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## Farm productive contexts and the dynamics of bovine viral diarrhea (BVD) transmission

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### Abstract

Bovine Viral Diarrhea (BVD) is a viral disease that affects cattle and that is endemic to many European countries. It has a markedly negative impact on the economy, through reduced milk production, abortions, and a shorter lifespan of the infected animals. Cows becoming infected during gestation may give birth to Persistently Infected (PI) calves, which remain highly infective throughout their life, due to the lack of immune response to the virus. As a result, they are the key driver of the persistence of the disease both at herd scale, and at the national level. In the latter case, the trade-driven movements of PIs, or gestating cows carrying PIs, are responsible for the spatial dispersion of BVD. Past modeling approaches to BVD transmission have either focused on within-herd or between-herd transmission. A comprehensive portrayal, however, targeting both the generation of PIs within a herd, and their displacement throughout the country due to trade transactions, is still missing. We overcome this by designing a multiscale metapopulation model of the spatial transmission of BVD, accounting for both within-herd infection dynamics, and its spatial dispersion. We focus on Italy, a country where BVD is endemic and seroprevalence is very high. By integrating simple within-herd dynamics of PI generation, and the highly-resolved cattle movement dataset available, our model requires minimal arbitrary assumptions on its parameterization. We use our model to study the role of the different productive contexts of the Italian market, and test possible intervention strategies aimed at prevalence reduction. We find that dairy farms are the main drivers of BVD persistence in Italy, and any control strategy targeting these farms would lead to significantly higher prevalence reduction, with respect to targeting other production compartments. Our multiscale metapopulation model is a simple yet effective tool for studying BVD dispersion and persistence at country level, and is a good instrument for testing targeted strategies aimed at the containment or elimination of this disease. Furthermore, it can readily be applied to any national market for which cattle movement data is available.

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*Keywords:* BVD, cattle trade movements, metapopulation model, productive classes, targeted intervention

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## 1. Introduction

Bovine Viral Diarrhea (BVD) virus is a pathogen responsible for a livestock disease of major concern in Europe, causing high prevalence in affected countries and important economic impacts (Lindberg et al., 2006). Induced costs are mainly due to production losses, derived from the immunosuppressive and abortive actions of the etiological agent, and to the biosecurity and immunization measures often implemented for its control or eradication (Thomann et al., 2017; Lindberg et al., 2006; Gunn et al., 2004). In addition, the disease can also facilitate the introduction and spread of other pathogens (Servizio Informativo Veterinario, 2011).

BVD normally displays mild clinical symptoms, though it may predispose affected animals to more severe forms of enteric and respiratory ailments, and in some cases result in the highly lethal Mucosal Disease. Transmission mainly occurs perorally or nasopharageally, but excretion in semen, as well as iatrogenic diffusion and environmental persistence have been reported (Lanyon et al., 2014; Niskanen and Lindberg, 2003; Traven et al., 1991; Kirkland et al., 1991; Meyling and Mikél Jensen, 1988). Pregnant cattle are the segment of the population that is most at risk, and of the greatest epidemiological relevance. If viral contact occurs during the very initial phase of gestation, abortion will likely occur. Contact during the first third of pregnancy has instead a high probability of resulting in an immunotolerant persistently infected (PI) calf. Infection during later stages of pregnancy can result in fetal malformations and a considerable number of abortions.

PIs are the main epidemiological agent responsible for disease diffusion and persistence within a farm (Ezanno et al., 2007). Their viral excretion is orders of magnitude larger than that of an immunocompetent transiently infected animal, and is life-long (Reardon et al., 2016; Lanyon et al., 2014). Pregnant dams that carry a PI are latent persistently infected animals (PIs) and hardly detectable by serological tests as they are immune (Lanyon et al., 2014). They are an epidemiologically important aspect of the infection dynamics as their offspring will introduce PIs in the farm, potentially leading to disease persistence. PI animals tend to be smaller and underdeveloped compared to their healthy peers. Their lifespan is considerably shorter and their productivity severely hampered, so that they are more likely to be sold, thus further increasing the spatial spreading potential.

No therapy exists for BVD other than symptomatic treatment. Vaccines are available, but their effectiveness is often limited by the extremely high infectious pressure of PI animals. For these reasons, the current approach to BVD prevention mainly revolves around the implementation of biosecurity measures aimed at preventing contacts between infected animals and pregnant cows (Courcoul and Ezanno, 2010; Lindberg et al., 2006; Ezanno et al., 2007; Lanyon et al., 2014; Ezanno et al., 2008). Large variations across countries are however observed, and efficiency of the implemented measures is hard to evaluate. Modeling thus provides a convenient framework to study BVD dynamics, identify key drivers for transmission and propose control and eradication strategies.

46 Much research has been devoted to the development of BVD models for  
47 within-farm spread (Viet et al., 2007; Ezanno et al., 2007; Gunn et al., 2004;  
48 Cherry et al., 1998; Innocent et al., 1997b,a; Sørensen et al., 1995; Damman  
49 et al., 2015; Smith et al., 2009; Ezanno et al., 2008; Viet et al., 2004). Models  
50 focused on the complexity of the infection dynamics (e.g. horizontal and ver-  
51 tical transmission, persistently infected and transiently infected animals) and  
52 its parametrization, the disease consequences on herd demography (e.g. impact  
53 on reproduction, probability of abortion, reduced lifespan), the role of herd  
54 structure and herd-management practices, the economic impact and the evalu-  
55 ation of interventions. Though the presence of a single PI in an infection-free  
56 herd was estimated to pose a considerable risk with potentially long-term conse-  
57 quences (Innocent et al., 1997a), reseeded events were found to be critical for the  
58 persistence of the disease (Viet et al., 2004; Damman et al., 2015; Smith et al.,  
59 2009). The external risk of BVD introduction was generally modeled through  
60 synthetic importation schemes, only effectively accounting for geography and  
61 trade. Courcoul and Ezanno first proposed a spatially explicit metapopulation  
62 approach to model the regional spread of BVD in a group of 100 dairy herds as-  
63 similated to patches (Courcoul and Ezanno, 2010; Ezanno et al., 2008). Trade  
64 movements were however synthetically modeled through a random network.  
65 As such, they did not capture the heterogeneities and temporal correlations  
66 observed in cattle mobility that were found to strongly impact epidemic dy-  
67 namics (Bajardi et al., 2011; Valdano et al., 2015; Ensoy et al., 2013; Vernon  
68 and Keeling, 2009; Ezanno et al., 2006). A data-driven spatial approach was  
69 proposed by Tinsley *et al.* that integrated data on cattle movements between  
70 beef farms in Scotland to simulate BVD spread at a larger scale and identify  
71 movement-informed interventions (Tinsley et al., 2012). To account for the com-  
72 plexity intrinsic to the network of cattle trade movements, the infection dynam-  
73 ics was however simplified through the use of a susceptible-infected-susceptible  
74 process where farms are treated as single units with no further population sub-  
75 structure. Moreover, only farms of one productive type were considered. An  
76 important discussion ensued, however, on quantifying the role of local contacts  
77 in infection persistence (Ersbøll et al., 2010; Graham et al., 2016), integrating  
78 them with an estimation of the effects of biosecurity measures as well as trade  
79 network movements (Gates et al., 2013), and understanding the implications of  
80 trading pregnant cattle or open cows with a calf at their side, clearly identi-  
81 fying an age-related probability of being a PI (Gates et al., 2014). Thulke *et*  
82 *al.* (Thulke et al., 2017) extends these works in the context of the Irish eradi-  
83 cation program with an in-depth consideration of the changes in costs involved  
84 in switching the diagnostic strategy from direct tissue testing to indirect sero-  
85 logical testing of a subsample of animals. A very important contribution is the  
86 study of the effects of latency in PI removal on the eradication time. However,  
87 the simulation requires high resolution data for its starting disease conditions,  
88 which are not always available, and the productive contexts are discretized as  
89 either beef or dairy, while the authors place greater stress on the role of animal  
90 age and sex.

91 The aim of our work is to propose a novel multiscale spatially explicit  
92 metapopulation approach to model the geographic dispersion of BVD at the  
93 national scale, accounting for within-farm dynamics and high-resolution cattle  
94 movement data. Heterogeneities of BVD incidence per farm and reintroduc-  
95 tion events are the result of the explicitly modeled dynamics, self-consistently

96 producing geotemporal estimates for spreading potential and probability of ex-  
 97 posure without the need for synthetic assumptions. We apply our study to the  
 98 cattle population of Italy and more specifically we focus on the role that dif-  
 99 ferent productive contexts may have in the spreading dynamics. We consider  
 100 the full animal-level Italian database of cattle trade movements, accounting for  
 101 different premises types (e.g. farms, slaughterhouses, markets, assembly cen-  
 102 ters, etc.) and four farm productive classes (beef with and without on-premise  
 103 reproduction, dairy or mixed). We simulate different transmission profiles and  
 104 generate simulated BVD prevalences at endemic equilibrium. Our findings on  
 105 the role of different productive contexts are then used to inform efficient targeted  
 106 interventions aimed at a considerable reduction of prevalence in the country.

## 107 2. Materials and Methods

### 108 2.1. Data

109 We use the complete dataset of all individual animal movements, births,  
 110 deaths and thefts covering the period from January 1st to December 31st 2014  
 111 provided by the Istituto Zooprofilattico Sperimentale (IZS) dell’Abruzzo e del  
 112 Molise, the Italian national reference centre for the bovine movement database.  
 113 The dataset is similar to the ones analyzed in (Bajardi et al., 2011, 2012; Natale  
 114 et al., 2011, 2009; Valdano et al., 2015).

115 For each movement, we have an anonymized animal ID along with the cor-  
 116 responding age, breed, sex, date of movement, origin and destination premises.  
 117 We consider three distinct categories of animals: males, females below repro-  
 118 ductive age, and females of reproductive age. For each premise, we have an  
 119 anonymized node ID, structure and production type labels and initial values for  
 120 each of the three animal categories. The percentage of females in each animal  
 121 holding on January 1st, 2014 is also provided.

122 The bovine dataset covers a total of 5.9 million movements between 144,403  
 123 premises throughout the country, involving 3.9 million bovines during the year  
 124 2014 (Figure 1a). The movement dataset is represented in the form of a time-  
 125 referenced directed weighted network, where nodes represent premises and links  
 126 represent bovine movements (Bajardi et al., 2011, 2012; Natale et al., 2011,  
 127 2009; Valdano et al., 2015).

### 128 2.2. Model

129 We propose a multiscale spatially explicit metapopulation approach that  
 130 simulates disease transmission between animals within each farm and disease  
 131 dispersal in space through the movement of infected animals. Animal premises  
 132 correspond to the patches of the model where BVD infection dynamics occurs,  
 133 and trade movements correspond to the spatial coupling between patches, bring-  
 134 ing the description of the disease spread from a local perspective to the national  
 135 scale.

136 The infection dynamics are based on a compartmental model that represents  
 137 the BVD spread in cattle herds, and includes the persistently infected animals  
 138 (PI) and the persistently infected (latent) animals (PIL) (Figure 1c). If at least  
 139 one PI is present within a farm, each week we use binomial sampling to generate  
 140 PILs from susceptible cows (S) according to the following equations:

$$\varepsilon_i^* \sim \mathcal{B}(N_i - (N_i^{PIL} + N_i^{PI}), \varepsilon\alpha_i), \quad (1)$$

141 where  $N_i$  is the total number of animals within premise  $i$ ,  $N_i^{PIL}$  and  $N_i^{PI}$  are  
 142 the number of PIL and PI animals within the same premise,  $\alpha_i$  is the fraction  
 143 of females of breeding age present at that time in the premise and  $\varepsilon$  is the  
 144 transmission parameter. In this equation,  $\mathcal{B}(n, p)$  is a binomial distribution  
 145 with  $n$  trials and success probability  $p$ . This is allowed to take place only in  
 146 farms, and only in productive contexts that allow breeding (i.e., not fattening  
 147 farms). This rate does not vary with the number of PIs.

148 To account for the gestation stages and birth events, PILs become PIs at  
 149 rate  $\varphi$ , expressed as  $\varphi = \frac{1}{2/3 \Delta t_g} (1 - p_a)$ , where  $\Delta t_g$  represents the average cattle  
 150 gestation length and  $p_a$  the probability of having an abortion. This parameter  
 151 does not represent the pregnancy period-at-risk of vertical transmission, but the  
 152 rate at which a PIL cow where transmission has already occurred gives birth to  
 153 a PI.

154 PIs are removed with rate  $\mu$  accounting for both the infection-induced mor-  
 155 tality and the culling of detected infected animals. In addition, rate  $M$  cor-  
 156 responds to both the possibility of developing the Mucosal Disease as well as  
 157 the increase in veterinary interventions that this clinical manifestation entails.  
 158 When this occurs, the farm will be cleared of all PI and PIL animals. The  
 159 parameter  $M$  is the only direct route for elimination of PILs, as they are unaf-  
 160 fected by the processes modeled through  $\mu$  (i.e. they are not clinically affected  
 161 by the disease and are hard to detect).

162 To account for immunity after transient infection, we model the transition  
 163 from Susceptible to Recovered with rate  $\varepsilon(1 - \alpha_i)$ . This immunity is considered  
 164 life-long and no further transitions are possible from this compartment, but the  
 165 animals may be traded regularly, possibly leading to the slaughterhouse.

166 All rates are converted to probabilities before their application in the model.

167 The infection dynamics are applied to all animal holdings. Heterogeneity  
 168 in within-farm disease dynamics is given by the farm productive class and as-  
 169 sociated herd management and demography. Here we consider four different  
 170 productive types of interest (Figure 1b), similarly to (Dutta et al., 2014; Natale  
 171 et al., 2009):

- 172 1. Dairy: all farms concerned with dairy production;
- 173 2. Beef with reproduction: farms hosting beef cattle with on-premise repro-  
 174 duction;
- 175 3. Beef without reproduction: farms fattening and raising beef cattle but not  
 176 having on-premise reproduction;
- 177 4. Mixed: all farms that cannot be ascribed to a single productive type.

178 Cattle movements between premises are responsible for the spatial disper-  
 179 sion of a BVD epidemic. These are sold and purchased from farm to farm or  
 180 through markets and may be divided into three categories of male cattle, and  
 181 female cattle below or above reproductive age. Animal movements, as well as  
 182 birth and deaths, are explicit and completely data-driven. The single-animal  
 183 movements from holding  $A$  to holding  $B$  for the week  $N$  are aggregated, since  
 184 data are daily based, and the number of males, females below reproductive  
 185 age and females above reproductive age is counted. Then, the number of PILs  
 186 and PIs moved is stochastically determined based on the classes of moved ani-  
 187 mals, and the counts at the origin and at the destination are updated. Within  
 188 each demographic category, animals are moved according to trade data and the  
 189 probability that a moving animal belongs to a given disease status is simply

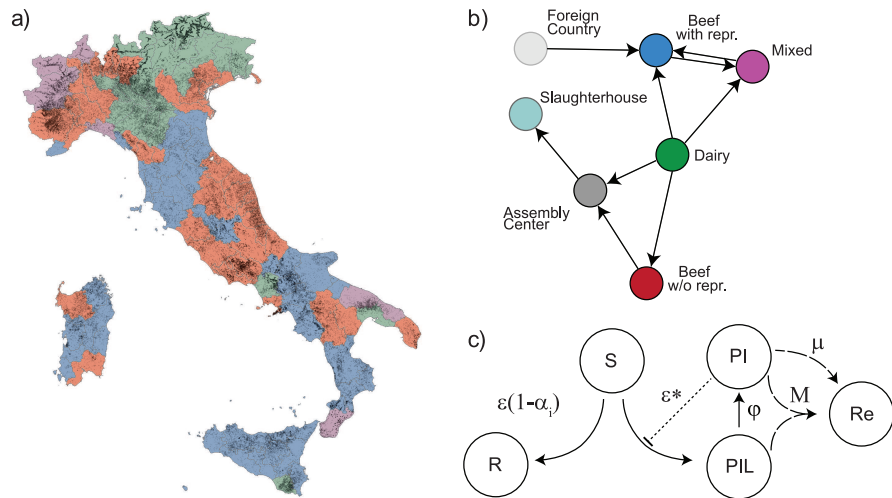


Figure 1: Metapopulation model for BVD transmission at the national scale. (a) Geographical visualization of the position of the 144,403 cattle premises in Italy of the 2014 movement database. Provinces are color coded according to the productive class mostly present in the area (red for beef fattening farms, blue for beef reproductive farms, green for dairy and violet for mixed attitude farms, as in panel (b)). Farms are represented as points on the map. (b) Schematic representation of the network of cattle movements where animal premises are labeled according to their type (farm, slaughterhouse, etc.) and productive class (beef with and without reproduction, dairy, mixed). (c) Scheme of the infection dynamics within each premise.

190 proportional to the fraction of animals in that disease class. Only females at or  
 191 above reproductive age may determine movement of a PI, while all classes may  
 192 move a PI. Newborns and animals imported from foreign countries are assumed  
 193 to be healthy and susceptible. While we do not account for the seasonality of  
 194 breeding explicitly, by using the real birth data as part of our collection of animal  
 195 movement the introduction of new susceptible animals follows the seasonal  
 196 patterns.

197 All transitions (related to the infection dynamics or the movements) are  
 198 modeled as discrete and stochastic processes to account for stochastic fluctu-  
 199 ations due to small population sizes inside premises. The time step of the  
 200 simulation is 1 week. The model is implemented in Scala using the Breeze li-  
 201 braries for Mathematics. Each premise uses a thread-local implementation of  
 202 the Mersenne-Twister random number generator from the Apache Commons  
 203 Math 3 library.

### 204 2.3. Model parametrization

205 The only free parameters of our model are the transmission rate  $\varepsilon$  and the re-  
 206 moval rate  $\mu$ . All other parameters are fixed and taken either from the literature  
 207 or from expert opinion. Reproductive age is set at 15 months with a gestation  
 208 length  $\Delta t_g = 36$  weeks. Both values are chosen as intermediate values between  
 209 the reproductive performances of dairy and beef breeds based on expert opinion.  
 210 We consider a probability of abortions  $p_a = 0.7$  (Damman et al., 2015; Ezanno  
 211 et al., 2007), thus yielding  $\varphi = 0.0125\text{week}^{-1}$ . We also examine the effect of  
 212 a larger period-at-risk, using two thirds of gestation. Keeping all other factors

Parameter name	Values	Units
Epsilon ( $\varepsilon$ )	0.0033 - 0.01 - 0.02	$week^{-1}$
Mu ( $\mu$ )	0.0033 - 0.01 - 0.02	$week^{-1}$
Phi ( $\varphi$ )	0.00125 - 0.00250	$week^{-1}$
M ( $M$ )	0.00769	$week^{-1}$
Years of simulation	60	
Seeding conditions	50	
Repetitions	10	
Seeding percentage	1	%

Table 1: Summary of all parameter values used in parameter exploration

constant, this yields  $\varphi = 0.025week^{-1}$ . The percentage  $\alpha_i$  of females of breeding age in animal holding  $i$  is set from data at the beginning of the simulations. Development of the Mucosal Disease is considered to occur after an average period of 2.5 years (i.e. 130 weeks), similarly to (Haskell, 2011; Kelling, 2004; Innocent et al., 1997a), thus yielding the rate  $M = \frac{1}{130weeks} = 0.00769week^{-1}$ .

Simulations start on January 1, 2014 and all cattle population is initialized in the susceptible class, except for a uniform seeding of 1% of all farms chosen at random. These farms are seeded with one PI each. This initial prevalence value was chosen as the lower estimate reported by Houe *et al.* (Houe, 1999) for the United Kingdom. The aim of our work is to study the equilibrium dynamics of the BVD epidemic, so we consider simulations running for several years on the 2014 weekly aggregated demographic and movement data with periodic boundary conditions, in a similar manner to Tinsley *et al.* (Tinsley et al., 2012). We use 1 year of data, as trade was rather stable in 2014, to neglect intrinsic changes over time due to the trade system and industrial expansions or reductions that can alter the equilibrium dynamics.

Three values of the removal rate parameter are used, i.e.  $\mu = 0.0033week^{-1}$ ,  $\mu = 0.01week^{-1}$ , and  $\mu = 0.02week^{-1}$ . The same range of values is used for the transmission parameter  $\varepsilon$ . Results were computed over 500 replications for each transmission scenario explored. All parameters are summarized in Table 1.

#### 2.4. Experimental scenarios of interventions

To support the findings of our study on the equilibrium dynamics of BVD circulation in Italy, we propose a set of experimental scenarios modeling interventions. They are aimed at isolating farms from the system, thus synthetically simulating the effect of 100% effective surveillance and control measures at the local scale. Assuming limited resources, we test removal strategies on a set of farms chosen with different approaches:

- random removal of farms
- targeted removal of farms based on productive context
  - removal of beef reproductive farms
  - removal of beef fattening farms
  - removal of mixed farms
  - removal of dairy farms



Parameter name	Values	Units
Epsilon ( $\varepsilon$ )	0.01 - 0.02	$week^{-1}$
Mu ( $\mu$ )	0.01 - 0.02	$week^{-1}$
Phi ( $\varphi$ )	0.00125	$week^{-1}$
M ( $M$ )	0.00769	$week^{-1}$
Repetitions	5	
Years of simulation	60	
Seeding conditions	5	
Seeding percentage	1	%
Intervention percentage	1 - 6 - 12 - 18 - 24	%
Total number of intervention scenarios	253	

Table 2: Summary of all parameter values used in experimental scenarios

246 For each percentage value of farms removed, the targeted experimental sce-  
247 narios are compared to the random removal, i.e. a choice not informed by the  
248 resulting epidemic relevance of each productive context.

249 We progressively increased the amount of farms we removed: 1%, 6%, 12%,  
250 18% and 24% of the total amount of farms in the network, either at random or  
251 limited to the chosen context. The highest value we employed is limited by the  
252 number of dairy holdings in the system. In the case of mixed farms, removal  
253 could only be performed up to 12%, due to the limited size of that productive  
254 context.

255 Each experimental scenario was repeated 25 times to stabilize model outputs.  
256 All parameters are summarized in Table 2.

## 257 2.5. Analyses

258 First, we analyzed the Italian cattle trade dataset for 2014 to characterize  
259 the different productive contexts in terms of farm size, trading patterns, and  
260 sex of animals.

261 Second, we observed the evolution in time of BVD prevalence in the cattle  
262 trade system, from the initial seeding condition to the equilibrium dynamics.  
263 Third, we explored the dependence of the simulated BVD prevalence on the  
264 transmission rate and on the productive contexts. We considered different mea-  
265 sures of prevalence, at the animal level and at the farm level, accounting for  
266 the productive type. More precisely, the local PI animal prevalence in farms of  
267 productive class  $c$  is computed as  $N_c^{PI}/N_c$ , where  $N_c^{PI}$  is the total number of  
268 PI animals in farms of productive class  $c$ , and  $N_c$  is the number of these farms.  
269 We also computed the contribution of PI in farms of productive class  $c$  over  
270 all farms, to account for the sharply different sizes of the productive categories:  
271  $N_c^{PI}/N_f$ , where  $N_f$  is the total number of heads in all farms in the country.  
272 The national PI animal prevalence across all productive types was computed as  
273  $N_f^{PI}/N_f$ , where  $N_f^{PI}$  counts the total number of PIs in all farms. At the farm  
274 level, we considered a farm to be infected if there is at least one PI (or PIL).  
275 The national PI farm prevalence is therefore given by  $n_c^{PI}/n_c$ , and by  $n_c^{PI}/n_f$ ,  
276 where  $n_c^{PI}$  represents the number of PI infected farms of productive class  $c$ ,  $n_c$   
277 is the number of farms of productive class  $c$ , and  $n_f$  is the total number of farms  
278 in the country. Analogous measures were defined also for PILs.

279 Fourth, we assessed the impact of the proposed experimental scenarios of  
 280 interventions by comparing the resulting BVD national farm prevalence at equi-  
 281 librium after the removal of a certain fraction of farms.

282 For each model output, average and 95% credible interval (95% CI) are  
 283 computed.

284 While other types of premise are present in our dataset and are accounted  
 285 for by our simulator, the focus of our work is the presentation and discussion of  
 286 the results pertaining to farms.

### 287 3. Results

288 Beef farms represent the most common productive context in the Italian  
 289 cattle trade system during the year 2014, with a total of 44,170 fattening farms  
 290 (33.58% of all farms) and 36,350 reproduction farms (27.64%), amounting to  
 291 more than 61% of the total number of farms (Figure 2a). When considering  
 292 total herd size, they tend to be small, with a median of 3 heads (95% percentile  
 293 120) in fattening farms and 7 heads (95% percentile 69) in the reproduction ones  
 294 (Figure 2b). Mixed production farms have a total size similar to beef farms with  
 295 reproduction (median 7 heads, 95% percentile 82), however they represent the  
 296 least common production type in our dataset (18,638 farms, 14.17%). Finally,  
 297 dairy farms represent 24% of the system (32,374 farms) and on average host  
 298 the largest number of total heads (median 23 heads, 95% percentile 207). The  
 299 presence of females varies substantially across productive contexts, with the  
 300 largest values reported for milk production (average 55% of females according to  
 301 data for January 1, 2014), reproduction purposes (41%) and mixed production  
 302 (38%), and the smallest presence in beef farms without reproduction (14%).

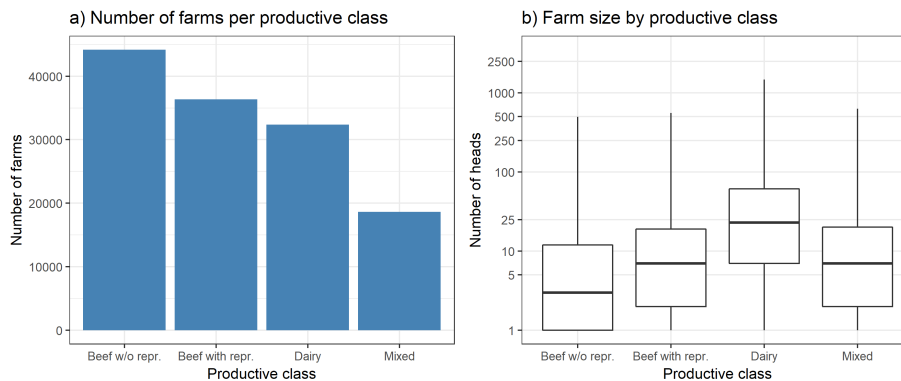


Figure 2: Description of productive contexts in Italy in 2014. (a) Number of farms per productive class. (b) Distribution of the farm size per productive class. Whiskers are calculated as  $median \pm 1.5 IQR$

303 Trading patterns too are largely affected by production classes, with average  
 304 trading volumes varying widely (Figure 3a). Dairy farms represent the most  
 305 common origin of animal movements (44.7% of all movements), whereas beef  
 306 farms without reproduction is the most common destination (54.3%). Move-  
 307 ments follow a seasonal behavior, already outlined in (Bajardi et al., 2011; Val-  
 308 dano et al., 2015), with a considerable drop in activity around summer when

309 animals are moved to pastures (these movements are not traced in the national  
 310 database). Distinct trading patterns are observed when tracing the movements  
 311 of female vs. male animals. A large number of male calves born every year in  
 312 dairy farms are continuously sold to beef fattening farms before being moved  
 313 to slaughterhouses at a later time (Figure 3b). The largest proportion of move-  
 314 ments to slaughterhouses (65%) is indeed performed by beef fattening farms. A  
 315 similar pattern is followed by beef farms with in-house reproduction. Female  
 316 cows are strongly traded across dairy farms throughout the year.

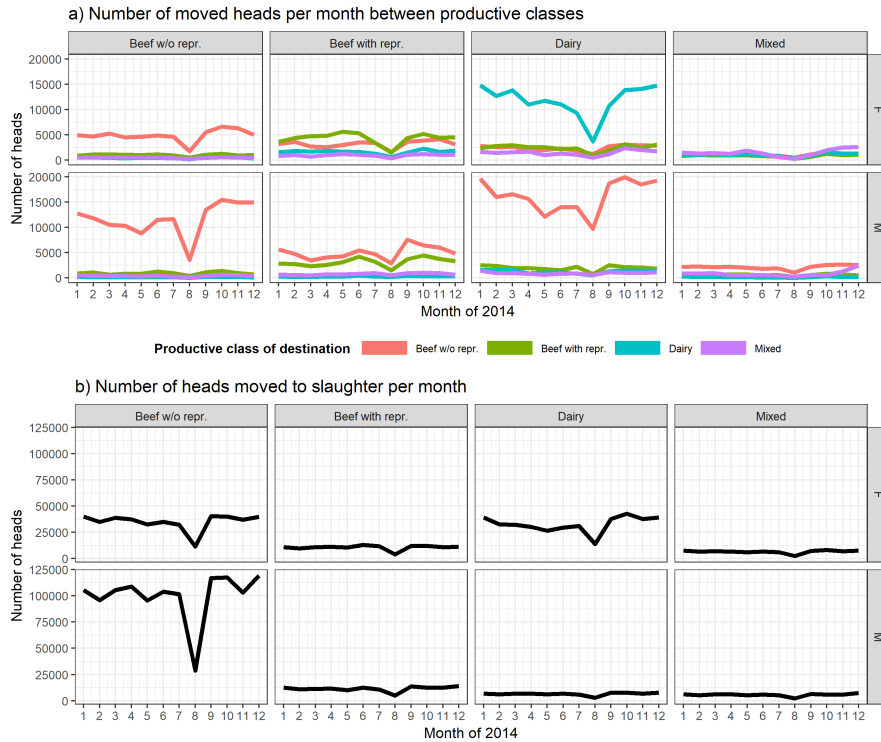


Figure 3: Movements of the 2014 cattle trade network in Italy. (a) Number of moved heads per month between productive classes. The title of each column correspond to the productive class of origin. Different colors refer to the productive class of destination. (b) Number of heads sent to slaughter each month. The title of each column correspond to the productive class of origin. In both panels, the top row reports the movements of female heads, the bottom row the ones of male heads.

317 This heterogeneous picture dependent on productive contexts and affecting  
 318 farm size, trading pattern and percentage of females becomes particularly  
 319 relevant when modeling the spread of BVD and accounting for horizontal and  
 320 vertical transmission as well as herd composition.

321 We explored nine total combinations of the  $\varepsilon$  and  $\mu$  parameters, and for  
 322 each combination we experimented with two values of  $\phi$  representing different  
 323 periods-at-risk during gestation. Under the transmission conditions considered,  
 324 our simulations reach the endemic equilibrium after about 20 years (Figure 4).  
 325 When  $\varepsilon$  is very low, the system maintains very low levels of prevalence, but the  
 326 disease still persists in the cattle population at levels below 0.01%. We do not  
 327 observe complete eradication for the parameters considered. For  $\varepsilon = 0.02$  and

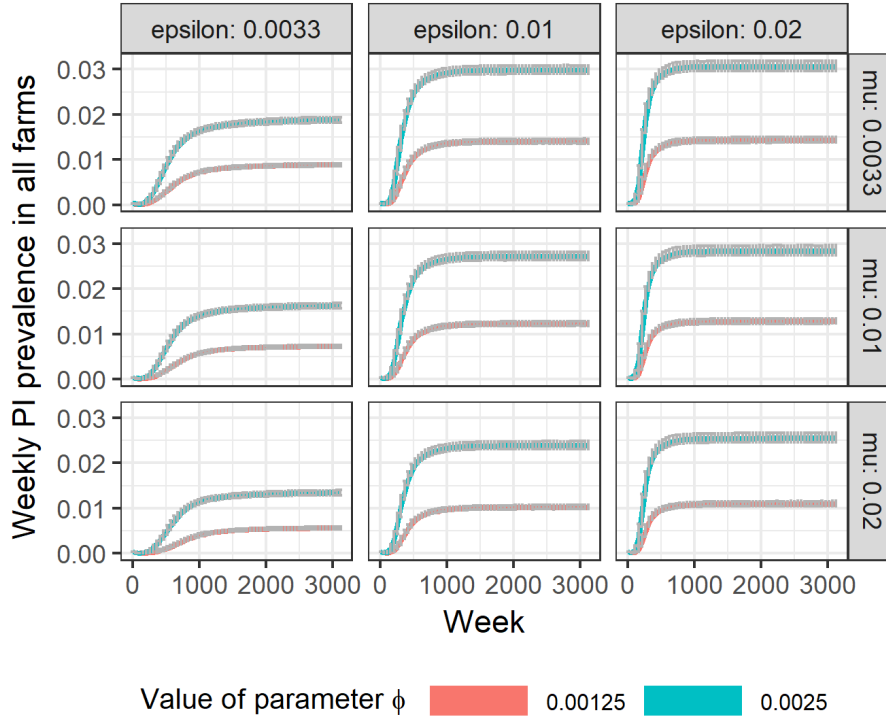


Figure 4: Exploration of the effects of parameter change on PI prevalence. Columns are values of the transmission parameter  $\varepsilon$ , rows are values of the elimination parameter  $\mu$ . For each subplot, the line represents the PI prevalence across all productive contexts. The linetype depends on the value of the parameter  $\phi$ , responsible for the evolution of PIs from PILs. The error bars are 95% credibility intervals of the mean.

328  $\mu = 0.01$ , the higher value of  $\phi$  results in a higher prevalence of up to 2.83%  
 329 (95% CI 2.74-2.96%) compared to 1.28% (95% CI 1.23-1.34%) of the lower value.  
 330 The value of the parameter  $\mu$  exerts less influence over the average prevalence,  
 331 resulting in a change from 3.05% (95% CI 2.96-3.19%) for the lowest value to  
 332 2.54% (95% CI 2.46-2.66%) for the highest one, for  $\varepsilon = 0.02$  and  $\phi = 0.00250$ .

333 For values of  $\phi = 0.00125\text{week}^{-1}$  and  $\mu = 0.01\text{week}^{-1}$ , our study predicts  
 334 a total PI prevalence between 1.22% (95% CI 1.18-1.28%) and 1.28% (95% CI  
 335 1.23-1.34%) from intermediate to high values of  $\varepsilon$ , respectively, when consid-  
 336 ering prevalence across all productive classes. These figures are in line with  
 337 the estimates previously reported in a predominance of studies showing similar  
 338 prevalence in the range of approximately 0.5% and 2% PI animals in differ-  
 339 ent countries (Houe, 1999), and thus support our choice for the two higher  
 340 values of the transmission rate explored in this study. For the rest of the  
 341 results we present, we will therefore focus mainly on this set of parameters:  
 342  $\mu = 0.01\text{week}^{-1}$ ,  $\phi = 0.00125\text{week}^{-1}$ ,  $\varepsilon = 0.01 - 0.02\text{week}^{-1}$ .

343 Interestingly, the described heterogeneities cause animal prevalence curves  
 344 at the farm level to rapidly differentiate, reaching different values of BVD cir-  
 345 culation at the endemic equilibrium. Dairy farms are the ones reporting the  
 346 largest percentage of PIs, independently of the transmission condition, followed

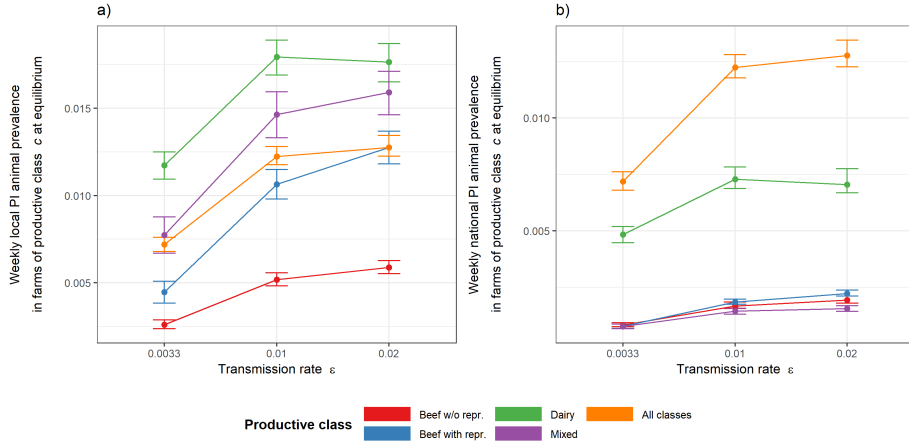


Figure 5: Weekly PI animal prevalence at endemic equilibrium. (a) Average weekly local PI animal prevalence in farms of productive class  $c$ ,  $N_c^{PI}/N_c$ , at endemic equilibrium as a function of the transmission rate  $\varepsilon$ . (b) Average weekly national PI animal prevalence in farms of productive class  $c$ ,  $N_c^{PI}/N_f$ , at endemic equilibrium as a function of the transmission rate  $\varepsilon$ . Colors refer to different productive classes or to the ensemble of all farms. Error bars are 95% credibility intervals of the mean.

347 by mixed farms (Fig. 5a). PI animal prevalence within the productive class  
 348 is equal to 1.76% (95% CI 1.65-1.87%) for dairy farms and to 1.59% (95% CI  
 349 1.46-1.71%) for mixed farms when  $\varepsilon > \mu$  (1.79% (95% CI 1.69-1.89%) and  
 350 1.46% (95% CI 1.33-1.60%) for  $\varepsilon = \mu$ , respectively). Dairy farms are the ones  
 351 contributing the largest amount of PIs to the system (Fig. 5b), leading to a  
 352 predicted overall animal prevalence of 0.7% (95% CI 0.67-0.78%) for the higher  
 353 transmission condition, and of 0.73% (95% CI 0.68-0.78%) for the intermediate  
 354 value. This is also due to the large size of dairy farms compared to the other  
 355 reproductive types.

356 Figure 5 clearly shows that the ranking of productive contexts that are  
 357 mostly affected by the disease is maintained across transmission conditions.  
 358 Most importantly, the overall contribution of PIs to the system by dairy alone is  
 359 55.23% (95% CI 54.91-57.65%) of the total, indicating that this productive type  
 360 is the strongest single contributor to the circulation of BVD. Beef farms without  
 361 on-site reproduction are the least affected. A picture similar to PI circulation is  
 362 also observed for the spread of PILs (50.51% (95% CI 49.74-51.44%) for dairy  
 363 vs. 29.64% (95% CI 29.09-30.23%) for mixed farms, as shown in Figure 6). Since  
 364 the generation of new PILs happens mostly in categories with high reproductive  
 365 capability, beef farms with in-house reproduction show a higher prevalence in  
 366 the case of PILs (up to 24.54%, 95% CI 23.46-25.73%) than fattening farms (up  
 367 to 2.13%, 95% CI 2.00-2.31%). The presence of PILs inside the beef fattening  
 368 farms is not due to a generative activity of the compartment itself, but to the  
 369 movement of PILs from other compartments. Finally we note that PILs reach  
 370 a higher simulated prevalence than PIs, at 28.06% (95% CI 27.18-29.35%) vs  
 371 1.28% (95% CI 1.23-1.34%) in the high transmission condition.

372 Dairy productive class results to be the most affected productive context also  
 373 when measuring the percentage of infected farms, with a predicted within-class  
 374 prevalence of up to 54.57% (95% CI 53.19-56.04%) and across-class prevalence

375 of 13.43% (95% CI 13.09-13.79%) (Figure 7). Beef fattening farms appear more  
 376 relevant in contributing to the national farm prevalence than observed before  
 377 for animal prevalence, likely because of the large number of smaller premises.

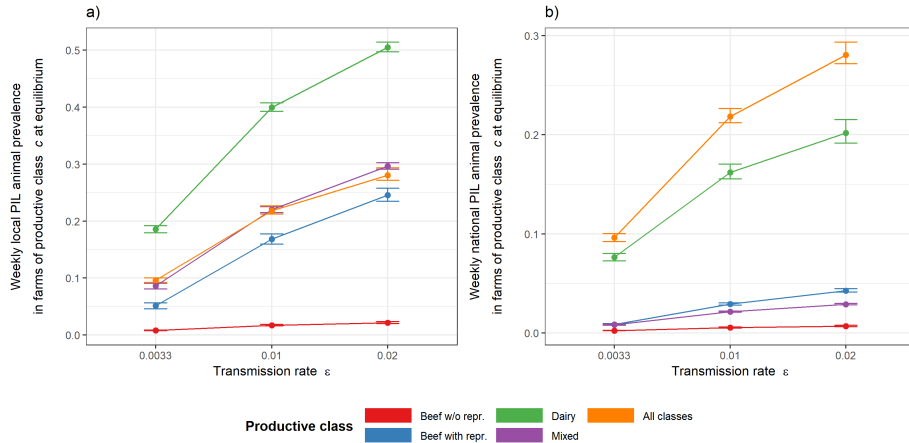


Figure 6: Weekly PIL animal prevalence at endemic equilibrium. (a) Average weekly local PIL animal prevalence in farms of productive class  $c$ ,  $N_c^{PIL}/N_c$ , at endemic equilibrium as a function of the transmission rate  $\epsilon$ . (b) Average weekly national PIL animal prevalence in farms of productive class  $c$ ,  $N_c^{PIL}/N_f$ , at endemic equilibrium as a function of the transmission rate  $\epsilon$ . Colors refer to different productive classes or to the ensemble of all farms. Error bars are 95% credibility intervals of the mean.

378 Given the central role of productive contexts in the simulated endemic per-  
 379 sistence of BVD in the cattle population in Italy, we test different experimen-  
 380 tal scenarios for intervention, comparing control measures randomly applied  
 381 to farms with targeted ones based on their productive class. A dairy-focused  
 382 intervention is predicted to be considerably more efficient in protecting the cat-  
 383 tle population than a random farm intervention, for any degree of application  
 384 of the intervention (Figure 8). Once 24% of the farms are removed, a dairy-  
 385 targeted intervention leads to a drop of 53.81% (95% CI 53.45-53.89%) of the  
 386 farm prevalence compared to the 29.51% (95% CI 28.84-30.03%) drop observed  
 387 in the case farms were chosen randomly. Control measures focused on other  
 388 productive classes are found instead to be less efficient than random interven-  
 389 tions, as shown for example by the predicted 28.34% (95% CI 28.11-28.68%)  
 390 drop when all beef farms with reproduction are targeted and the 15.21% (95%  
 391 CI 14.80-15.56%) decrease when all mixed farms are selected. Beef fattening  
 392 farms are the least effective target, with a total expected prevalence reduction  
 393 of 12.32% (95% CI 10.60-13.75%).

#### 394 4. Discussion

395 We use a spatially explicit metapopulation approach to model BVD endemic  
 396 dynamics in the cattle population in Italy, based on demographic and mobil-  
 397 ity data for the year 2014. We find that farm productive contexts strongly  
 398 impact the circulation of the disease in the country, due to the specific sizes,  
 399 herd structures and trading patterns associated to different productions. Dairy

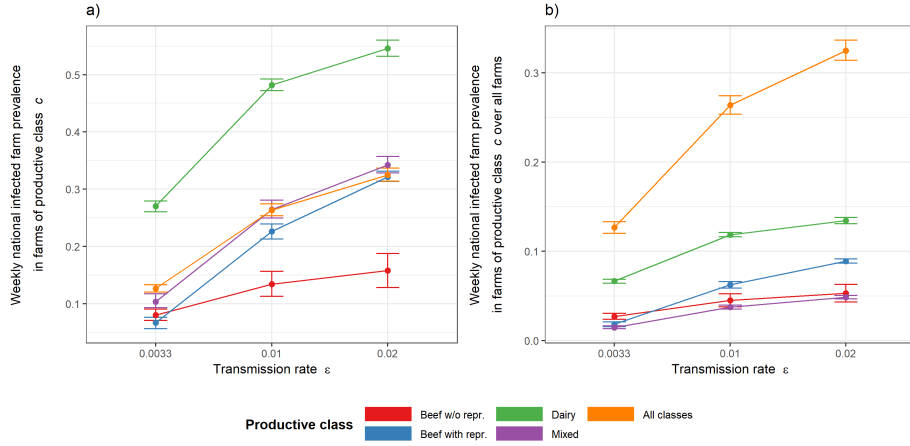


Figure 7: Weekly PI farm prevalence at endemic equilibrium. (a) Average weekly national PI farm prevalence in farms of productive class  $c$ ,  $n_c^{PI}/n_c$ , at endemic equilibrium as a function of the transmission rate  $\epsilon$ . (b) Average weekly national PI farm prevalence in farms of productive class  $c$  over all farms,  $n_c^{PI}/n_f$ , at endemic equilibrium as a function of the transmission rate  $\epsilon$ . Colors refer to different productive classes or to the ensemble of all farms. Error bars are 95% credibility intervals of the mean.

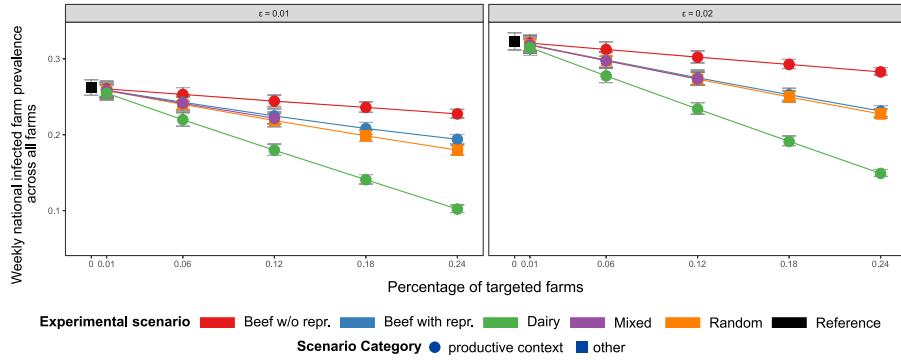


Figure 8: Random vs. targeted interventions. (a) Average weekly national infected farm prevalence in farms of productive class  $c$ ,  $n_c^I/n_c$ , at endemic equilibrium as a function of the percentage of farms affected by the intervention. A farm is infected when it contains at least 1 PI or 1 PIL. Transmission rate is set to  $\epsilon = 0.01$ . (b) as (a) for  $\epsilon = 0.02$ . Different colors refer to different experimental scenarios for interventions. Error bars are 95% credibility intervals of the mean.

400 farms generate the largest number of persistently infected (PI) and latent persistently  
 401 infected (PIL) animals. Basing their production mainly on self-sustenance  
 402 through raising their own offspring internally, these farms represent the ideal  
 403 habitat for a self-perpetuating and persistent BVD virus infection. Calves are  
 404 indeed more often in close proximity with pregnant dams, present on the farm  
 405 throughout the year, and this effect may in reality be further amplified by the  
 406 fact that PIs are probably sold with preference because of reduced growth or  
 407 insufficient productivity. As they also dominate national disease prevalence in  
 408 the number of infected premises, we suggest dairy farms to be the ideal target

409 for limited-resources control and interventions. Our results predict that dairy-  
410 focused measures would be more than twice as effective in prevalence reduction  
411 as measures applied randomly to the same number of farms independently of  
412 their productive context. While representing a synthetic scenario for interven-  
413 tion, our proposed model could translate in the implementation of accurate and  
414 efficient local surveillance and biosecurity measures within a specific produc-  
415 tive context, or immunization practices where available. For example, in areas  
416 where the disease is present and vaccination is not implemented, control strate-  
417 gies based on the analysis of bulk milk at dairy farms would greatly reduce  
418 the overall costs of testing while ensuring a good coverage and efficiency at the  
419 system level, as it has been done for other diseases (Muratore et al., 2017). In  
420 Switzerland, near-eradication has been achieved by serological testing of every  
421 head, followed by bulk milk surveillance of disease-free farms (Thomann et al.,  
422 2017). This might also be performed in Italy as well, should sufficient resources  
423 become available. Given the importance of trade movements, quarantine mea-  
424 sures following movements and the regulation of sales according to the disease  
425 status of a farm or a region would also be extremely important in BVD mitiga-  
426 tion, as previously also suggested by (Courcoul and Ezanno, 2010) and as done  
427 for other diseases.

428 Other productive classes have a more limited role in the spread and mainte-  
429 nance of BVD. Fattening farms, for example, tend to be receivers and gatherers  
430 of PI animals. However these are mainly sent directly to slaughterhouses, thus  
431 reducing their impact on further spatial spread. Beef farms with on-site re-  
432 production and mixed production farms are both potentially more dangerous  
433 than fattening farms in propagating the disease because of their transversal and  
434 non-trivial patterns of trade movements across different productive classes. As  
435 mixed attitude farms are mostly small, the resources required for monitoring  
436 them may be limited, and these are the contexts that may individually profit  
437 most from restoring their full productive potential through disease eradication.  
438 However, the use of targeted measures in our simulations predicts that even  
439 complete coverage of this productive class would be no better than the random  
440 application of these interventions. The relative importance and urgency of mea-  
441 sures that are specific to this productive type are probably largely dependent  
442 on a limited local context, and their consideration at a national scale may be  
443 ineffective.

444 Our study predicts a total PI prevalence between 1.22% (95% CI 1.18-1.28%)  
445 and 1.28% (95% CI 1.23-1.34%) from intermediate to high transmission condi-  
446 tions, respectively, when considering prevalence across all productive classes  
447 (for  $\phi = 0.00125\text{week}^{-1}$  and  $\mu = 0.01\text{week}^{-1}$ ). These figures are in line with  
448 the estimates previously reported in a predominance of studies showing similar  
449 prevalence in the range of approximately 0.5% and 2% PI animals in different  
450 countries (Houe, 1999), and thus support our choice for the two higher values  
451 of the transmission rate explored in this study.

452 Direct comparisons with disease prevalence estimates in Italy is difficult,  
453 however, since most sources focus on specific areas or single premises or premise  
454 types (Cavirani et al., 2013; Nigrelli et al., 2009; Luzzago et al., 1999; Ferrari  
455 et al., 1999), thus limiting their generalizability to the national level. Also, the  
456 lack of a nationwide control and surveillance plan in the country implies a strong  
457 heterogeneity of vaccination patterns and control measures. Given the current  
458 situation, our findings may help better informing the design and implementation



459 of a national strategy for intervention and surveillance.

460 Prevalence data will become available over the course of three to four years  
461 once a plan is put into action (Thulke et al., 2017), and any modern interven-  
462 tion strategy should be sufficiently agile to continuously update itself as new  
463 information is obtained.

464 From a modeling point of view, our approach couples within-farm infection  
465 dynamics with cattle trade movements at the national scale, accounting for data-  
466 driven demography and herd structure. This is an important expansion to the  
467 existing modeling literature for this pathogen, as previous works have mainly  
468 focused on the within-farm scale, investigating the infection dynamics within  
469 the herd structure (Viet et al., 2007; Ezanno et al., 2007; Gunn et al., 2004;  
470 Cherry et al., 1998; Innocent et al., 1997b,a; Sørensen et al., 1995; Damman  
471 et al., 2015; Smith et al., 2009; Ezanno et al., 2008; Viet et al., 2004), spurred  
472 by the intrinsic complexity of BVD disease transmission and the lack of accurate  
473 parameter estimates. Importations, however, have been recognized to be impor-  
474 tant for the maintenance of the disease in the farm (Courcoul and Ezanno, 2010;  
475 Ezanno et al., 2008), and synthetic processes for introductions have been consid-  
476 ered. Data-driven movements at the national scale were previously integrated  
477 in a farm-to-farm transmission dynamics, neglecting within-farm structure and  
478 transmission between animals (Tinsley et al., 2012). Neighboring farm effects  
479 were considered in a 100-patches metapopulation model for BVD, however trade  
480 patterns were assumed to be homogeneous in topology and fluxes (Courcoul  
481 and Ezanno, 2010). Several studies have shown on the other hand the large  
482 heterogeneity associated to trade movements (Bajardi et al., 2011; Kao et al.,  
483 2006; Vernon and Keeling, 2009; Lindström et al., 2010; Dutta et al., 2014). In  
484 the Italian dataset for 2014, for example, the number of yearly exchanges with  
485 neighboring farms for animal purchases ranges from 1 to 7019 (1-656 for animal  
486 sales), and animals are moved in yearly batches of 1 to 1534 units. More impor-  
487 tantly, the amount of incoming and outgoing traffic is very heterogeneous across  
488 premises, with many of them exchanging few animals, and some hubs featur-  
489 ing several connections to many other holdings (Valdano et al., 2015). Finally,  
490 comprehensively considering all productive contexts as well as the entire cattle  
491 trade system (144,403 premises vs. 100 dairy farms in (Courcoul and Ezanno,  
492 2010)) allows us to capture the entire trade dynamics, where farms of differ-  
493 ent productive classes are coupled together by non-homogeneous movements, as  
494 well as with marketplaces and other types of premises.

495 The adopted approach presents, however, some limitations. We do not model  
496 transiently infected animals to limit the complexity of our modeling approach  
497 when considering multiple scales up to the national scale. Their role in the  
498 persistence of the disease is still controversial, with modeling studies consider-  
499 ing (Thulke et al., 2017; Viet et al., 2004; Cherry et al., 1998; Innocent et al.,  
500 1997a) or not (Gunn et al., 2004; Sørensen et al., 1995) the associated compart-  
501 ment. Our choice may thus lead to farm prevalence values on the lower side of  
502 the 33-53% estimated in the literature (Nigrelli et al., 2009; Luzzago et al., 1999;  
503 Houe, 1999). These farm-level figures, however, need to be interpreted with cau-  
504 tion, given that the definition of infected farm varies widely across studies (e.g.  
505 depending on the minimum number of PI, or PIL, or transiently infected ani-  
506 mals present in the farm). We also assume that all animals introduced from  
507 abroad are healthy and susceptible. Foreign animal imports account for 18%  
508 of all movements, and 85% of that number follows a direct path to a fattening

509 farm and then to slaughter. Because of this, we consider them to have a limited  
510 influence on disease dynamics. The cattle movement dataset did not report  
511 the country of origin, preventing us to assign an imported animal a country-  
512 dependent probability of being infected. For these reasons, we implicitly assume  
513 imported cattle are healthy. Extending our study to include cross-border move-  
514 ments would definitely provide a more comprehensive picture of the diffusion  
515 dynamics, however it is beyond the scope of the present analysis and would  
516 require the integration of several different datasets. We use a single value for  
517 the  $\varepsilon$  disease diffusion parameter across the system, and use the percentage  $\alpha$   
518 of females of reproductive age on premises to simulate different generation and  
519 spreading potentials across the various productive classes. This approach does  
520 not account, for example, for the varying length of the cow-calf contact window,  
521 or for the spectrum of possible biosecurity measures. We find that our choice is  
522 consistent with the intent of maintaining a data-driven approach and limiting  
523 the number of ad-hoc parameters we consider. It is very difficult to reliably  
524 infer how modern a premise is, and therefore its management routines or biose-  
525 curity practices, with the available data. Further studies and field work would  
526 be necessary to expand the available knowledge on this particular aspect.

527 While we consider the entire geotemporal dataset of trade movements be-  
528 tween premises, we do not include pastures, as these are not compulsorily  
529 tracked in the national database. Mixed production farms and beef farms are  
530 those that may be mostly affected by the lack of these movements, since the  
531 practice of moving to pasture in Italy is typical of small, traditional farms.  
532 While the role of pastures in livestock disease dynamics is currently the ob-  
533 ject of preliminary investigations (Palisson et al., 2017) due to lack of data and  
534 different national practices, neighboring relationships used in (Courcoul and  
535 Ezanno, 2010) to model animal escapes or contacts at pasture were found to  
536 only influence epidemic size.

## 537 **Conclusions**

538 Through a novel data-driven multiscale modeling approach, we show that  
539 farm productive contexts play an important role in the dynamics of BVD diffu-  
540 sion due to their herd composition and the trading patterns they establish. We  
541 find that BVD epidemic is dominated by dairy farms, containing the highest  
542 number of infected animals and representing the largest contribution to the na-  
543 tional farm prevalence. Our model captures the heterogeneity of BVD dynamics  
544 in a realistic way. Most importantly, our study suggests possible avenues for  
545 the implementation of efficient interventions based on the targeted application  
546 of control measures to dairy farms. This may contribute to the mitigation and  
547 eradication of the disease, and reduction of associated costs. Though the pre-  
548 sented work focuses on a single country and a specific disease, the approach can  
549 easily be applied to other geographical or epidemiological contexts where trade  
550 and herd composition are important element for disease diffusion.

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555 **Conflict of interest**

556 The authors declare no conflict of interest

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563 contract no. ANR-13-ANWA-0007-03 (LIVEepi).

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