8: the combination of antigen ELISA testing of all calves and vaccinating all animals moving to common pastures; S9: animals moving to common pastures were tested by RT-PCR and animals over 6 months of age were vaccinated.

	Test & culling		Vaccination	
Scenario	All calves	All animals pasturing	All adults	All animals pasturing
S1	-	-	-	-
S2	-	+	-	-
S3	-	-	-	+
S4	-	+	-	+
S5	+	-	-	-
S6	-	-	+	-
S7	+	-	+	-
S8	+	-	-	+
S9	-	+	+	-



Sekiguchi et al. Figure 1



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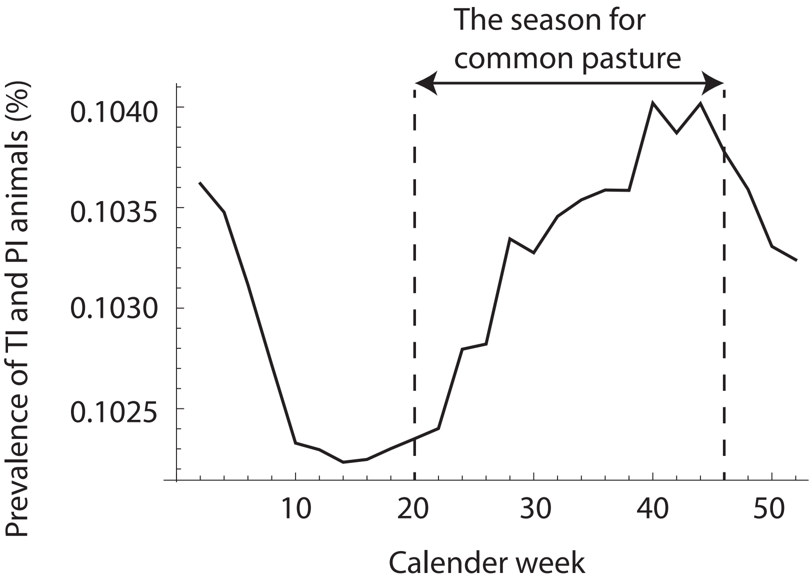

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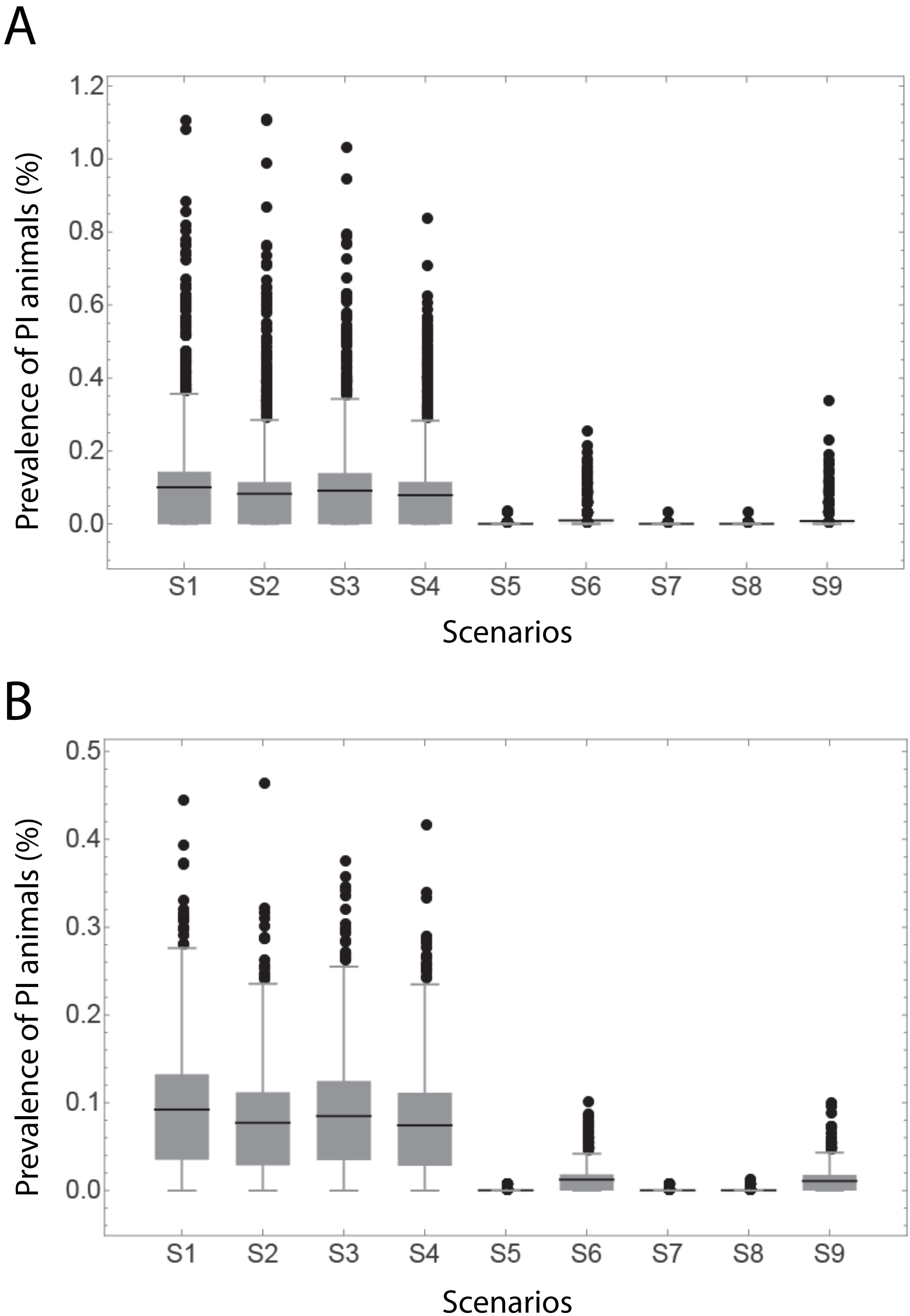

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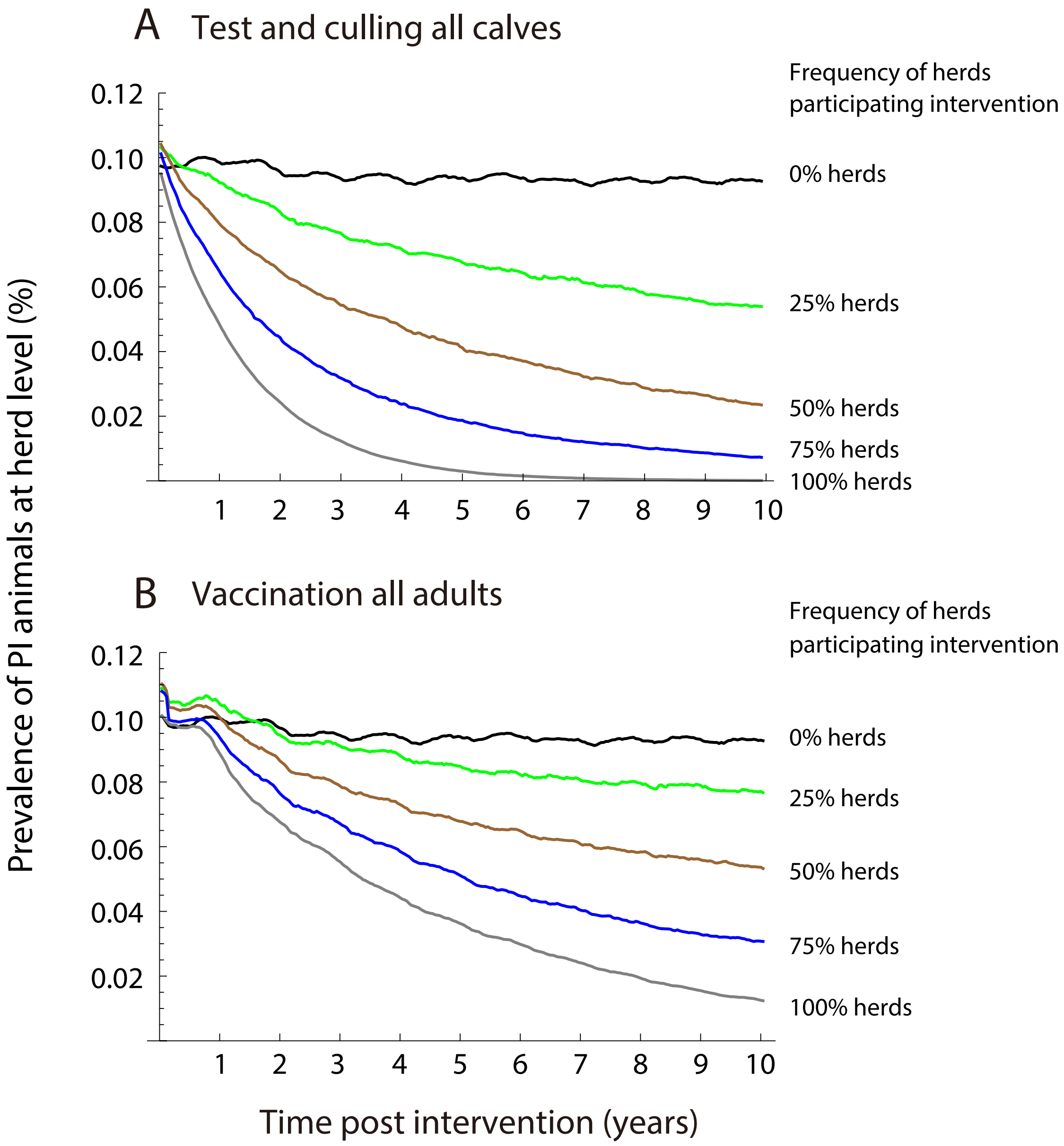

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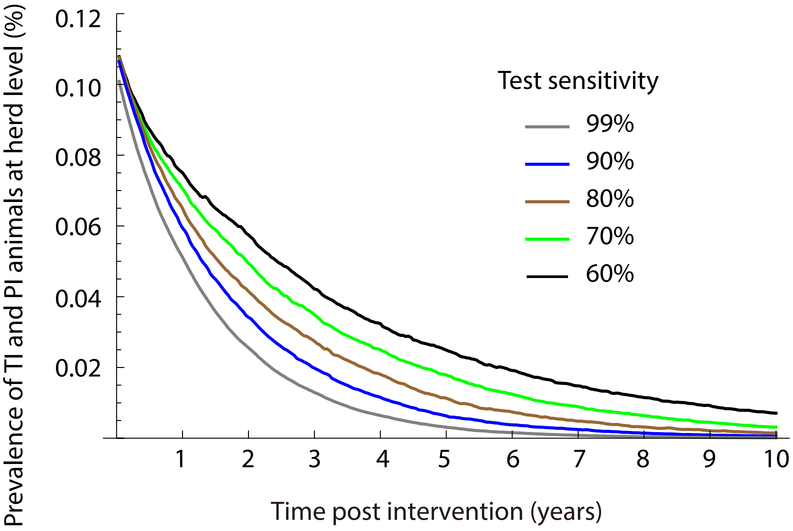

Sekiguchi et al. Figure 6