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Risk factors for detection of bovine viral diarrhoea virus in low-risk herds during the latter stages of Ireland's eradication programme

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ABSTRACT

Background: A national programme to eradicate bovine viral diarrhoea (BVD) has been in place in Ireland since 2013. To inform decision making in the end stages of eradication, and support the development of post-eradication surveillance strategies, an understanding of risks of infection in a low prevalence system is required.
Methods: A case-control study design was implemented. The study population comprised bovine herds that had calves born and tested negative for BVD virus (BVDV) every year from 2013 to 2019 (n = 46,219 herds). We defined cases as herds which had one or more test positive calves for the first time in 2019 (n = 204). Controls (n = 816) were randomly sampled from the herds which remained test negative in 2019. The effects of herd size, management system, inward movements, including those of potential trojan dams (pregnant animals brought into the herd that could potentially be carrying infected calves *in utero*), and proximity to herds testing positive in the preceding year, were investigated. Network analysis approaches were used to generate variables measuring connections with test positive herds through inward cattle movements. A generalised linear mixed model, including a county-level random effect, was used to explore these risk factors.
Results: Our final model retained ln (herd size) (Odds Ratio (95% CI): 1.72 (1.40, 2.12)), distance from test positive herds (0.54 (0.44, 0.66) for each extra land-parcel boundary crossed to reach the closest herd which tested positive the preceding year), and ln (potential trojan dams + 1) (1.29 (1.05, 1.60)). The same variables were retained in the model where herds with confirmed transient infections only (n = 25) were excluded.
Conclusions: Our findings suggest that care with biosecurity at farm boundaries and visitors and equipment entering the farm, and avoidance or careful risk assessment of purchasing potentially pregnant animals, may help prevent introduction of BVDV to low-risk herds. At policy level, consideration of herd size, proximity to test positive herds and purchasing patterns of potentially pregnant cattle may help target surveillance measures towards the end of the eradication programme.

1. Introduction

Bovine viral diarrhoea virus (BVDV) is an important pathogen of cattle causing substantial economic losses and animal welfare challenges from diarrhoea, infertility, abortions, reduced growth and illness associated with immune suppression (Gunn et al., 2003, 2004, 2005; Stott et al., 2012). A cost-benefit analysis estimated that, in Ireland, €102 million per annum of bovine viral diarrhoea (BVD) related losses would be saved through eradication (Stott et al., 2012). To address this, there has been a compulsory eradication programme in place in Ireland since 2013, preceded by a voluntary programme in 2012 (Graham et al., 2021). Similarly to other countries including Switzerland, Germany, Belgium and Northern Ireland, the Irish programme requires the testing of all calves born each year for BVDV, to identify and remove persistently infected (PI) calves as rapidly as possible (Charoenlarp et al., 2018; Graham et al., 2021; Presi and Heim, 2010; Quinet et al., 2016;

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Wernike and Beer, 2019). This programme is based on testing by PCR or antigen test to directly detect BVDV, but widespread serological testing for antibodies against BVDV is not currently conducted (Graham et al., 2021; Thulke et al., 2018). At the start of the compulsory eradication programme in 2013, 11.27% of breeding herds and 0.78% of calves tested were BVDV test positive. In 2019, prevalence had reduced to 0.78% of herds and 0.05% of calves tested, and this fell further to 0.56% of herds and 0.03% of tested calves in 2020 (Animal Health Ireland, 2021a).

The Irish BVD eradication programme has been informed by a series of epidemiological studies. During the voluntary phase of the programme in 2012, region, herd size and inward cattle movements were identified as risk factors for the detection of BVDV, and calf mortality was associated with BVD (Graham et al., 2013). A further study of the voluntary phase showed that the retention of calves considered PI for purposes of the programme (hereafter referred to as “BVD+”) increased the likelihood of further BVD+ calves being born in the subsequent year (Graham et al., 2015a), while reasons for their retention were also investigated (Clegg et al., 2016; Graham et al., 2015b). As well as retention of BVD+ animals, proximity to infected herds was recognised as a risk factor for BVD. A study based on 2014 data reported that herds having any neighbour with a BVD+ animal had an increased risk of testing positive the following year (Graham et al., 2016). A detailed animal-level study showed that the percentage of BVD+ calves attributable to inward movements of pregnant cattle carrying PI foetuses (“trojan dams”) increased as the programme progressed, from 7.1% in 2013 to 10.6% in 2015 (Reardon et al., 2018).

With expanding knowledge, policy has evolved to address PI retention and the risk of infection from neighbours (Graham et al., 2021). Currently, there is increasing stakeholder focus on challenges specific to the periods shortly prior to and following eradication, including targeted surveillance in the context of low herd and animal prevalence, and strategies that will be needed to substantiate BVDV freedom (European Commission, 2016a).

The detection of BVDV in herds with no previous history of infection is of concern, particularly towards the later stages of national eradication. This was partially considered by Barrett et al. (2020) who investigated risk factors for the detection of BVD+ animals in herds during 2017, following at least 12 months of BVDV freedom. Barrett et al. (2020) identified BVDV infection history, herd size, increasing numbers of calves being born (herd expansion), purchase of cattle including potential trojan cattle and the animal-level density of BVD infection within 10 km of the herd as risk factors which informed policy adjustments. Since that study, there has been further detection of BVDV in herds which previously tested negative. Of the 550 test-positive herds in 2019, 489 herds had recorded registered births and test results for calves in every year of the testing programme between 2013 and 2019. Of these, 204 (42%) herds had positive tests for the first time in 2019. Up to this point, there has been considerable focus in the Irish programme on those infection sources that are recognised as the primary risk factors, including PI animals and trojan dams. However, towards the latter stages of an eradication programme the less common, potentially including risk factors in these low-risk herds, may become of relatively greater importance (Klepac et al., 2013). This study is the first to examine risk factors for BVD in this low-risk population in Ireland. New evidence of BVD in herds which have consistently tested negative throughout the eradication programme is potentially similar to the scenario that we will see post-eradication. Therefore, our study may be particularly informative in terms of risks of re-introduction as we consider the post-eradication prevention of BVD.

As well as addressing the need to understand potential risk factors for re-introduction of BVD after eradication, we capitalise on novel approaches to understand the role of cattle movements and proximity to BVD test positive herds as sources of BVDV to low risk herds. As the BVD eradication programme has progressed, there have been concomitant advances in data management and methodological techniques, with the potential to better understand potential drivers for spread of BVD. For example, Graham et al., (2013, 2016) and Charoenlarp et al. (2018) previously highlighted land fragmentation as a potential complicating factor in the spatial analyses of BVD. In the last few years, we have developed the ability to consider each land parcel associated with the majority of Irish herds using the Land Parcel Information System (LPIS, Zimmermann et al., 2016). Network analysis techniques are now also available to better understand linkages between infected and susceptible herds through cattle movements (Tratalos et al., 2020). Analysis from herd investigations suggest that transmission across neighboring farm boundaries and introduction of transiently infected animals as plausible sources of infection (Guelbenzu-Gonzalo, 2021). Both of these risks can be explored further through the application of these new approaches.

In this study, we investigate risk factors for detection of BVDV in the latter stages of the national eradication programme, specifically in those Irish herds in 2019 that had tested negative in each of the previous six years of the compulsory programme. We employ new approaches to investigating the risk of infection from proximity to herds with test positive histories and through inward cattle movements.Specificially, we test the hypothesis that herd size, management system, inward movements of cattle and proximity to test positive herds are associated with detection of BVDV in low-risk cattle herds in Ireland.

2. Methods

2.1. Data

Test results from the Irish BVD eradication programme are processed on behalf of the Department of Agriculture, Food and the Marine (DAFM) and Animal Health Ireland (AHI) by the Irish Cattle Breeding Federation (ICBF) alongside animal and herd-level unique identifiers. DAFM manage databases comprising of all animal, herd, movement and land parcel data. All data usage in this project was conducted in compliance with General Data Protection Regulation of the European Union (European Commission, 2016b).

DAFM’s Land-Parcels Identification System (LPIS) (Zimmermann et al., 2016) was used to delineate the extent of the land occupied by each cattle herd. Following Tratalos et al. (2020), centroid coordinates for each herd were also derived from these data, with the exception of approximately 5% of herds not recorded in the LPIS system. These latter herds were mapped by randomly assigning a location within the electoral division they were located in.

2.2. Software

Data processing was performed in Microsoft SQL Server 2012. The GIS software package ArcGIS 10.6. was used to amalgamate land parcels by herd and then to measure shortest distances between herds. All other analyses were conducted in the R statistical environment (R Core Team, 2019).

2.3. Identification of herds with first detection of BVDV in 2019 and background description of eradication programme

BVD eradication programme data at the level of individual tests, and animal birth data from 2013 to 2019 were reviewed and herds were categorised based on:

- Whether the herd had calves born every year from 2013 to 2019.
- Whether the herd had positive or inconclusive (subsequently referred to as “positive”) BVDV test results in any year before 2019.

The test result for the herd and year was defined as:

- "BVD+ " if at least one calf tested positive on two sequential tests with at least 21 days between them or at least one calf was culled after a single positive test.
- "TI" (transiently infected) if no calves had "BVD+ " status but at least one had a positive result followed by a negative result, with the last recorded result being negative.
- Test negative if the herd had calves born but no positive tests.

To determine whether test negative history had an overall protective effect, herd-level incidence was compared between herds with and without history of detection of BVDV before 2019.

2.4. Case – control study

2.4.1. Case and control definition

A herd-level case-control study was designed to investigate potential drivers of BVDV introduction to herds without any prior evidence of BVDV infection. The source population included all Irish bovine herds with at least one calf born in every year from 2013 to 2019. From these, a study population of herds ('study herds') was selected which had no positive test results for BVDV from 2013 to the beginning of 2019. This selection was to allow us to specifically investigate risk factors for herds in which positive results were detected for the first time. From this study population, cases were defined as herds which had one or more test positive calves born for the first time in 2019 (n = 204 herds) and control candidates were defined as those which tested negative every year up to and including 2019 (n = 46,015 herds). A random sample of 816 controls was taken from these latter herds.

For consistency with case definitions in previous studies (Barrett et al., 2020; Clegg et al., 2016; Graham et al., 2016, 2015a, 2015b), we repeated all of our analyses with the same controls, but with cases including only herds with BVD+ status in 2019 (n = 179 cases). That is, we excluded the 25 cases whose test positive calves were all confirmed as transiently infected.

2.4.2. Power analysis

We used the "epiR" package (Stevenson et al., 2020) to perform a power analysis. With 204 cases and 816 controls, based on a confidence interval of 95%, a 50% exposure prevalence amongst controls, and a required study power of 80%, the effect of a binary variable with an odds ratio (OR) of 1.56 was expected to be detected.

2.4.3. Herd size and expansion

Herd sizes from 1st January, 1st May and 1st September for 2018 and 2019 were averaged to generate a herd size variable for each herd. Herd expansion, as described by (Barrett et al., 2020), was estimated by subtracting the number of calves born in 2015 from the number of calves born in 2019 in each herd.

2.4.4. Herd management system

The herd management categories defined by (Brock et al., 2021) who used Irish cattle data, were calculated for 2019 for case and control herds. Categories used were Beef, Dairy, Mixed, Store and Fattener categories. Herds with Trader and Unknown categories were excluded.

2.4.5. Inward movements

2.4.5.1. Potential trojan dams. Potential trojan dam introductions to the herd were explored by generating a count of cattle which (1) gave birth to calves in 2019 and (2) spent some or all of their window of susceptibility, that is day 30–120 of gestation when the bovine foetus is vulnerable to persistent infection with BVDV (Brownlie et al., 1987), in a different herd to the one where they gave birth. In the multivariable model, we used purchasing patterns of potential trojan dams as a candidate explanatory variable, as our findings relating to this variable could be applied in the future to help target riskbased surveillance for BVDV.

Retrospectively, after conducting the main multivariable analyses, we described (1) how many of the potential trojan dams went on to give birth to test positive calves and (2) how many of the potential trojan dams spent some or all of their window of susceptibility in herds which tested positive for BVDV in 2018 or 2019.

2.4.5.2. Other inward movements. Potential explanatory variables associated with inward movements included counts of animals brought into the herd ('in-strength') and counts of connections with discrete herds ('in-degree') between 01 January 2018 and 21 July 2019 (the risk exposure period). This window was calculated based on the earliest and latest possible windows of susceptibility for calves born in 2019 (26th April 2018–24 th July 2018), and allowing for circulation of transient infection for approximately four months in advance of the start of the earliest window of susceptibility from 1st Jan 2018 (Goto et al., 2021).

Adapting the methodology of (Fielding et al., 2020), connections with BVDV test-positive herds via inward contact chains (ICC) were measured. For each month of the risk exposure period, test positive herds within the ICC of cases and controls were counted. Between one and up to eight links back in the ICC within a four-month window up to the month of interest were considered. These counts of test positive herds in the ICC were then summed for the whole exposure period, excluding duplicate linkages. Counts in the ICC were generated for all test positive herds and for BVD+ herds only in the ICC. ("BVD+ herds only", as opposed to all test positives, means confirmed transient infections were excluded and only herds with animals considered PI for eradication purposes were considered).

2.4.6. Proximity to BVDV test positive herds

2.4.6.1. County-level random effect. Counties are spatial administrative units in Ireland (n = 26). The county in which each herd was registered in was identified form their herd number. The possibility of broad scale spatial clustering of test positives, as well as unquantified local factors, was taken into account by incorporating a county-level random effect on the intercept. Random-slope models were not considered here due to the relatively simple hierarchical structure of the dataset and the sample size.

2.4.6.2. Centroid-based proximity measures. As our case definition was based on detection of BVDV in 2019, we aimed to quantify proximity to infection the preceding year (2018) as a potential risk factor. Counts of 2018 test positive herds within 2, 4, 6, 8 and 10 km of each case and control were generated based on herd centroids. Further, density estimates based on positive herds divided by total herds were generated for each radius. The distance in metres to the closest 2018 test positive herd was also calculated. In addition to considering proximity to all test positive herds, separate measures of proximity to 2018 BVD+ herds only were generated.

2.4.6.3. Land parcel-based proximity measures. In addition to the centroid-based measures described above, land parcel-based measures were also generated. These used the same approach as for centroid-based measures but measured from the edges of land parcels associated with each herd instead of the centroid. In addition, counts of direct neighbours (with land parcel edges within one metre) were generated. In an effort to better capture the potential biology of transmission across farm boundaries, trans-boundary steps to the closest 2018 test positive herd were also quantified. Similarly to the centroid-based measures, in addition to considering proximity to all test positive herds, separate measures of proximity to 2018 BVD+ herds only were generated.

2.4.7. *Model building*

After considering plausible biological models and having summarised and plotted the data at univariable level, we modelled the risk of being a case with a binomial generalised linear mixed model with a logit link as a function of (1) ln (herd size), (2) ln (potential trojan dams +1), (3) management category, (4) one of 54 alternative measures of proximity to test positive herds and (5) one of 18 alternative measures of inward movements. The county where the herd was registered was included in the model as a random effect on the intercept. The term “ln” refers to the natural logarithm of the variables in this study.

There were 18 alternative inward movement measures, and 24 and 30 alternative centroid and land parcel-based measures of proximity to test positive herds respectively (Supplementary Table 1). This meant there were 972 (18 *(24 +30)) candidate full models with the five variables listed above.

Models were implemented with the “lme4” package (Bates et al., 2015). To detect collinearity, correlations between explanatory variables were investigated via plots, correlation coefficients and the variance inflation factor (Fox and Weisberg, 2019). Model fit was assessed by comparing observed and expected values and the Hosmer-Lemeshow test (Hosmer and Lemeshow, 2000).

2.4.8. *Model selection*

Candidate models with AIC values equal to or less than the 5th percentile of the full range were reviewed further (Harrison et al., 2018). For selected models, we conducted stepwise model selection using likelihood ratio testing (LRT), reporting ORs for each step. Standardised ORs (Gelman, 2008) were also reported for the variables retained in the final model. The standard deviation of the county-level random effect was also reported. To facilitate comparison between the magnitude of fixed and random effects, the median odds ratio associated with the random effect, calculated as described by Austin and Merlo (2017) was also presented.

Predicted values based on explanatory variables retained in the final model were extracted for plotting using the “effects” package (Fox and Weisberg, 2019).

Whilst we focussed on reporting the models which we selected for LRT, we also reported the impact on multivariable model AIC of the alternative options for variables describing proximity to test positives and inward cattle movements.

3. Results

3.1. *Background description of eradication programme*

Of the 550 test-positive herds in 2019, 489 had registered births and test results for calves in every year of the testing programme from 2013 to 2019. Of these, 204 (42%) herds had positive results for the first time in 2019. Despite this, having only test negative results in previous years was associated with greatly reduced odds of positive results when compared to herds which had positive results before 2019 [OR: 0.23 (95% CI: 0.19–0.28)].

3.2. *Cases and controls*

From our 816 controls, six herds were located on islands and, as we could not fully investigate proximity to test positive herds in these, they were excluded. A further two herds had “Unknown” or “Trader” herd management categories and were therefore also excluded. After these exclusions, 204 cases and 808 controls remained. All cases and controls had centroid coordinates available for analysis of proximity to test positive herds. Therefore, centroid-based proximity measures to any test positive and BVD+ only herds could be generated for these. A subset of 202 cases and 794 controls also had land parcel data available. That is, spatial polygons delineating each fragment of land associated with the herd were available (Zimmermann et al., 2016). For these cases and controls, we generated both centroid-based and land parcel-based proximity measures of proximity to any test positive and to BVD+ only herds. Fig. 1 shows approximate anonymised locations of cases and controls in Ireland.

3.3. *Description of potential explanatory variables in the case-control study*

Fig. 2a–c show that cases had larger herd size, fewer trans-boundary steps between them and the closest herd which tested positive the preceding year (2018), and more potential trojan dams. Fig. 1d shows that dairy and mixed management systems were associated with larger herd sizes compared to beef and store herds. Full details of univariable analyses, which show significant differences between cases and controls for all potential explanatory variables considered, are available in the supplementary materials (Supplementary Table 1, Supplementary Figures 1–4).

3.4. *Multivariable model results*

3.4.1. *Final model selection*

The candidate full model with the lowest AIC contained the explanatory variables ln (herd size), herd management category, ln (potential trojan dams +1), trans-boundary steps to the closest 2018 test positive herd and the ICC variable considering up to 8 linkages back to a BVD+ herd. When we applied a LRT to this model, ln (herd size), ln (potential trojan dams +1) and trans-boundary steps to closest 2018 test positive herd were retained. Herd management category and the ICC variable considering up to 8 linkages back to a BVD+ herd were dropped. The ORs of each variable at each step of model selection, and the standardised ORs for the final model, are reported in Table 1 and

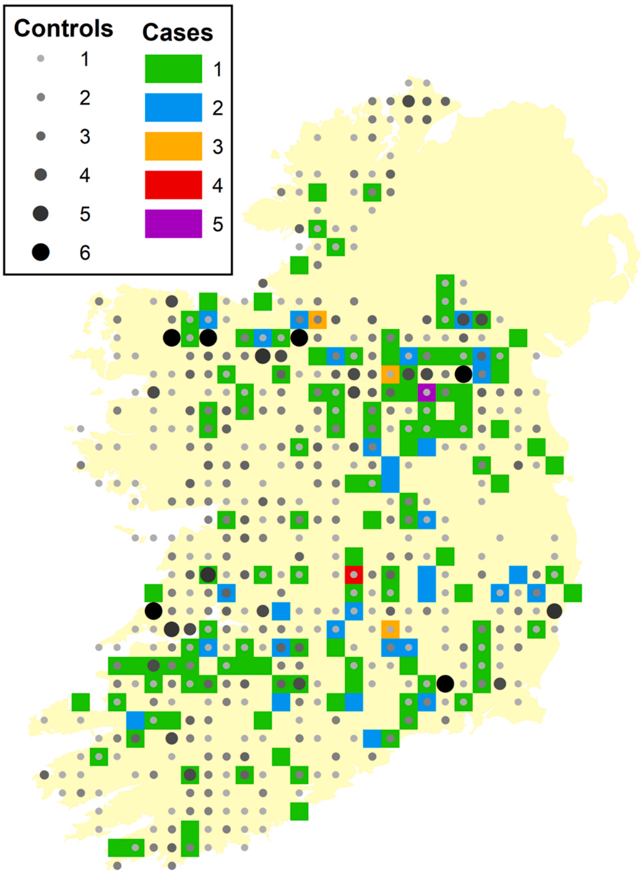

Fig. 1. Anonymized approximate locations of cases and controls.

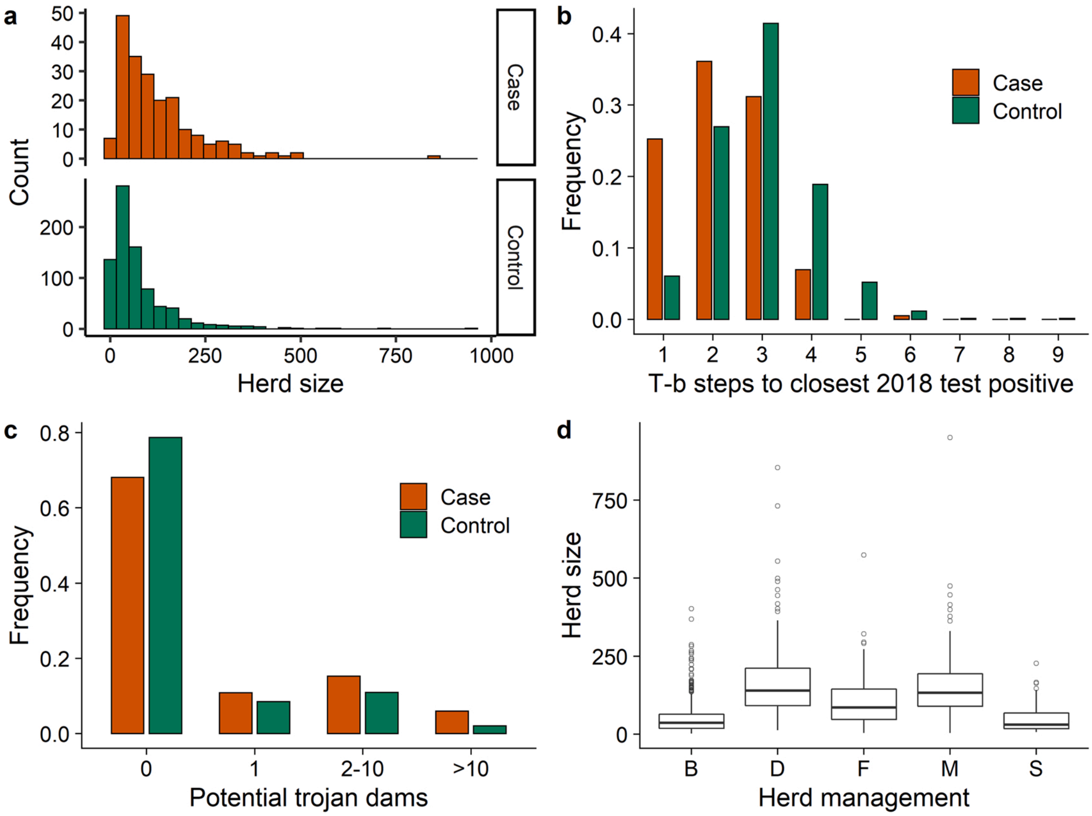

Fig. 2. Plots comparing case and control herds in regard to (a) herd size, (b) trans-boundary (t-b) steps to the closest 2018 test positive (c) categorised counts of potential trojan dams. Plot (d) shows herd sizes of different management categories, either beef (B), dairy (D), fattener (F), mixed (M) or store (S).

Supplementary Table 2 gives further detail on LRT results. Based on this final model, Fig. 3a-c describe the predicted probability of being a case based on ranges of values of herd size, trans-boundary steps to the closest 2018 test positive herd and count of potential trojan dams. Fig. 3d plots observed against fitted values. Supplementary figure 5 shows the effect of each county-level random effect on the intercept of the final multivariable model.

3.4.2. *AIC comparison of two best fit models*

Whilst “trans-boundary steps to the closest 2018 test positive” was associated with the lowest AIC candidate full model (AIC=874), the centroid-based count of 2018 test positive herds within 2 km also featured amongst the lowest AIC full model candidates (AIC=877). Therefore, a second LRT was conducted with the alternative full model using the “centroid-based count of 2018 test positive herds within 2 km” as the proximity variable. Ln (herd size), ln (potential trojan dams +1), count of 2018 test positive herds within 2 km and the ICC variable considering up to 8 linkages back to a BVD+ herd were retained in the final alternative model, and herd management category was dropped. This alternative final model had an AIC of 872. The more parsimonious final model (subsequently termed “final model”) containing “trans-boundary steps to the closest 2018 test positive” ln (herd size) and ln (potential trojan dam +1), but no ICC variable, had a marginally lower AIC of 871.

To ensure that exclusion of herds missing land parcel data was not biasing our results, we repeated our analyses for all available cases and controls with centroid data. That is, herds missing land parcel data were not excluded and therefore only centroid-based proximity measures could be considered. Consistently with findings reported above, the final model in this sensitivity analysis retained the ln (herd size), ln (potential trojan dams +1), count of 2018 test positive herds within 2 km and the ICC variable considering up to 8 linkages back to a BVD+ herd and dropped herd management category (Supplementary Tables 3 and 4).

3.4.3. *Further exploration of proximity and inward movement variables*

3.4.3.1. *Proximity variables.*

Fig. 4 shows that the “trans-boundary steps to the closest 2018 test positive” and “count of 2018 test positive herds within 2 km of the herd centroids” were the proximity variables associated with the lowest AIC values amongst candidate models, but also that all measures of proximity to test positive herds improved the multivariable model fit. For the majority of these measures, those quantifying proximity to any 2018 test positive herd were associated with lower AIC values compared to those quantifying proximity to 2018 BVD+ herds only (Fig. 4).

We conducted a sensitivity analysis to investigate whether removing the county-level random effect altered the pattern of fixed effect retention during model selection. Although removing the county-level random effect resulted in a poorer fit to the data, the same final models were selected. We show the results of this sensitivity analysis in Supplementary table 5.

3.4.3.2. *Inward movement variables.*

Fig. 5 shows that ICC variables considering larger numbers of links back in the movement chain were associated with slightly lower AIC values compared to lower numbers of links. However, their impact in lowering the AIC of the most parsimonious model was marginal (Fig. 5b) and not sufficient to be retained based on LRT (Table 1, Supplementary table3). Fig. 5 also highlights lack of support for including “in strength” or “in degree” movement variables in the models.

Further details of the candidate full model selection process are available in the Supplementary results 1.

3.4.4. *Consideration of BVD+ case herds only*

When the 25 case herds with confirmed transient infections only were removed from our dataset, and the same modelling process

Table 1
Odds ratios (OR) for each explanatory variable at each stage of the model selection process for the final model. Standardised ORs (Std OR) are also presented for the final model. Ln=natural log. T-b = trans-boundary. ICC measure (8 steps) = Inward contact chain quantification of BVD+ herds up to eight steps back. *P value from a likelihood ratio test (LRT) comparing final multivariable model with and without explanatory variable. Full details of LRT results are available in Supplementary Table 2. A county level random effect (n = 26 counties) was incorporated in the model. The standard deviation of the random effect was 0.50 at each step of model selection. Median OR associated with the random effect, for comparison to fixed effects, was 1.63.

Variable	OR (95% CI) Full model	OR (95% CI) Step 1	OR (95% CI) Final model	Std OR (95% CI) Final model	P value*
Ln (herd size)	1.57 (1.22, 2.00)	1.71 (1.39, 2.11)	1.72 (1.40, 2.12)	3.03 (1.98, 4.64)	< 0.001
T-b steps to closest test positive	0.53 (0.44, 0.65)	0.54 (0.44, 0.66)	0.54 (0.44, 0.66)	0.26 (0.17, 0.41)	< 0.001
Ln (potential trojan dams +1)	1.22 (0.98, 1.51)	1.25 (1.00, 1.55)	1.29 (1.05, 1.60)	1.44 (1.07, 1.95)	0.018
ICC measure (8 steps)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)			0.103
Management system					0.631
Beef	Referent				
Dairy	1.44 (0.86, 2.42)				
Fattener	1.01 (0.48, 2.16)				
Mixed	1.10 (0.59, 2.03)				
Store	0.54 (0.21, 1.39)				

repeated, the same final models were selected. (Detailed results not shown.).

3.4.5. *Herd expansion*

We did not include herd expansion in our main model selection process as it was correlated with herd size (Pearson correlation coefficient = 0.58) and we deemed herd size to be more relevant biologically. However, as an extra investigation, we exchanged herd expansion for herd size in the final model and herd expansion was not retained ($X^2 = 1.43$, df=1, p = 0.23).

3.4.6. *Extra descriptive analyses of potential trojan dams*

3.4.6.1. Potential trojan dams which went on to give birth to test positive calves. As shown in Supplementary Table 1, 66 (32.4%) of the 204 case herds and 169 (21.0%) of the 808 control herds had potential trojan dams present. This constituted 564 births from potential trojan dams in case herds and 755 births from potential trojan dams in control herds, giving a total of 1319 potential trojan dams in the study population. Test records showed that 27 (2.1%) of these potential trojan dams went on to give birth to calves which tested positive for BVDV in 26 different case herds. These 27 births of BVD test positive calves from potential trojan dams represented 7.4% of the total 365 test positive calves in case herds. These were born in 26 (12.7%) of the case herds. For comparison, we conducted the same analyses for any test positive herd in the full Irish population in 2019 (n = 550 test positive herds and 1136 test positive calves). We detected 107 test positive calves born from potential trojan dams, constituting 9.4% of all test positive calves. These were born in 80 (14.5%) of the overall test positive herds in Ireland. Although these suspect trojan births appeared to constitute slightly higher proportions of test positive calves and herds in the general population compared to our case herds, this difference was not significant (Calf level: X-squared = 1.4, df = 1, p = 0.24; Herd level: X-squared = 0.4, df = 1, p-value = 0.53).

3.4.6.2. Windows of susceptibility spent in herds which tested positive in 2018 or 2019. Of the 564 potential trojan dams in case herds, 17 spent at least part of their window of susceptibility in a herd which tested positive for BVDV in 2018 or 2019. Six of these went on to have test positive calves. Therefore, 22.2% (6/27) of potential trojan dams in case herds, which went on to give birth to test positive calves, spent at least part of their window of susceptibility in herds which tested positive in 2018 or 2019. For comparison, amongst the 107 potential trojan dams in the general population that gave birth to test positive calves, the proportion of these dams which spent at least part of their window of susceptibility in 2018/19 test positive herds was similar (23/107, 22.0%). Of the 755 potential trojan dams in control herds, seven spent at least part of their window of susceptibility in herds which tested positive in 2018 or 2019 but did not go on to give birth to test positive calves.

4. Discussion

In the later stages of the Irish BVD eradication programme, detection of BVDV infections in herds that consistently tested negative will assume a greater importance. Understanding the risk factors associated with these new infections is required both to target efforts during the later phases of eradication and for the design of risk-based surveillance strategies post-eradication. We address this through a case-control study based on a population of herds which have consistently tested negative since the beginning of the compulsory eradication programme in 2013. We considered herd size, management system, cattle movements and proximity to test positive herds as potential risk factors associated with detection of BVDV. Our analysis showed that the most important risk factors were herd size, proximity to herds which tested positive the preceding year, and introduction of potential trojan dams.

4.1. *Herd size*

Herd size has been a consistent risk factor for BVDV infection throughout the Irish BVD eradication programme (Barrett et al., 2020; Graham et al., 2016, 2013). A meta-analysis of European BVD risk factor studies similarly shows herd size as an important risk factor (van Roon et al., 2020).

Larger herds may be at greater risk of exposure to BVDV through introduction of infection through introduced cattle, shared boundaries with neighbouring farms and location in proximity to other large herds in high cattle density areas. We have attempted to capture some of this in our model by incorporating a county-level random effect, land parcel-based measures of proximity to infection, and a suite of cattle movement metrics. However, herd size may still function as a partial proxy measure for some of these elements. Field epidemiological investigations suggest that BVDV introduction may be possible via visitors and equipment entering the farm (Gethmann et al., 2015; Guelbenzu-Gonzalo et al., 2021). Herd size may also be associated with these potential indirect BVDV transmission pathways.

After disease introduction, as larger herds have more cattle managed together, there may be an increased chance of exposure of a pregnant animal in the window of susceptibility. Within-herd seroprevalence of BVDV increases with herd size, suggesting increased transmission possibilities within larger herds (Barrett et al., 2018).

4.2. *Management system*

Similarly to previous Irish work (Barrett et al., 2020; Graham et al., 2013), management system was not retained in our final model. Dairy and mixed herd management systems were associated with cases in our

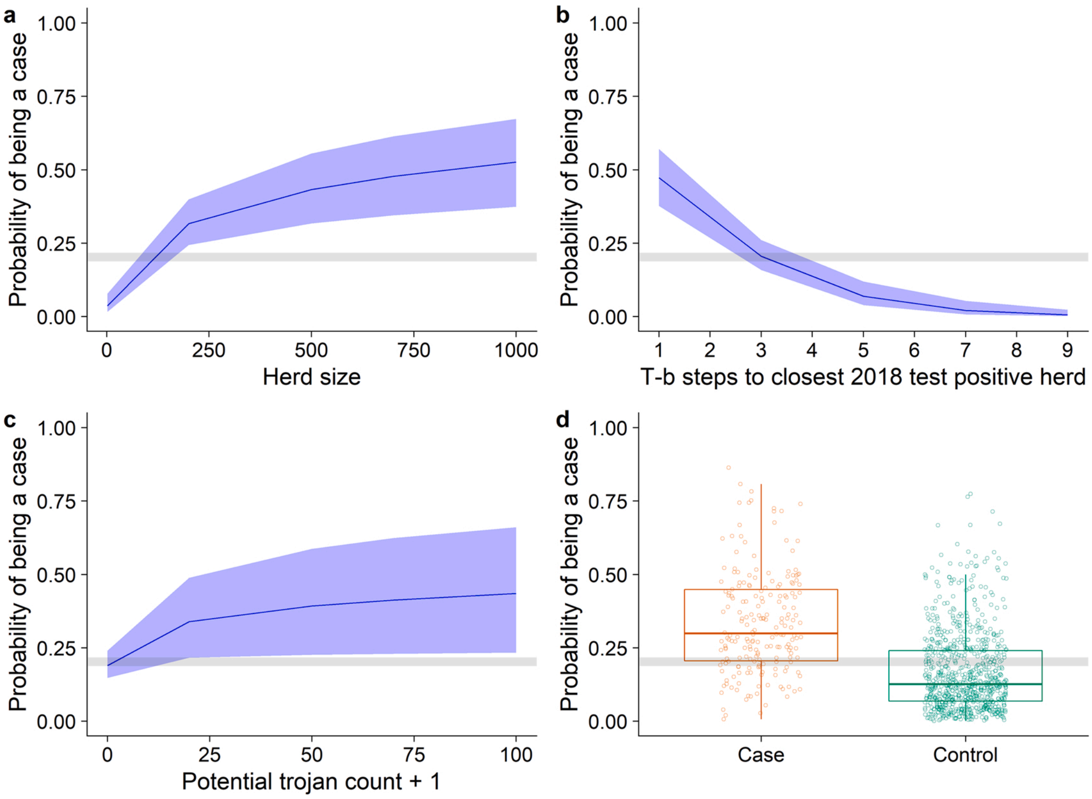

Fig. 3. The predicted probability of being a case from the final model in Table 1, based on (a) herd size, (b) trans-boundary (t-b) steps to the closest 2018 test positive, and (c) count of potential trojan dams. The boxplot in (d) summarises the fitted probability of being a case amongst true cases and controls. The grey horizontal line in each plot represents the proportion of cases in the dataset.

univariable analyses, but this may be because they have larger herd sizes. Fattener and store herds, which were under-represented amongst cases, have fewer calves born compared to other herd types (Brock et al., 2021).

4.3. Proximity to infected herds

Model fit was improved with each of the measures of BVDV infection in the neighbourhood that we considered. However, the candidate full models with the lowest AIC values incorporated the number of trans-boundary steps to the closest 2018 test positive herd. There are three possible reasons for this. Firstly, the “distance to closest” approach effectively weights infected herds according to distance from the herd of interest. Secondly, consideration of all the land-parcels associated with each herd (fragmentation) may capture herd to herd contacts that would otherwise be missed. Finally, counting steps across land-parcel boundaries rather than distance in metres may better account for ‘over the fence’/’nose-to-nose’ transmission of BVDV. We had a better fit to our data using trans-boundary steps to the closest 2018 test positive herd compared to minimum distance in metres, based either on farm centroids, or on polygon edges of each land parcel associated with the herd. This suggests that the ‘distance to closest’ approach, even when considering all land fragments associated with each herd, was not the sole reason for the helpfulness of counting trans-boundary steps to the closest test positive. Instead, consideration of ‘over the fence’/’nose-to-nose’ transmission may have helped to explain BVDV positive results in case herds. The count of 2018 test positive herds within the shortest measured distance (2 km) of the herd of interest centroids gave the next best fit to the data, resulting only a marginally higher AIC value when it replaced number of trans-boundary steps to the closest 2018 test positive herd in the multivariable model. This further supports the finding that close proximity to infected neighbours is a risk factor for BVDV infection. This resonates with recent findings in New Zealand (Han et al., 2018), where a Bayesian network model shows that only close animal contacts between farms were directly associated with BVD status. However, it is not possible from our findings to be definitive as to whether transmission of infection is via direct or indirect pathways, or a combination of both. As well as over-the-fence transmission, the trans-boundary steps variable could be potentially capturing indirect transmission via locally acting professionals such as veterinary practitioners, cattle technicians or farm staff who work with cattle in multiple different local herds. As well as animal-to-animal transmission, these indirect transmission mechanisms have been suggested as potential reasons for BVD test positives in herd investigations (Guelbenzu-Gonzalo et al., 2021).

Our finding that proximity to herds with any test positive results contributed to a better explanation of cases compared to proximity to BVD+ herds only may be associated with amplification of the signal of proximity to infection. Alternatively our findings may support the role of transiently infected herds in onward transmission of BVDV when stronger risk factors for infection such as retained PI animals are eliminated, as suggested by a recent report from Japan (Goto et al., 2021). However, this hypothesis requires further investigation in light of the weight of experimental evidence showing that transiently infected animals are less relevant for transmission compared to PI animals (Lindberg and Houe, 2005).

Graham et al. (2016) showed that having any neighbour with a BVD+ animal was a risk factor for having a BVD+ calf but did not compare models measuring infection across wider radii from the herd of interest. A study in the early stages of the Northern Irish eradication programme investigated a series of neighbourhood risk factors for BVDV test positive herds (Charoenlarp et al., 2018). This study showed that risk increased with the number of positive herds within a 4 km radius. However, in that study, other measures such as the distance to the

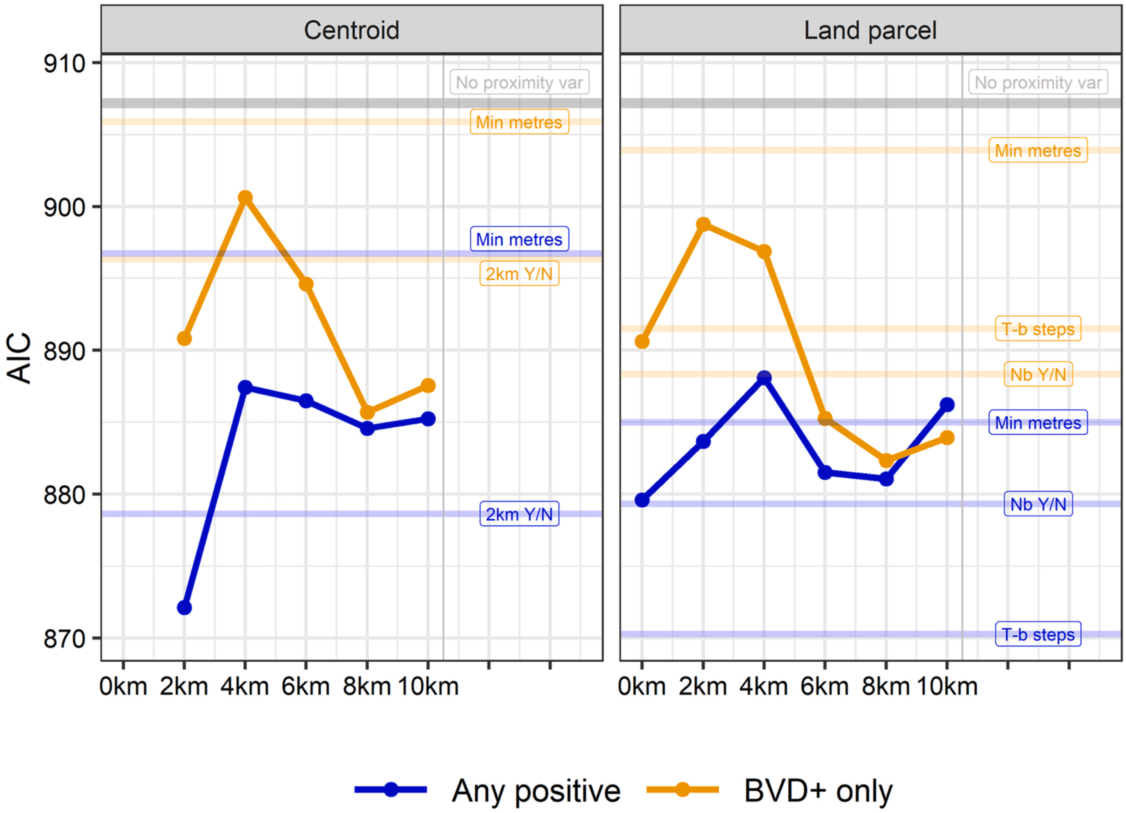

Fig. 4. A summary of the impact on the AIC of the multivariable model of different variables measuring proximity to 2018 test positive (blue) or BVD+ (yellow) herds, based on either centroid- (left plot) or land parcel- (right plot) based measures. The heavier font points and lines represent counts of any test positive/ BVD+ herds within radii between 0 and 10 km of the herd (x-axis). The lighter font horizontal lines and associated labels represent other proximity measures. “No proximity var” = AIC of multivariable model without incorporating any proximity variable. “Min metres” = Minimum distance measured in metres to the closest test positive/BVD+ herd. “2 km Y/N” = binary outcome of whether there is a test positive /BVD+ herd within 2 km. “Nb Y/N” = binary outcome of whether the herd has a direct neighbour which is test positive/BVD+ . “T-b steps” = transboundary steps to the closest test positive / BVD+ herd. For clarity, we have not added the density estimates of test positive herds within the various radii, as these were associated with very similar AIC values to the corresponding count estimates shown on the plots.

closest positive herd, density of test positive herds within 4 km, proportion of test positive animals within the nearest herds did not improve model fit. The general finding that test positive neighbours are important is consistent between our study and the Northern Irish study. Some of the differences in other findings relating to other measures of proximity to infection may be driven by the early stage of the Northern Irish eradication programme analysed by Charoenlarp et al. compared to the low prevalence context in our study. Factors related to within-herd infection history and retained PI animals were likely still important risk-factors in the Northern Irish study whereas these were less likely to feature amongst risk factors in our lower risk population.

Barrett et al. (2020) investigated measures of BVDV infection within 1 and 10 km radii as potential explanatory variables for BVD+ herds and found that density of BVD+ cattle within 10 km of the herd of interest to have a stronger association with cases. Our proximity measures are based on test results at herd rather than animal-level and are therefore not directly comparable to the measures of Barrett et al. However, the incorporation of a county-level random effect was of assistance with our model fitting, suggesting that consideration of wider infection prevalence, suggestive of a “neighbourhood effect” in addition to direct proximity to infection, is helpful. Such a “neighbourhood effect” could possibly be realised through nose-to-nose contact over boundaries or transmission via fomites and personnel moving between farms (Guelbenzu-Gonzalo et al., 2021). We conducted sensitivity analyses to ensure that incorporation of a county-level random effect was not obscuring important fixed effects relating to proximity. Although omitting county resulted in a poorer fit to the data, the same fixed effect explanatory variables were retained in the final model. In summary, the combination of these findings suggest that, relative to all of the proximity variables which we considered, close proximity to any test positive herd is most helpful in explaining detection of BVDV in our study population.

4.4. Cattle movements

Potential trojan dam introductions were retained in our final model. Similarly, Barrett et al. (2020), focussing on BVDV test results of calves born in 2017, found that introductions of female cattle older than twelve months helped explain the detection of BVD+ cases following at least 12 months of BVDV freedom. Graham et al. (2013) also reported that dams introduced within nine months of calving helped explain BVD+ cases in 2012. Our results suggest that trojan dams remain associated with detection of BVDV in previously negative herds in 2019, although LRT and standardisation of odds ratios suggest that herd size and proximity to herds with a positive test history are relatively more strongly associated with detection of BVDV.

For our “potential trojan dam” variable, we counted dams which gave birth in each study herd in 2019 and also spent at least part of their window of susceptibility in a different herd, regardless of whether they subsequently gave birth to a test positive calf. We did not initially perform detailed analyses into which of these animals gave birth to test positive calves, as we wished to include variables in our model which could potentially be used in the future to target risk-based surveillance. Further, Reardon et al. (2018) have already reported detailed, animal level investigations into trojan births. These authors found that 7.1%,

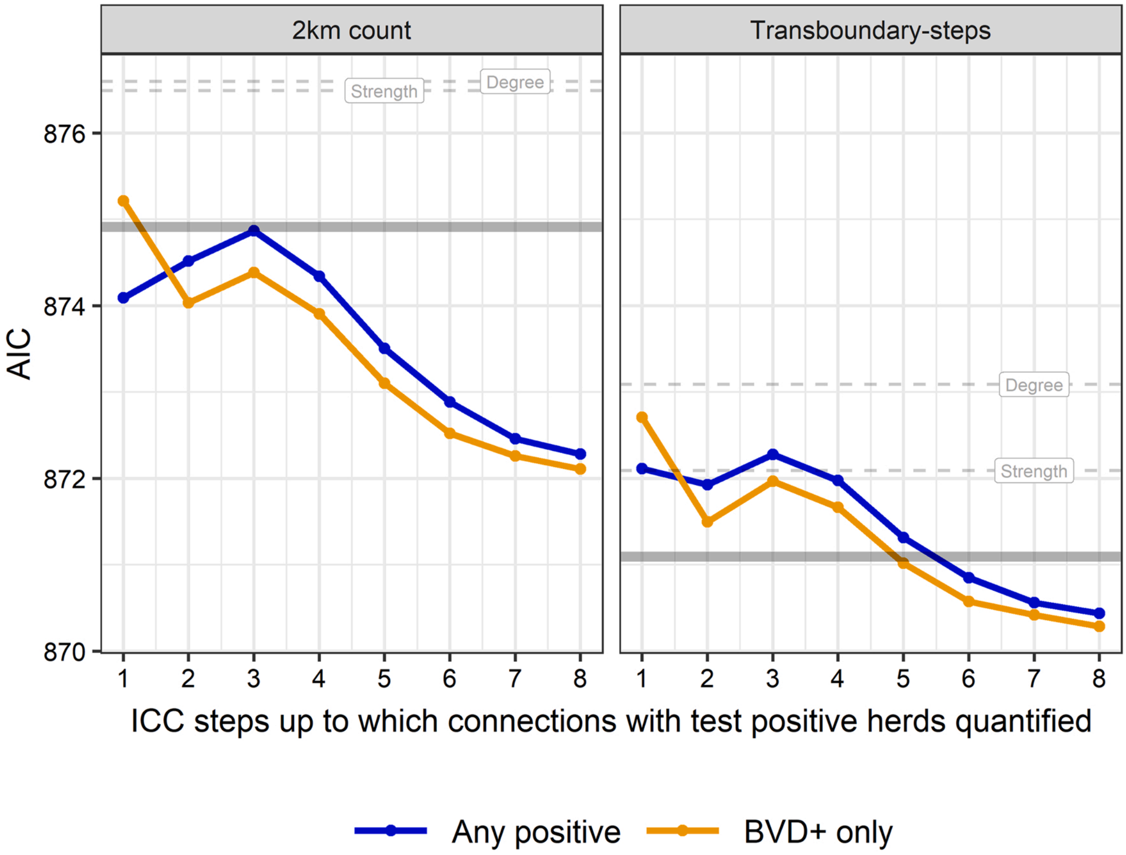

Fig. 5. A summary of the impact of using different inward contact chain (ICC) variables measuring linkages to test positive (blue) or BVD+ (yellow) herds on the AIC of multivariable models. The plot on the left is based on the multivariable model including the count of test herds within 2 km of herd centroid proximity variable. The plot on the right is based on the final model including trans-boundary steps to closest test positive herd as the proximity variable. The dashed grey horizontal lines represent the AIC of models including strength or degree (as labelled on plot). The solid grey horizontal lines represent the AIC of the models without including strength, degree or ICC variables.

9.2% and 10.6% of BVD+ birth events in 2013, 2014 and 2015 respectively were attributed to likely trojan dams. For the same years, Reardon et al. reported 9.9%, 11.8% and 13.3% of BVD+ herds had at least one BVD+ calf born to a likely trojan dam. A retrospective count, conducted after the main analyses in our study, showed similar proportions to Reardon et al. Only 2.1% of the potential trojan dams in our study went on to give birth to test positive calves. This low proportion may suggest that the "potential trojan dam" variable is capturing particular inward cattle movements which represent a separate BVDV introduction risk, in addition to trojan dams. This is again consistent with the findings of Barrett et al. (2020) and Graham et al. (2013) who found that the introduction of female cattle helped explain BVD+ results at herd level.

Unlike the previously unreported ICC variables, we can compare "in-strength" (number of cattle brought into herd) to previous BVD studies. The lack of retention of this variable in our models contrasts with that of earlier findings (Barrett et al., 2020; Graham et al., 2016, 2013; van Roon et al., 2020). However, a key difference between our study and others is that we are focussing on a population that remained BVDV free for six years and was differentiated into cases and controls based on first detection of infection in the seventh year. Both cases and controls in this population may have better biosecurity compared to the wider population. Our background study of all Irish cattle herds showed that herds with a test negative history had greatly reduced odds of testing positive in 2019 compared to herds with test positive histories. Additionally, mandatory controls (Anon, 2017) on the movement of animals from BVD+ herds may have now effectively reduced transmission nationally through cattle movements.

To our knowledge, our study is the first to assess connections with BVDV test positive herds through ICCs as a potential risk factor for BVDV introduction. In contrast to the case with bovine tuberculosis in Britain (Fielding et al., 2020), ICC variables were not retained in our most parsimonious final model which contained land parcel boundary steps to the closest 2018 test positive herd as the proximity variable. The ICC variable was retained in the model with the -second-best proximity variable (2 km centroid-based count of 2018 test positive herds), but it is difficult to explain biologically why the ICC variables considering larger numbers of steps back in the movement chains were most helpful. This warrants further exploration, possibly with a larger dataset.

4.5. Limitations

Our study had several limitations. Firstly, for our ICC explanatory variables, considering herd level infection history in movement chains, as reported by Fielding et al. (2020), may be more appropriate for a disease like bovine tuberculosis where there are higher levels of undetected infection in test positive herds (Wolfe et al., 2009).

A second possible limitation is our assumption about the dynamics of transient infection. Although it is was based on extensive discussions and a recent field report (Goto et al., 2021), our assumption that transient infection can circulate within a herd for four months may also require further interrogation.

Thirdly, no diagnostic test is perfect. Apparent false negatives, for example PI dams which previously tested negative being detected after giving birth to PI calves, are a potential source of infection which we could not fully account for with our methodology. This was reported as an issue towards the end of the Swiss programme (Presi et al., 2011). In the Irish programme, all dams of BVD+ calves are retested for BVDV, regardless of negative test history. Further, if the dams subsequently test positive, all of their calves are traced and retested. In 2019, 25 of these apparent false negative dams were detected in association with 1136 calves which tested positive or inconclusive, but none of these false negatives were in our study herds. As well as this extra effort to detect apparent false negative animals in the programme, there is confidence in the diagnostic quality of the surveillance. A recent review estimated that the diagnostic sensitivity for detection of BVDV within the Irish programme was 99.45%. The “worst case” specificity (taking all positives as false positives in 2020) was estimated to be 99.96% (Graham et al., 2021).

Finally, consideration of animal-level measures of neighbourhood infection, alongside the herd-level measures which we used, may have yielded extra information on local infection dynamics. However, Graham et al. (2016), who investigated both animal-level and herd level measures of infection in the neighbourhood, selected a final model including any BVD+ neighbouring herd, regardless of how many BVD+ animals were within it.

We avoided building very complex models and focussed on approaches with the strongest biological rationale, as we had a relatively small sample size. The fact that we had 204 cases out of a total of 550 test positive herds from 71,773 herds with calves born in 2019 reflects the success of the eradication programme to date.

4.6. *Future directions*

Next steps may include translation of these findings into a surveillance prioritisation tool for use towards the end of the BVD eradication programme. Machine learning approaches using data from the full Irish population may be used in addition to this work to improve targeting of surveillance. Further studies into the spatial epidemiology of BVD in Ireland, incorporating virus typing, are also planned.

4.7. *Conclusion*

We have shown that herd size, proximity to herds with test positive history and inward movements of potential trojan dams are associated with newly detected BVDV in low-risk herds.

The association of cases with close proximity to test positive herds suggests that care with biosecurity at farm boundaries and with visitors and equipment entering the farm may be helpful preventative measures at farm level. Our findings associating inward movements of potential trojan dams suggest careful risk assessment of purchase of potentially pregnant animals may also be warranted. For policy makers, consideration of herd size, proximity to other infected herds and purchasing patterns of potentially pregnant animals may help target surveillance measures towards the end of the eradication programme.

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Declaration of Competing Interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2022.105607.

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