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LANDSCAPE FEATURES AND RESERVOIR OCCURRENCE AFFECTING THE RISK FOR EQUINE INFECTION WITH BORNA DISEASE VIRUS

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ABSTRACT: Borna disease (BD) is a severe endemic and fatal disorder caused by the neurotropic Borna disease virus (BDV) which mainly occurs in horses and sheep. Borna disease virus belongs to the order *Mononegavirales*, which includes many reservoir-bound viruses with high zoonotic and pathogenic properties including the filoviruses and lyssaviruses. Clinically manifest BD occurs in endemic areas of Germany, Switzerland, Liechtenstein, and Austria. A seasonal accumulation of cases in spring and summer, incidences that vary from year to year, and the recent detection of BDV in bicolored shrews (*Crocidura leucodon*) in Swiss endemic areas argue for a natural reservoir. We established a geographic information system analysis of the distribution of 485 equine BD cases in Bavarian (Germany) endemic areas and of the occurrence of 285 records of *C. leucodon* captured in Bavaria. Boosted regression trees were used to identify driving factors of habitat choice and virus prevalence. The distribution model of *C. leucodon* and the prevalence model for BDV had very good accuracy. Mean annual precipitation <900 mm, mean annual temperatures of 8 C, elevation <350 m, low forest cover, and a high percentage of urban fabric and arable land describe the optimal habitat for *C. leucodon*. Occurrence probability of *C. leucodon* was significantly higher in Bavarian BDV-endemic areas than in random areas in Bavaria. The prevalence of BD was higher in urban areas with annual mean precipitation of 800–900 mm, annual mean temperature of 8 C, and elevation >500 m. Our results indicate that the distribution model can accurately predict BD occurrence. Based on these results, practical safety precautions could be derived. The BDV model represents a suitable system for reservoir-bound, neurotropic *Mononegavirales* because it allows analyzing ecologic and biologic aspects that determine virus abundance, maintenance in reservoir species, and transmission to end host species.

Key words: GIS analysis, infectious diseases, prevalence modeling, zoonotic and neurotropic agents.

INTRODUCTION

Borna disease (BD) is an endemic, sporadically occurring, usually fatal disorder caused by the neurotropic Borna disease virus (BDV). Main natural hosts for BDV are horses and sheep but natural BDV infection occurs occasionally in other Equidae, farm animals, and zoo or companion animals (Rott and Becht, 1995; Staeheli et al., 2000; Richt et al., 2007; Richt and Herden, 2008; Herden and Richt, 2009). In its biological behavior BDV is unique (De la Torre, 2006; Herden and Richt, 2009), but in several aspects it is comparable to other zoonotic and neurotropic *Mononegavirales*, thereby also applicable as a representative and suitable model system. Typically many of the neurotropic and zoonotic *Mononegavirales* are maintained inconspicuously in reservoir species but can cause severe and often lethal diseases in the end host. The underlying mechanisms for virus maintenance in reservoir species, and correlation to particular landscape features, are still only rudimentarily understood. Thus, deeper insights into environmental factors and resulting reservoir abundance are needed to assess risk of infection for the end host. For survival in the reservoir species, circumvention of the antiviral host immune response is important (Brown et al., 2006; Schneider and Ayres, 2008;

Griffin 2010). It can result in immune tolerance and viral persistence in the reservoir species and is often associated with shedding of high quantities of infectious virus without severe clinical signs. For example, BDV infection of neonatal or adult immune-compromised Lewis rats (*Rattus norvegicus*) leads to a disseminated virus distribution with high virus titers in their organ systems (Narayan et al., 1983; Stitz et al., 2002), in contrast to the strict neurotropism of BDV in adult rodents (Porombka et al., 2008; Werner-Keišs et al., 2008; Herden and Richt, 2009). The transmission path via secretions and excretions (e.g., saliva, urine) has been verified in experimental studies (Sauder and Staeheli, 2003). It is assumed that intranasal infection via the olfactory nerve represents the natural route of infection (Morales et al., 1988; Herden and Richt, 2009). This could indicate that end hosts such as horses and sheep might be infected via contaminated food or litter. In the end host, BDV typically causes BD based upon a T cell-mediated immunopathologic process resulting in severe nonpurulent meningoencephalitis (Staeheli et al., 2000; Priestnall et al., 2011). Mortality in horses approaches 90% (Dürrwald and Ludwig, 1997; Grabner et al., 2002; Richt et al., 2007).

Clinically manifest equine BD occurs in endemic areas of eastern and southern Germany, Switzerland, Liechtenstein, and Austria. For Bavaria, Germany, where several endemic areas exist, over 500 cases of equine BD have been documented since 1990 (Reichelt, 2010). A seasonal accumulation of cases in spring and early summer, incidences that vary from year to year, and the recent detection of BDV infection in bicolored shrews (*Crocidura leucodon*) in endemic areas in Switzerland strongly suggest a natural reservoir and a heterogeneous occurrence of reservoir species that largely depends on climate and geographic conditions (Staeheli et al., 2000; Dürrwald et al., 2006; Hilbe et al., 2006; Herden and Richt, 2009; Puorger et al., 2010). *Crocidura leucodon* is native to Central Europe and prefers dry, temperate habitats and occurs in woodlands and grasslands. These shrews burrow tunnels under rock piles or thick brush and are also found in urban fabric (e.g., gardens, farmlands, and farm buildings; Kraft, 2008).

Our aim was to determine ecologic, geographic, and biologic factors that can influence abundance and maintenance of BDV by analysis of equine BD cases and occurrence data of *C. leucodon* in Bavaria based on geographic information systems (GIS). The application of GIS analysis for prevalence modeling and risk assessment of emerging viruses and vectors has already been shown to be useful (Purse et al., 2004; Cooke et al., 2006; Linard et al., 2007) in modeled viruses including bluetongue virus in the Mediterranean area (Purse et al., 2004) and West Nile virus in the Mississippi, United States area (Cooke et al., 2006). Most predictions are based on climatic and geographic variables that could affect virus and reservoir abundance. An adequate analysis is only possible in an innovative interdisciplinary approach combining mammalian ecology, molecular and epidemiologic virology, and veterinary pathology. Due to the phylogenetic and biologic proximity of BDV to other neurotropic and zoonotic *Mononegavirales*, the utility of the BDV model was tested and evaluated in general but also for its applicability for animal-equine health management. For the GIS analysis we hypothesized a link between BDV infection and the occurrence of a natural host such as *C. leucodon*. Once the factors that increase the risk of equine infection with BDV are identified, these could be avoided in the keeping of potential end hosts such as horses.

MATERIALS AND METHODS

We calculated a distribution model for *C. leucodon* and a prevalence model for BDV. Models were fitted using boosted regression trees (BRTs) implemented in the statistical

TABLE 1. Occurrence of Borna disease virus and *Crocidura leucodon* across habitat types. For *C. leucodon* the detection method is given.

	Borna disease virus		*Crocidura leucodon*				
	Presence		Presence				
Occurrence	*n*	%[a]	*n*	%[a]	Owl pellets (%)[b]	Carcass (%)[b]	Trapping (%)[b]
Urban fabric	82	17	83	29	76	21	4
Industrial area	7	1	1	0	0	100	0
Arable land	142	29.3	116	40.7	91.4	7.8	0.9
Pastures	69	14	30	11	90	7	3
Heterogenous agricultural areas	68	14	44	15	86	9	5
Forests	115	23.7	10	3.5	50.0	40.0	10.0
Inland water shore	2	0	1	0	0	0	100

[a] Percent by habitat type.

[b] Percent by detection method.

program R (R Development Core Team, 2010) with the gbm libraries (Ridgeway, 2006) and the modifications of gbm.step provided by Elith et al. (2008). Two main parameters were required to fit a BRT model. The first was the learning rate that controls the model complexity. High learning rates only allow for a small number of trees fitted in the model but with high individual influence (Elith et al., 2008). The second was the tree complexity, which controls whether interactions are fitted. For example, a tree complexity of 2 would allow for two-way interactions. Based on these two parameters the optimal tree number was chosen for prediction (Elith et al., 2008). There are two possible approaches to determine the best learning rate and tree complexity: an independent test set or cross-validation (Elith et al., 2008). We chose the method of 10-fold cross-validation and compared the deviance reduction between models. We chose the settings for learning rate and tree complexity when the deviance was minimized (Elith et al., 2008; Williams et al., 2010). In both of the final models the learning rate was set to 0.001 and tree complexity was set to 5. To introduce randomness into the BRTs we chose the default bag fraction of 0.5. This has the advantage of higher accuracy and a reduction of over-fitting (Friedman, 2002). We chose best predictors for both models using the function gbm.simplify (Elith et al., 2008). For the distribution model for *C. leucodon* we chose the variables elevation (German Federal Agency for Cartography and Geodesy, Giessen, Germany), annual mean temperature (Hijmans et al., 2005), mean annual precipitation (Hijmans et al., 2005), and occurrence of forest, urban fabric, and arable land (European Environment Agency, Copenhagen, Denmark). The variables of elevation, precipitation, temperature, and the occurrence of urban fabric explained best the variation in the prevalence model for BDV. The BRTs were calculated using R. Model performance was evaluated by area under curve (AUC) and relative error analysis (Reineking and Schröder, 2004). The AUC is a single-number measure for evaluating machine learning algorithms (Ling et al., 2003) and describes the area under the receiver operating characteristic curve, which is a plot of the true positive rate vs. the false positive rate achieved by varying discrimination thresholds. The relative error describes the deviation of the prediction from the actual record. For all of the models the classification of Hosmer and Lemeshow (2000) was adopted: AUC>0.9 = "very good," AUC>0.8 = "good," and AUC>0.7 = "acceptable" performance.

For the distribution model we used 285 records of *C. leucodon* in Bavaria, Germany (Kraft, 2008) captured between 1990 and 2007. These data were collected throughout Bavaria. To keep regional bias low, three sampling methods were combined (Kraft, 2008). Presence data of *C. leucodon* were recorded by trapping, searching for carcasses, or examining owl pellets. Continuity of *C. leucodon* remains in owl pellets in the study area throughout the years is high (98.25%; Kraft, 2008; Table 1). The same number of species pseudo-absence points was generated. These pseudo-absence points were created as random points in the GIS ArcGIS Desktop (ArcMap Version 9.3.1, ESRI Inc., Redlands, California, USA) by Hawth's Analysis Tools v3.27 (Beyer, 2004). Pseudo-absence points were generated with a minimum distance of 1,000 m to presence and other pseudo-absence points. These pseudo-absence points

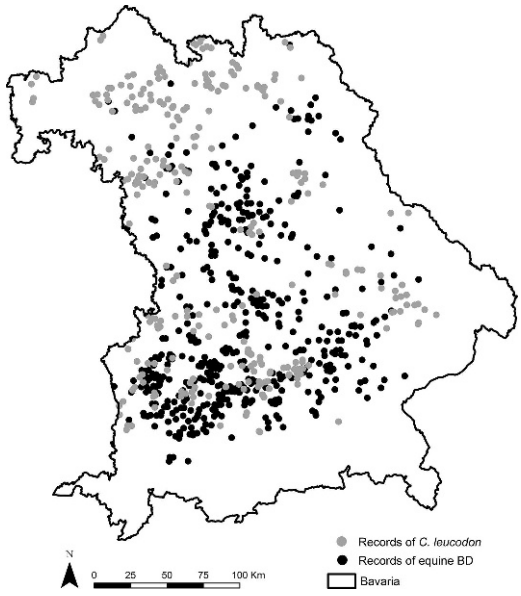

FIGURE 1. Presence records for the bicolored shrew (*Crocidura leucodon*; $n=285$) and records of equine Borna disease (BD) cases ($n=485$) in Bavaria, Germany.

were generated without reference to sampling bias completely at random (Phillips et al., 2009). This is an often-used method (Elith and Leathwick, 2009), even though it might strongly influence the quality of the final model (Engler et al., 2004). However, the use of pseudo-absence points increases model performance compared to presence-only modeling (Chefaoui and Lobo, 2008). To allow for spatial inaccuracy in the point data we buffered all presence and pseudo-absence points with a radius of 100 m. For BRT analysis we used the average of the mean annual temperature, precipitation, altitude, and the percentage of forest, urban fabric, and arable land cover in these buffers.

The prevalence model is based on 485 cases of equine BD recorded between 1990 and 2011, and the same number of pseudo-absence random points, buffered and distanced like in the distribution model for *C. leucodon*. The records were composed of documentations of the Bavarian Animal Disease Fund, the First Medical Animal Hospital of the University of Munich, the National Investigation Office South Bavaria in Oberschleissheim, the National Investigation Office North Bavaria in Erlangen/Nürnberg, the Institute of Virology of the Justus-Liebig-University of Giessen, and the Veterinary Office of Bavaria. In all of Bavaria BD is subject to registration and, depending on the region where BD occurs, different institutes are responsible for data registration. By collecting BD presence data from all available institutes we were able to minimize geographic information bias in our data (Table 1). Any BDV infection was confirmed in each case intra vitam as well as by postmortem diagnostics (Reichelt, 2010). To allow for spatial inaccuracy BD presence data were also buffered with a 100-m radius and the buffer average was used for modeling.

To cross-validate any relationship between the occurrence of *C. leucodon* and cases of BD, we predicted BD occurrence by the use of the distribution model of *C. leucodon*. If the distribution model of *C. leucodon* can accurately predict occurrence of BD cases then we would expect a high AUC.

For statistical analysis we used Statistica 9 (StatSoft, Tulsa, Oklahoma, USA). Due to a nonparametric distribution we compared occurrence probability between endemic BDV and random areas with Mann-Whitney *U*-tests.

RESULTS

Records of *C. leucodon* were dispersed throughout Bavaria with a focus in the northwest and the central south (Fig. 1). Records of equine BD clustered in the central southwest, reflecting the endemic Bavarian areas (Fig. 1).

The distribution model of *C. leucodon* had very good accuracy (AUC 0.9; Fig. 2). The total mean deviance was 1.386 ± 0.035 SE and the mean residual deviance was 0.73 ± 0.023 SE. The optimal number of trees was reached at 3,900. Based on the relative influence, mean annual temperature (28.2%) and percentage of forest cover (22.4%) are the best predictors of *C. leucodon* distribution. The BRT response curves revealed that mean annual precipitation <900 mm, mean annual temperatures of 8 C, elevation <350 m, low forest cover, and a high percentage of arable land and urban fabric describe an optimal habitat for *C. leucodon* (Fig. 3a–f).

The prevalence model for the BDV had very good accuracy (AUC 0.9). The total mean deviance was 1.386 ± 0.045 SE and the mean residual deviance was 0.83 ± 0.031 SE. The optimal number of trees was reached at 3,600. For this model mean

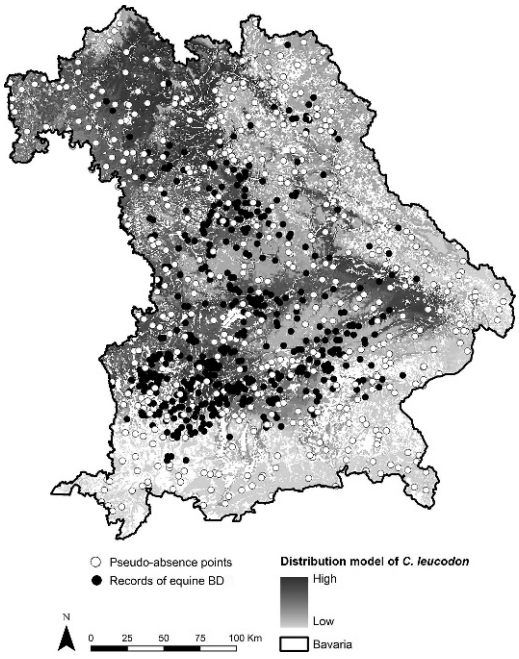

FIGURE 2. Dispersion of 485 records of equine Borna disease (BD) cases between 1990 and 2011 and random points on the probabilistic model for the occurrence of bicolored shrews (*Crocidura leucodon*).

annual temperature (44.7%) and mean annual precipitation (24.4%) were the main predictors. The BRT response curves showed that prevalence of BD was higher in areas with an annual mean precipitation of 750–900 mm, annual mean temperature of 8 C, elevation >500 m, and a high percentage of urban fabric (>10%).

Cross-validation of BD cases with the distribution model of *C. leucodon* revealed that the distribution model can accurately predict BD occurrence (AUC 0.7). Occurence probability of *C. leucodon* is significantly higher in BDV endemic areas from 1990–2011 (n=485, median occurrence probability of *C. leucodon* = 0.35, min-max = 0.00–0.90) than in random areas in Bavaria (n=485, median=0.19, min-max=0.00–0.90; U=101155.0, P=0.0002).

DISCUSSION

GIS analysis as a tool for prevalence modeling and risk assessment of emerging viruses and vectors has been shown to be useful (Purse et al., 2004; Cooke et al., 2006; Linard et al., 2007). Most predictions are based on climatic and geographic variables that could affect virus and reservoir abundance. To allow such modeling, primary generation of reliable datasets is a prerequisite for prediction of spread-dissemination of a virus and its reservoir species and further risk assessment of infection under present and modulated conditions (e.g., climate change or human disturbance). Therefore, in our study occurrences of BD in 1990 and 2011 were correlated with a known virus reservoir, *C. leucodon.* Respective data have been generated in Bavaria where endemic areas are well known. Recent investigations confirm *C. leucodon* as a reservoir species also in Bavaria (J.A.E., unpubl. data). Our initial analysis revealed that BDV occurrence was not randomly distributed throughout Bavaria but centered in the southwest, reflecting current endemic areas (Heinig, 1969; Kolodziejek et al., 2005; Reichelt, 2010). This frequency of occurrence was correlated best with high mean annual temperatures, low precipitation, and a high percentage of urban fabric. In these endemic areas incidence of *C. leucodon* was higher than expected by chance. This might be explained by the preference of *C. leucodon* for dry habitats such as grasslands but also rural areas and farm buildings such as stables (Nowak, 1999; Kraft, 2008). *Crocidura leucodon* is a known reservoir for BDV (Hilbe et al., 2006; Puorger et al., 2010) and, while infection risk in horses might be low while they are kept on pasture, this might change when horses are stabled. To prevent damage of the greensward of wet meadows, and due to a higher risk of trauma or infection with diseases including the common cold or equine influenza, owners often keep their horses preferentially stabled, especially during autumn and winter. Because *C. leucodon* is often found in stables and outhouses during

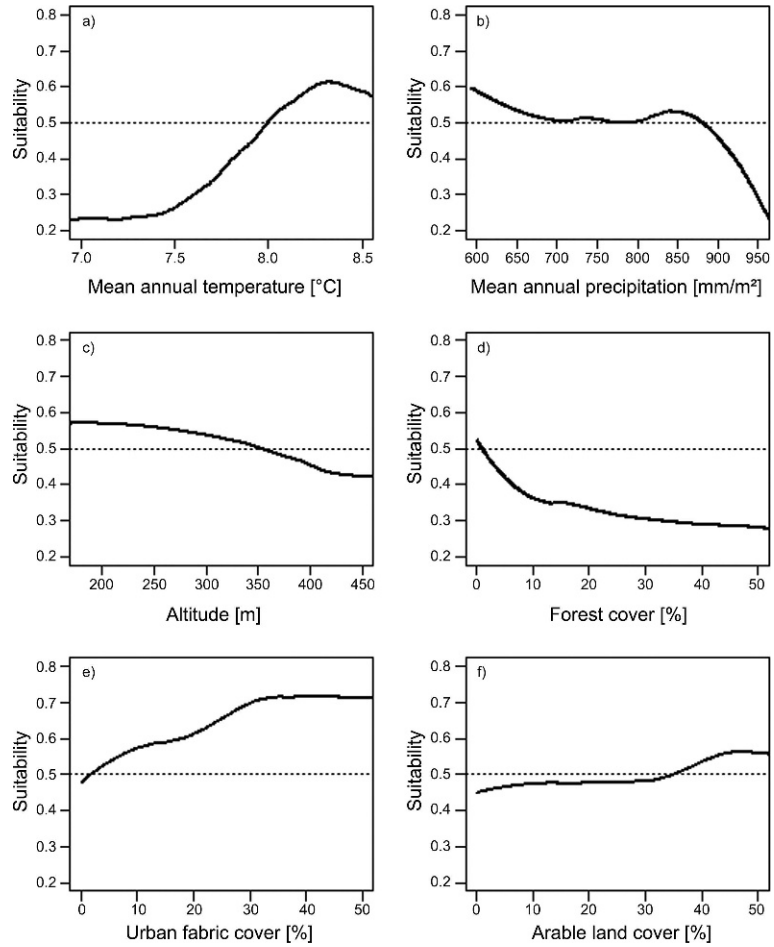

FIGURE 3. Boosted regression tree response curves of the distribution model for the bicolored shrew (*Crocidura leucodon*). A value above 0.5 indicates suitable habitat. (a) Mean annual temperature, (b) mean annual precipitation, (c) elevation, (d) forest cover, (e) urban fabric cover, (f) arable land cover.

times of restricted food availability (e.g., in winter or bad weather; Kraft, 2008), the transmission of BDV from reservoir to the end host most likely occurs in the stable, where more-intense contact with contaminated food or litter occurs. This can be hypothesized to be the crucial time frame in which the virus spreads to horses and other Equidae. Expecting an incubation period of 2–6 mo, as assessed by recent natural cases of BDV infection (Jacobsen et al., 2010; Reichelt, 2010; Priestnall et al., 2011), the accumulation of BD cases in spring and early summer fits well with this scenario. Moreover, *C. leucodon* is mainly insectivorous but, under food shortage, it can be omnivorous (Krapp, 1990), which further increases potential transmission via food or litter. It has been noted that BD occurs more often on farms with mixed stock of horse, sheep, and cattle and lower hygiene standards (Dürrwald et al., 2006).

Due to its recovery within the past 30 yr, *C. leucodon* no longer has special conservation status in Germany (Temple and Terry, 2007). In Bavaria it is one of the most common small mammals within its distribution area (Kraft, 2008). This might be due to an increase of the mean temperature and milder winters. In the northwest of Bavaria, *C. leucodon* is also

abundant (Kraft, 2008) but cases of BD occur only occasionally with increasing tendency. This might reflect the lower rate of infection in the recovered *C. leucodon* population in this area. Thus, the recovery of the population might correlate with more BDV infections between the years 2000–2009 (Reichelt, 2010). To date, nothing is known about the spread of BDV infection in the reservoir species. It remains to be addressed whether other small mammals (e.g. other insectivores) can act as reservoirs for BDV, but previous studies in wild rodents have not provided evidence for BDV infection (Vahlenkamp et al., 2002; Kolodziejek et al., 2005; Hilbe et al., 2006; Puorger et al., 2010). Our own recent studies indicate an antibody prevalence of approximately 4% among 700 small mammals trapped in Bavaria (Herzog and Essbauer, unpubl. data). Experimentally, bank voles (*Myodes glareolus*) exhibited disseminated spread of BDV and genome integration of BDV fragments (Kinnunen et al., 2011). Nothing is known about BDV in bats despite their serving as reservoirs for many other *Mononegavirales* (Calisher et al., 2006; Wong et al., 2007). Several bats, including *Myotis nattereri* (Natterer's bat), *Pipistrellus pipistrellus* (common pipistrelle), *Eptesicus serotinus* (serotine bat), and *Myotis mystacinus* (whiskered bat) occur in barns and stables in large reproduction colonies (Dietz et al., 2009). Data from experimental and natural BDV infections indicate that the host spectrum is broader than anticipated (Staeheli et al., 2000; Richt and Herden, 2008), which further underscores the suitability of this model for reservoir and species transmission analysis in general. This assertion is supported by our results, which show that the areas with highest prevalence for BD in Bavaria are at a higher elevation than expected for *C. leucodon*. This might suggest another reservoir species, such as *M. glareolus*, which is more abundant in higher habitats (Kraft, 2008). Overall, we have found a coarse spatial pattern in the relationship between BDV and *C. leucodon*. This is valuable for generating new hypotheses, but the biologic and ecologic relationships of BDV and *C. leucodon* need further investigation.

Regarding equine health management, occurrence of rodents and insectivores in horse stables should be prevented. The most effective method is to store food in tight-locking reservoirs such as decommissioned top-opening freezers or double-walled containers. Limiting air circulation to mostly the upper parts of the stable and sealing the ground-level regions could also prevent small mammals from entering. Stables and barns should be kept clean and roughage and litter should be checked for living or dead small mammals, body parts, and feces before feeding or spreading of bedding material. Instead of large quantities of bedding, which present an attractive nesting site for mice, rubber stall mats could be inlaid and overlaid with a thin coat of straw or wood chippings. If rodents or insectivores are already present intensive pest control is required (Hone, 2007).

The BDV system has been proven useful for analyzing ecologic, geographic, and biologic aspects that determine virus abundance, maintenance in reservoir species, and transmission to end host species. This is as a suitable model for other reservoir-borne, neurotropic *Mononegavirales* but also for risk assessment for animal-equine health management.

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