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Individual-based model for the control of Bovine Viral Diarrhea spread in livestock trade networks

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Abstract

Bovine Viral Diarrhea (BVD) is a cattle disease that causes substantial financial losses, in particular to the dairy industry. Hence, several countries including Germany introduced compulsory disease control programs. For the case of Germany in particular, all animals had to be tested and persistently infected animals (PI animals) were removed from the population. The program was successful in reducing the number of PI animals, but was overtly expensive. Alternative approaches were therefore discussed to eliminate the remaining PI animals and alter the testing system in order to reduce costs. Contributing to these efforts, we developed an agent-based model that aimed to cover all relevant aspects of the disease biology and would allow to evaluate different control strategies. For the biological part of the infection spread, the model includes horizontal and vertical transmission, transient and persistent infections. Moreover, several control strategies including import of animals, trade restrictions, vaccination, as well as various testing schemes were included. The model was furthermore defined to be stochastic, event driven and hierarchical, with cattle movements as the main route of spreading between farms. For the spread within farms, we included susceptible-infected-recovered (SIR) dynamics with an additional permanently infectious class. The interaction between the farms was described by a supply and demand farm manager mechanism governing the network structure and dynamics. Additionally, we carried out a sensitivity analysis of the input parameters to study the impact of extreme values on the model. Since the population size in the model is limited, we tested the influence of the initial population size on the model results. Our results showed that the model could accurately describe the dynamics of the disease in the presence and absence of disease control. Although we developed the model for the spread of BVD, it may be adapted to similar diseases of cattle and swine.

1. Introduction

Contagious disease containment in the form of some intervention strategy, e.g., testing or immunization practices, is among the goals of any biosecurity program. In the last decades efforts on the behalf of governments have been implemented at country levels for the purpose of contagious disease containment in live-stock, especially for the case of the European Union, with the advent of integrated union policies. A major contagious disease that has been afflicting the cattle industry is *Bovine Viral Diarrhea* (BVD) (Greiser-Wilke et al., 2003; Ståhl and Alenius, 2012; Gethmann et al., 2015).

The impact of BVD on the cattle industry, both beef and dairy, is immense due to losses in animals and, in the dairy sector, reduced milk yield. Several studies estimated the economic losses between 9.2 and 133 EUR per cow and year (Valle et al., 2005; Houe, 2003; Gunn et al., 2005; Fourichon et al., 2005), while Bennett (2003) estimates the costs for the United Kingdom between 34 and 86 million EUR per year.

Due to the economic consequences of BVD, several countries implemented contagious disease control systems (Lindberg et al., 2006; Metcalfe, 2019; Ståhl and Alenius, 2012; Moennig et al., 2005; van Roon et al., 2020). These countries applied different control strategies or modified them over time (Lindberg et al., 2006; Metcalfe, 2019; Ståhl and Alenius, 2012; Moennig et al., 2005).

Several studies explored the impact of BVD and the respective containment practices and their potential for the economy for different countries (Greiser-Wilke et al., 2003; Ståhl and Alenius, 2012; Santman-Berends et al., 2015; Pinior et al., 2017).

The aim of these studies were to analyze the in-herd dynamics in an aggregated fashion regarding animal population (Damman et al., 2015), or to explore the empirical network effect of cattle movements on BVD spread with simple dynamics (Tinsley et al., 2012). Some of them combined the two aforementioned elements in metapopulation models generically (Courcoul and Ezanno, 2010) and in a multiscale, data-driven fashion (Italy) (Iotti et al., 2017; Iotti et al., 2019) to predict the spatial spread of BVD aiming to investigate several intervention strategies. Others also formulated expert systems to test present and potential policies based on data-driven simulations (Ireland) (Graham et al., 2016; Thulke et al., 2017). Furthermore, data-driven assessments of policies against BVD and their financial impact have been performed for Austria (Marschik et al., 2018), and scrutinized for Germany (Gethmann et al., 2019).

For the specific case of Germany, a compulsory BVD control program has been in place since 2011. The program is based on detection and removal of PI animals from the population. Therefore, animals are examined for BVD infection by ear notch or blood testing shortly after birth, or before they are moved to a different farm (Wernike et al., 2017). Only animals that tested negative for BVDV may be transported. Since the beginning of the compulsory BVD program, the PI prevalence was reduced from about 0.4% to less than 0.02% (Wernike et al., 2017). The current regulations on the containment of BVD are based on the mandate issued implemented in 2011. It has focused on the detection and removal of persistently infected (PI) animals by testing calves with an antigen or virus detection test soon after birth (Ministry of Food, 2008). Anamendment was introduced in 2016 stipulating a quarantine of 40 days on farms suspected of harboring PI animals after testing (Ministry of Food, 2016).

As the current BVDV control program is expensive due to the high number of animals to be tested, the Federal Ministry of Food and Agriculture commenced an investigation, whether the current program would lead to a free population and whether there could be an alternative strategy (a combination of several control measures) that would be better regarding costs and effectiveness. To address this question we decided to develop an individual, agent-based model with the following requirements:

- to model the cattle population on animal level, including birth, deaths, and slaughters,
- to model the cattle trade for the population based on existing trade data,
- to model the spread of BVDV in the population (within and between farms), taking into account different compartments: susceptible (S), transiently infected (TI), persistently infected (PI), recovered (immune, R), vaccinated (V), and animals with maternal antibodies (MA),
- to model different control strategies, like testing and removal, vaccination, trade control, or combinations of these strategies, and
- to include daily time steps.

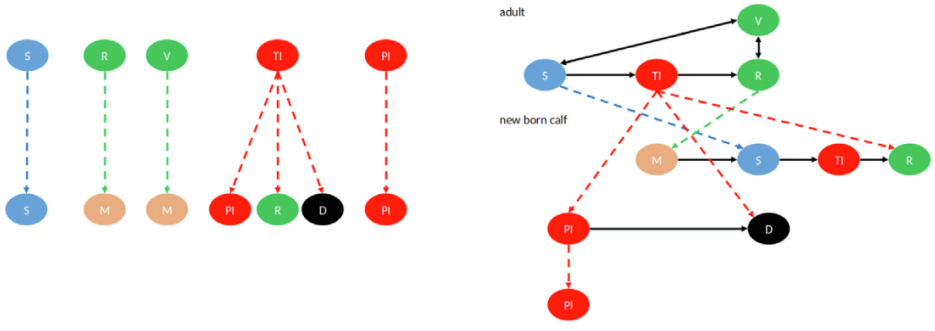
With the current work, we aim to employ the refined approach of an agent-based model for the combined dynamics of animal movements and in-herd infections as opposed to aggregate methods (Bosse et al., 2012). This modelling approach allows for a great level of detail to be included in the system. The model is flexible and allows testing combinations of different control measures (strategies) aiming at BVDV eradication. With some changes in the disease spread parameters, the model may be adapted to other diseases.

2. Materials and methods

Model development In this section, we describe the technical aspects as well as the biological background of the model. All the related details following the ODD (Overview, Design concepts and Details) protocol (Grimm et al., 2010) can be found in a technical work of ours on the subject (Bassett et al., 2018).

As a first step, we analyzed the German cattle trade database regarding (1) age distributions of male and female cattle, (2) farm size distribution, (3) cattle trade, (4) PI prevalence, and (5) age distribution of PI animals. We carried out a literature review and collected data for the BVDV spread within farms (Viet et al., 2004). Furthermore, we discussed the following infectious parameters with experts: (1) number of animals that are infected by one PI or TI animal, (2) the consequence of infection during pregnancy, (3) the survival time of PI animals, and (4) diagnostic sensitivity and specificity of the tests. This resulted in a compartmental model for the BVDV spread dynamics (Fig. 1).

Subsequently, for the simulation of BVD spread through the German cattle movement network we formulated an agent-based, stochastic, event-driven and hierarchical code in C++ (https://github.com, 2020). We decided for the model to be agent-based (the animals being agents) with the aim to capture a great level of detail as reported in Bosse et al. (2012). Furthermore,



(a) Vertical states. (b) Combined horizontal and vertical states.

Fig. 1. Transition schematics of (a) the vertical (through births) and (b) combined with horizontal (through contact) SIR-like infectious states. The dashed lines denote vertical transmission paths, i.e., from mother to calf, while the solid lines horizontal ones or the death of an animal. Note that a path to the demise of the animal is also taken into account as state "D". Additionally, the states "V" and "M" take into account temporary immunization effects induced by vaccination and protection through maternal antibodies, respectively.

we introduced hierarchy in the sense that actions could correspond to different aggregates of agents (animals), thus enabling actions for a group of animals (herd), for a node (premise) in the network and for the systems as a whole (for introducing intervention strategies). We assumed stochasticity as necessary for both breeding and infectious features, so as to model their complex, real-world fluctuations adequately. Moreover, we built the model in an event-driven fashion (Fishman, 2013) in order to benefit from the trade-off between following the trajectory of an agent in continuous time and observing it only when a relevant, previously scheduled event is executed (Vestergaard and Génois, 2015). For cattle, we defined a class that includes each event for an animal, e.g., birth date, infectious status (PI, S, R, etc.), offspring, insemination events, test dates and test result, trade events. Details can be found in Bassett (2019).

The dynamics of the model were designated in two separate processes, namely the in-farm (premise) dynamics and the animal flow (movement) between the farms. For the former, we employed the *Susceptible-Infected-Recovered* (SIR) scheme with a permanently infectious class found in Viet et al. (2004) (see Fig. 1), while for the latter, a rule that every premise should demand or offer animals only when its population lacks or exceeds certain quotas, respectively. In the case of the infectious, in-farm dynamics, wassumed well-mixed conditions, i.e., no spatial structure and equal probabilities for all the susceptible animals to be infected. Accordingly, following standard SIR dynamics we defined a stochastic, instantaneous transmission rate for the infections in question that dictated the inflow of infections in the pool of susceptible animals for each farm in a Markovian manner (Bassett et al., 2018; Vestergaard and Génois, 2015). Nevertheless, the simulation envisions in-farm partitioning into herds, which introduces hetero geneities in the in-farm infectious dynamics.

Since the BVD control strategy influences trade patterns, we could not directly use the patterns evident from cattle databases. For that reason, we opted for trade through a supply-and-demand rule for farms to buy or sell animals, which consisted of the network dynamics of the simulations. To this end, we assumed all farms to be solely dairy due to their high significance in the BVD spread in Germany[1] (Gethmann et al., 2015; Iotti et al., 2017), and supplied them with the simplest supply and demand rule

$$\text{surplus/deficit} = |N_{quota} - N_{instant}|, \tag{1}$$

i.e., the requirement that the number of animals offered or demanded (no special criterion applied for their selection) should be determined by the difference of an animal quota for each particular farm (specified upon initialization) N_{quota} with the number of animals in the farm at the time of the movement $N_{instant}$. A surplus occurs when $N_{quota} > N_{instant}$, and a deficit in the opposite case. To ascertain moreover that the system is neither dissipative nor inflationary i.e., that relation (1) is satisfied for each farm by the rest of the farms of the system, we include a source and a drain farm, which are not directly linked. These farms physically correspond to imports from outside the system, i.e., from another country and to animal exits from the system at slaughterhouses, respectively. The precise details for both the infectious and the network dynamics can be found in our technical, ODD report (Bassett et al., 2018).

In addition, the model includes system-level intervention strategies including different options for testing (animal testing for virus, spot testing for antibodies) and accordingly animal removals, non-targeted vaccination (immunization) as well as individual farm isolation (quarantine) for explicitly specified periods of time. The testings and removals were similar to the ones carried out in reality and the slight ordinance updates of 2017 were also taken into account. A tabular summary of the control measures can be found in Table S1 of the Supplementary material.

Further, we evaluated the existence of antibodies (Ab) in animal herds, accounting for the aspect of BVD control where a test takes place to sample young animals between 9 and 12 months. If the testing produces antibodies this means that an infection within the farm had ensued either by a TI or a PI animal. Therefore, we set the model so that if a positive Ab test occurs, the herd will be tested for the virus (antigen test) in order to identify the PI animal. Moreover, we included a simplified vaccination strategy, as vaccination against BVDV can be complex in reality (Moennig et al., 2005; Barrett et al., 2011). In the model we assume that young female stock will be vaccinated before the first insemination and that animals are then re-vaccinated annually. Moreover, we grouped the vaccinated animals in the immunized R compartment to simplify the analysis.

The system-wide strategy implementation prohibits a direct comparison with data recorded before 2006 in the German cattle database (*Herkunftssicherungs- und Informationssystem für Tiere*, HIT) (https://www.hi-tier.de, 2020) due to the lack of a federal mandate and thus different measures that had been applied in the various federal states. We did compare, however, the available data obtained from the HIT database with the results of the simulation model. Finally, we mention the sensitivity analysis on control parameters such as infectious transmission rate, vaccine and infectious identification (test) efficacy in Bassett et al. (2018). The related code is publicly available on GitHub (https://github.com, 2020).

Simulation setup. For setting up and initializing simulations in the model,we used expert opinion and the literature (Gethmann et al., 2015; Damman et al., 2015; Tinsley et al., 2012; Iotti et al., 2017; Ezanno et al., 2007; Hoscheit et al., 2016; Bioglio et al., 2016). The exact details for the selection of all the parameters and the distributions employed can be found in the technical description of the model (Bassett et al., 2018). The same holds for benchmarking with previous works of the literature. Here, we only mention the minimal relevant settings, a detailed description can be found at Bassett (2019).

- The simulation time has to include the initial phase as well as the testing of different control strategies. In our case, we used 20,000 or 30,000 time steps (days).
- The diagnostic sensitivity of the involved tests (antigen and antibody) was set to 99.8%, while their diagnostic specificity was assumed to be 100%.
- The probability that a vaccination would successfully immunize a susceptible animal was set to 99.85%.
- The infectious transmission coefficients for transiently and persistently infected animals, as defined in Viet et al. (2004), were set to $\beta_{TI} = 0.03$ and $\beta_{PI} = 0.5$.
- We limited the model to farm sizes greater 10 animals.
- The periodicity, with which all the farms were queried as to their population status, was set to 7 days.
- Due to an initial transient of the simulation, we set the control measures at the 10,000th time step (day) of the simulation and offset the date to 01/01/2011 to be able to compare the model with the observations.

For the initialization of the population of farms we used the farm size distribution of Thuringia as well as that of Germany as a whole. Because of computational limitations, we scaled down the farm size distribution of Germany and tested the effect of different scaling factors. Regarding the initialization of the four different states of the population in each farm, we first divided the farms

[1] Beef farms are virtually always in-nodes and thus do not contribute to the contagiousness of BVD, while mixed farms were not considered due to the one-herd, one-farm assumption for simplicity.

into two classes: those having PI animals and those devoid of them. Then we set the first class to be a total of 2% of all the farms. Furthermore, we set a 2% probability for the animals entering the system in every instance of an import from the source farm to be PI, to account for a minimal BVD spread breaching the biosurveillance border system. This feature can be annulled and we make special reference to its effect in the results. Finally, we set the states of the animals for the population of each farm to be distributed according to the following probabilities for the two classes:
$(S, TI, R, PI)_{\mathrm{PI}} = (0.46, 0.06, 0.46, 0.02)$ and $(S, TI, R, PI)_{\mathrm{PI-free}} = (0.79, 0.005, 0.205, 0)$. These figures depicted the status of BVD in Germany upon the commencement of the nationwide biosecurity measures in 2011 with a normalized population of farms and corresponding animals.

Data sets. As implied in the previous paragraph, the data-driven part of the model appeared upon the initialization with the input of a farm size distribution from a csv formatted file (Conraths and Gethmann, 2015). This file consisted of two columns of integer numbers, one standing for farm size and the other for the number of farms of this size. Each row linked the number of farms with the number of animals they corresponded to. We also scaled the German farm size distribution ($\approx 13 \times 10^6$ animals in $\approx 157{,}000$ farms) to the size of the German federal state of Thuringia ($\approx 350{,}000$ animals in $\approx 1{,}600$ farms) by a factor of ≈ 0.0279.

Identification of infected animals. The objective of any biosurveillance policy is to detect infected animals correctly. In the case of BVD the related policies focus on the detection of the PI animals through either an *antigen* or an *antibody* test (Lanyon et al., 2014). Essentially the difference of the two tests consist in the direct detection of the virus, which is permanent in the PI animals, and the appearance of BVD virus antibodies in an animal indicating its infection (therefore transient) at some past point. In our model, we included both types of tests.

Similar to the German regulation, an *antigen test* is performed in the simulation within the first week after birth of an animal (ear notch test) or before trading an animal to another farm (blood test). These tests identify infected (both transiently and persistently) animals. Once it is negative, the animal will receive a life-long status ‘‘non-PI”. If the test is positive, most of the animals will be removed from the population (slaughter, export) within a certain period. A small fraction of animals will be re-tested to exclude the probability being transiently infected. The model will give the option to vary the fraction of retested animals as well as the time between birth and testing, and the time between a positive test and removal.

The second type of testing schemes that is included in the model is the testing for antibodies. In our model, we focus on the testing of young stock, so called ‘‘spot testing” (Houe et al., 2006; Humphry et al., 2018). This is a semesterly or annual test that identifies recovered animals similar to policies in Scotland (Thulke et al., 2017; Brülisauer et al., 2010). It is performed at the specifiec times at the farm level, for a random selection of animals (Supplementary material Table S2).

3. Results

The model developed in this study is a flexible framework reflecting the behavior of BVDV in a population and allows testing various control strategies. We first describe the general model output without application of a control strategy (Section 3.1), followed by sections, in which the various control measures or strategies are analysed (Section 3.2). Finally, we compare the model output with the current BVDV control strategy to validate the model.

3.1. Describing BVDV spread without control

3.1.1. Describing the model behavior for multiple farms

After a well-understood (Rohani, 2008; Keeling, 2005) initial epidemic transient peak (after $\approx 1{,}000$ days, see Fig. 6) representing the outbreak from the initial infectious seeds within the farm level (see the initial conditions in the *Materials and Methods* section) and from in-between farms (through movements) the infectious state fractions of the system tend to an equilibrium state after about 5,000 days with a PI prevalence of around 1.1%.The number of days to reach to this stage varies slightly depending on the system size and farm structure. Thereafter, population size and trade patterns are constant in the simulation (Fig. 6).

3.1.2. Infectious variance of the model

To test the stochastic nature of the simulation we performed a sensitivity analysis on the PI prevalence percentage as a function. The model exhibited the same behavior in all simulation runs performed (100 simulations). The minimum and maximum proportion of PI animals was always within the expected range (Figs. 2, 3).

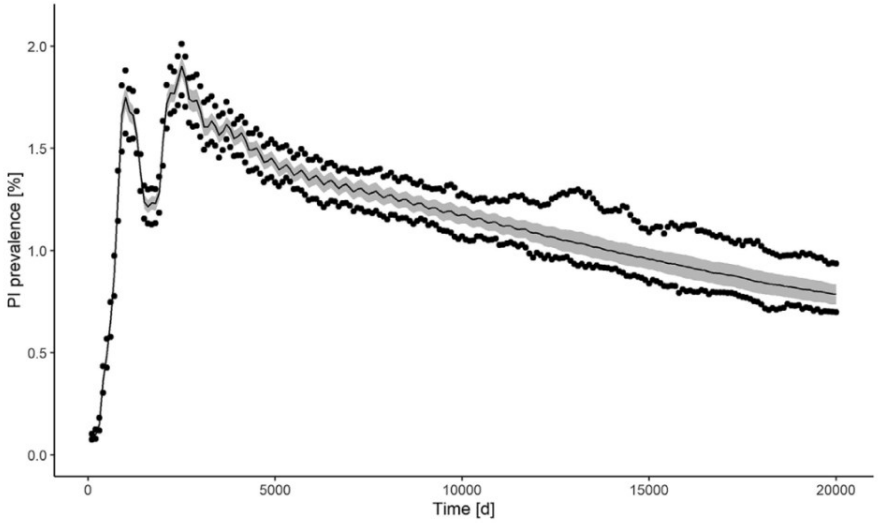


Fig. 2. Mean PI prevalence over time without control. The variance results from different simulation runs for the farm size distribution of Germany (scaled down). The line represents the mean prevalence, the dots the minimum and maximum prevalence, while the grey area the standard deviation.

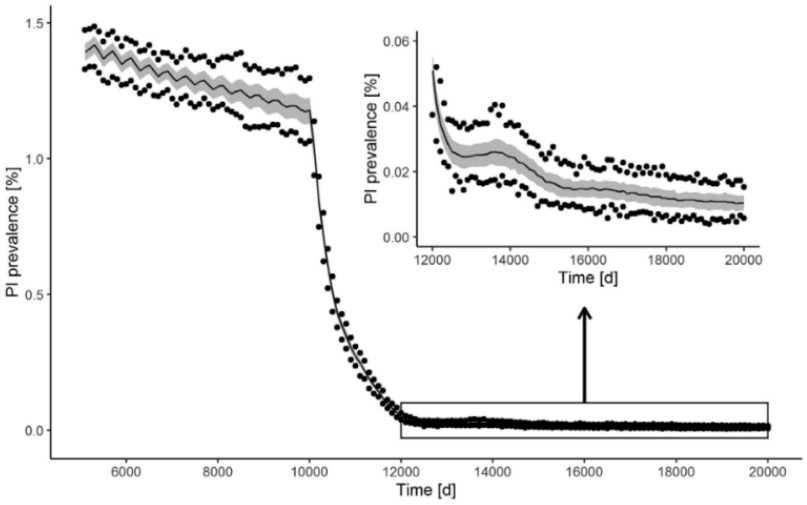


Fig. 3. Mean PI prevalence over time with the current control measures. The variance results from different simulation runs for the farm size distribution of Germany (scaled down). The line represents the mean prevalence, the dots the minimum and maximum prevalence, while the grey area the standard deviation. The inlet depicts a magnification of the last segment of the plot.

3.1.3. Influence of the population size on BVDV spread

We also tested the influence of the farm population size on the simulation outcome. We observed an increase of the PI prevalence for a system size between 1,000 and 5,000 farms. Subsequently the PI prevalence remained nearly constant (Figs. 4, 5).

3.1.4. Effect of trade on PI prevalence

When analyzing the trade patterns of the model, we realized that all the animal introductions from the source farm (''imports") for the given farm distribution, with which the simulation was initialized, ended at the 1,884th time step (10,159 introductions in total) and the last PI animal entering the system was observed at the 561st time step. To understand if the external PI amplification intensified the epidemics, we also ran the simulation for a 0% probability of PI introductions upon animals entering the system through the source farm. In that case, the introductions lasted until the 1,891st time step (10,369 of total introductions). If there were no PI introductions into the system, the epidemic peak was slightly lowered compared to that of PI animals introduced with a 2% probability. Yet, the PI prevalence remained the same in both cases by the 10,000th time step, rendering the effect of the introduction of PI animals negligible for the scenario without control. Regarding the trading patterns, we observed that most of the farms were selling the animals for slaughter compared to the trade between the farms.

3.2. Disease spread control in multiple farms

3.2.1. Model behavior for testing strategies

After the onset of the control measures (testing, removing of PI animals and trade control according to the German regulation), the PI animals were identified and removed. Subsequently, the number of PI animals in the population dropped from about 4,000 animals to less than 100. The number of recovered (R) animals dropped significantly and the respective number of susceptible (S) increased (Figs. 6, 7).

3.2.2. Effect of the test sensitivity

We also analyzed the effect of the sensitivity and specificity of the virus detection test on the PI prevalence (Section S4.3 in the Supplementary material).

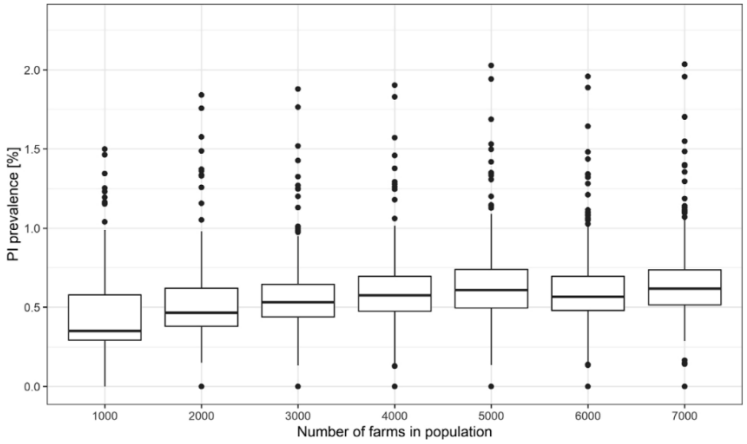


Fig. 4. Effect of the farm sizes (number of animals in a histogram fashion on the horizontal axis) on the overall distribution of the PI animals throughout the simulation with outliers.

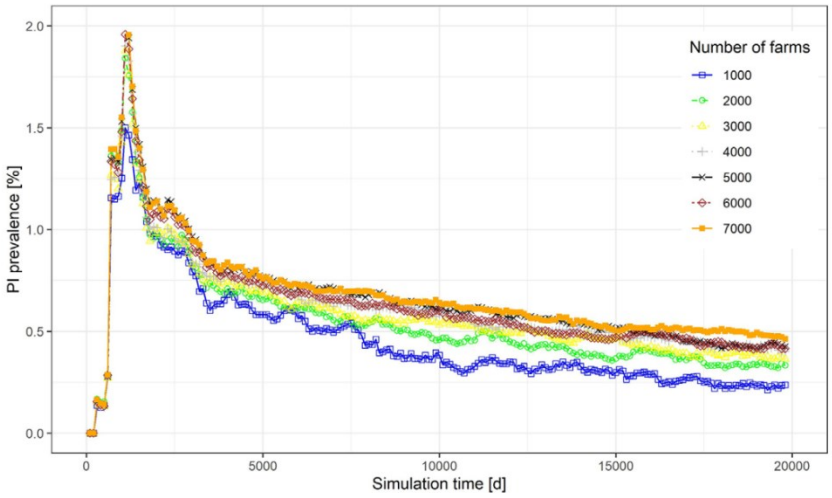


Fig. 5 PI prevalence over time for different farm sizes. Each different line depicts the PI prevalence for a farm size as per the legend.

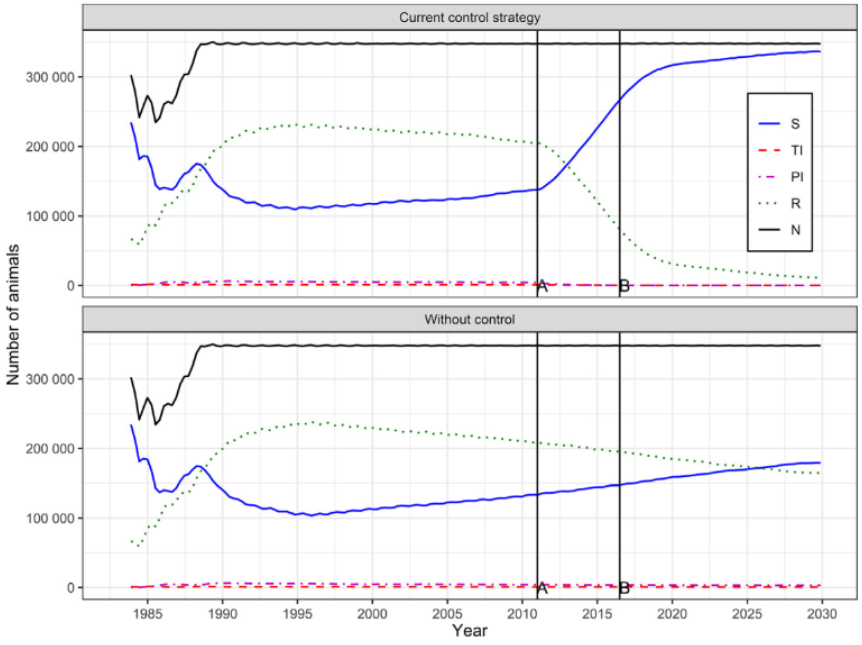


Fig. 6. Number of susceptible (S, blue solid), transiently infected (TI, red dashed), persistently infected (PI, magenta dash-dotted), recovered (R, green dotted) animals, and total (N, black solid) number of animals with and without the current control. The vertical line "A" shows the time point, when control measures are started, while the vertical line "B" shows the time point, when the German regulation was changed.

3.2.3. Model behavior for BVDV control using vaccination strategies

In our simulation, we started the vaccination in July 2017 (Fig. 8). The results show, that the number of recovered animals rapidly increased and remained at a high level. The number of TI and PI animals on the contrary remained on a low level, but did not disappear within the observed period.

Furthermore, an extensive sensitivity analysis of the effect of vaccination on the infections is presented in Section S4.4 of the Supplementary material.

3.2.4. Model behavior for BVDV control using spot testing

Throughout the simulation, we started the spot testing in July 2017 (Fig. 8). After switching to spot test strategy, there is an increase and a subsequent decrease in PI prevalence (Fig. 9). A periodicity in the PI population can be observed following the periodicity of the spot testing. The (declining) peak width of the PI population in Fig. 9 signifies the semesterly periodicity of the spot test, which is used to remove PI animals generated in the compromised period, when no testing is performed.

4. Discussion

Overall, the results presented in this study suggest that the model can accurately describe the disease spread of BVDV within a cattle population. It includes BVDV spread due to trade within and between farms. The model outcome is in line with reported

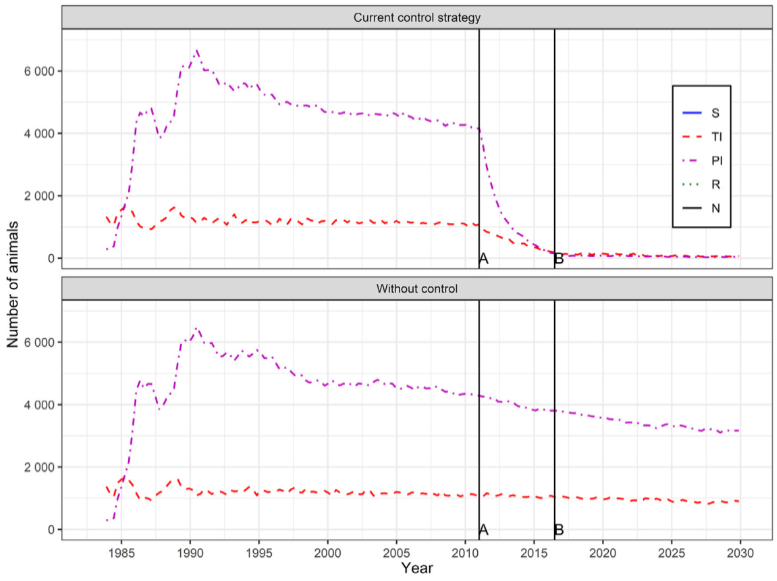


Fig. 7. Number of transiently infected (TI, red dashed), and persistently infected (PI, magenta dash-dotted) animals with and without the current control. The vertical line "A" shows the time point, when control measures are started, while the vertical line "B" shows the time point, when the German regulation was changed.

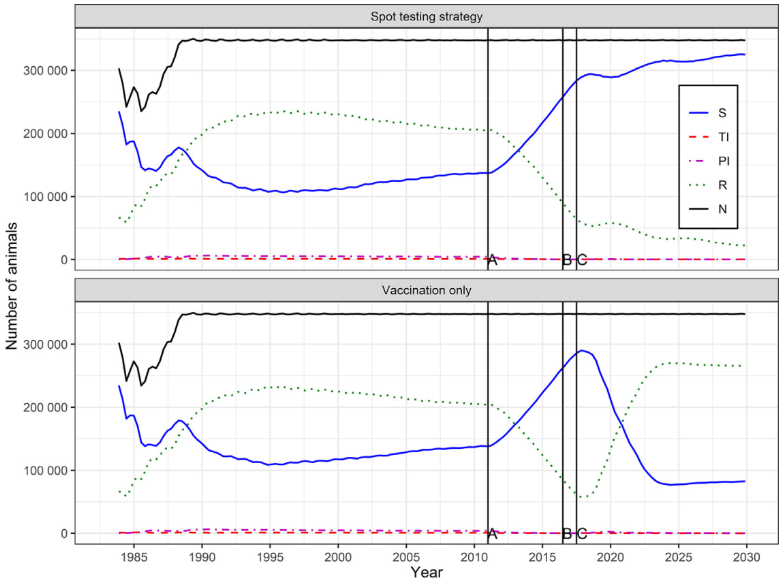


Fig. 8. Number of susceptible (S, blue solid), transiently infected (TI, red dashed), persistently infected (PI, magenta dash-dotted), recovered (R, green dotted) animals, and total (N, black solid) number of animals with and without the current control. The vertical line "A" marks the time point when control measures are started, the line "B" refers to the time point when the German regulation was changed, and the line "C" indicates when spot testing (upper panel) or the vaccination strategy (lower panel) is started.

data in the literature (Moennig et al., 2005) and observations within the German agricultural system. The model allows to perform various control measures, such as testing (ear tag, blood test, spot test), vaccination (with different vaccine efficacies) and trade control. Control measures can be implemented at any time of the model's runtime and may be combined to create control strategies. Moreover, disease parameters, e.g., mortality, and virulence (see Supplementary material) can be adapted. We applied the model to the situation in Germany and tested 13 different control strategies (Gethmann et al., 2019). As control strategies can be combined and parameters adapted to those of any other country, the model may be used for different countries and different control strategies. Since the model provides various facets of output information,e.g., the numbers of diseased, dead, traded and vaccinated animals, it

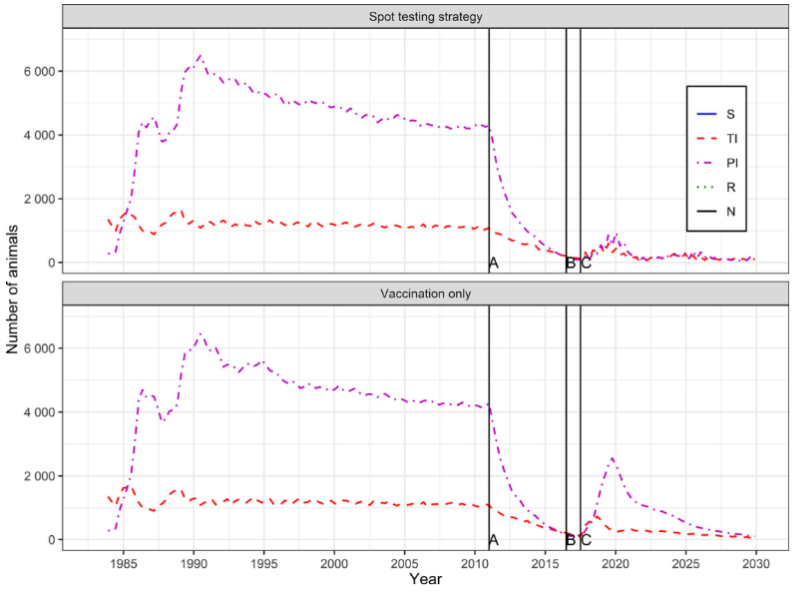


Fig. 9. Number of transiently infected (TI, red dashed), and persistently infected (PI, magenta dash-dotted) animals with and without the current control. The vertical line ‘‘A” marks the time point when control measures are started, the line ‘‘B” refers to the time point when the German regulation was changed, and the line ‘‘C” indicates when spottesting (upper panel) or the vaccination strategy (lower panel) is started.

can be used to find critical points in control systems and to compare estimates of economic calculations for different control options (cf. Refs. Gethmann et al., 2015 and Gethmann et al., 2019). The code is freely available and documented on GitHub (https://github.com, 2020). Accordingly and taking into account the universality of contact-based disease transmission as conveyed through SIR-like dynamics and network flows introducing spatial heterogeneities, the model could be modified and adapted to simulate at least other endemic contagious diseases of cattl, e.g., paratuberculosis or infectious bovine rhinotracheitis.

Nonetheless, when comparing the model results with the prevalence observed in the German cattle population, we need to consider several subtleties. Firstly, the actual PI prevalence in Germany was estimated to range between 1% and 2% (Moennig et al., 2005), which is in line with our results ($\approx$ 1,2% see Section S4.5 in the Supplementary material). Secondly, several federal states in Germany started voluntary BVD control programs in 1998 (Wernike et al., 2017), a fact which is not reflected in our simulations, since we set control strategies applying to the whole network of farms, encompassing all German federal states as explained in the methods’ section. It is reasonable to expect that these voluntary, localized control programs must have reduced the total PI prevalence in the overall population. As no systematic records exist on the prevalence after the start of these voluntary programs, the model cannot be compared to reality before 2006 and in practice before 2011, which saw the onset of the compulsory control program at the federal level (Wernike et al., 2017). Concretely, the difference in the factual PI prevalence was predicted in the simulation rather shifted in the future (in the first quarter of 2024) against the 0.01% reduction in the first quarter of 2017. Otherwise, in respect to data fidelity, the model displays, as expected, a similar behavior in both scenarios with and without the control of the current control program.

Pertaining to the model itself, in general, factors influencing the epidemic equilibrium are the transmission rates of infection as given in Bassett et al. (2018) and Viet et al. (2004), and the heterogeneity of the network, i.e., the farm size distribution. The catalytic factor affecting the final state of the PI animals seems to be the PI transmission coefficient β_{PI} as demonstrated in table 5 of Section S4.2 in the Supplementary material, which backs the biology of BVDV (Viet et al., 2004).

In terms of robustness, the sensitivity analysis of the most important variables i.e., the statistical sensitivity, the vaccine working probability and the β_{TI}, showed that the model is insensitive to stochastic fluctuations and adheres to the behavior expected by experts, i.e., that even an imperfect test can lead to a reduction in PI prevalence (see Section S4.3 in the Supplementary material). Remarkably, the result of the influence of the transmission rates in our model are somewhat contrary to that of Ezanno et al. (2007) mainly because the between-herd (animal group in the authors’ case) dynamics were not considered in our simulation as opposed to that work. To be precise, although the form of the infectious dynamics was nearly identical (cf. Ref. Bassett et al., 2018), the authors of Ref. Ezanno et al. (2007) considered only a five animal herd group, therefore introducing pronounced finite size effects into their results. Furthermore, in our simulations, due to the effect of vertical transmissions, i.e., PI animals latently appearing in the system after a infection of a pregnant cow, the effect of the PI transmission coefficient β_{PI} dominates over β_{TI}. In addition, the sensitivity analysis of Ezanno et al. (2007) on the PI animals’ death rates is not directly comparable to our work, as we presume a uniform random distribution for that purpose.

Moreover, our results are akin to a number of studies (Damman et al., 2015; Tinsley et al., 2012; Graham et al., 2016; Thulke et al., 2017; Viet et al., 2004) demonstrating the predictive power and insight that computational models can provide in the efforts of governance regarding epidemic spread containment in domesticated animal populations. In addition, the model keeps the farm sizes as well as the population size constant on average. On that account, the fact that animal introductions from the source farm were halted early on in the simulations (1,884th time step) demonstrated that for the given initialization, the system quickly settled on a self-sustained trade to satisfy relation (1) upon every management period (week). Similarly, from the animals entering the fact

that PI animals ceased to enter even earlier (561st time step) than the overall animals signified the end of the BVDV spread amplification from external triggering. Finally, regarding the temporal effect of spot testing, the PI periodicity observed in the population is induced by the spot periodical testing. The (declining) peak width of the PI population in Fig. 9 signified the semesterly periodicity of the spot test, which would remove PI animals generated in the time frame of no testing.

In contrast to what we investigated, in reality the spot test will be carried out over the whole year, so that the periodicity will not be observed. However, the spot test's periodicity is a parameter that can be adjusted at any arbitrary time step in the model, thereby being fully capable of a continuous representation (testing throughout the year).

In addition, the inclusion of subtleties such as weighted or biased trading or dynamics at the node level would delve to an ever greater level of detail. This may help to capture features such as the preferential trade (attachment) or the observed declining trend of farms in Germany in the last decade (according to the Federal Statistical Office of Germany (https://www.destatis.de, 2020)). Last but not least and from a theoretical point of view of future implementations, the computation of a threshold quantity from parameters of the simulation for the epidemic outbreak could be computed in a metapopulation manner as in Ref. Colizza and Vespignani (2008). From there onward various vaccination strategies for herd immunization can be encompassed to alter the epi-demic thresholds as in House and Keeling (2011).

As far as single farms are concerned, our analysis revealed that PI introduction will lead to an increased PI and TI prevalence within the farm. This is a consequence of the increased secondary, transient transmissions induced to susceptible animals from the introduction of PI animals in the system. These behaviors are both intuitively expected as the number of secondary, transient infections should be mainly proportional to the number of PI animals in the system, since they are the main contributor of the epidemic spread for both the well-mixed (local) and spatially distributed (network) dynamics.

Despite the overall merits of the model exhibited so far, there is still room for improvement. As a first point, the trade pattern including the generation of animals in the source farm (‘‘imports”) is continuously active only at the beginning of the simulation. To mend this, the code would need to be adapted in a way, that a certain exchange between farms and the (virtual) import of animals can be defined. One option would be to add a predefined trade matrix with a given number of trade contacts between farms. A disadvantage of this solution is that the matrix must be dynamic as the trade patterns will be influenced by the infectious status and the control measures. Another option would be to force farms to sell more animals than they need in order to keep the source farm's imports flowing in the system. In addition to this, the in-farm herd structure could be altered to account for mixed farms (beef and dairy). This could be achieved by maintaining trading of a specific herd within the farm (dairy) with other farms, while another herd (beef) would not trade but contribute to the infectious dynamics of the farm.

Another point is the fact that the system size (number of farms in the simulation) does not scale with the computational requirements in memory. By including more farms the memory resources required to run the simulation grow exponentially even for small ones, while increasing the number of animals in only a few farms is much more slow in depleting memory. In our case, the model runs serially on a standard desktop of CPU 2.2 GHz and 16 GB RAM up to a system size of between 10,000 to 15,000 farms, depending on the distributed number of animals. Consequently, it was not possible to simulate the farm size distribution of Germany (about 140,000 farms), hence we had to scale down the German farm size distribution. We tested however the effect of the downscaling and observed that the PI prevalence was increasing up to 6,000 farms and then remained constant (Fig. 5).

Regarding the establishment of BVD in a farm population our results indicated that there might be a critical population size of the farms leading to a persistent epidemic without intervention. In the cases where intervention still led to an endemic final state the farm sizes contributing to the epidemics were shifted to the largest farms of the systems. This is a consequence of the SIR dynamics taking place at the farm level: a well-mixed, large population with endemic conditions (infectious versus recovery rate ratio) including demographic changes can exhibit an endemic equilibrium point (Rohani, 2008), given of course the one-herd per farm condition that we studied. Nevertheless, as the simulation is stochastic, one can expect fluctuations of the farm size threshold (in our simulation's farm size distribution it was at a farm size of 250 animals) for endemicity. Conversely and in regard to the prevalence of BVD on the network, a parameter that can be further inquired is the sensitivity of the infection spread among farms to the initial farm size distribution, i.e., to the heterogeneity of the distribution.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found at: https://hdl.handle.net/21.11116/0000-0009-009B-8.

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