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Seasonality and risk factors for myxomatosis in pet rabbits in Great Britain

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ABSTRACT

Myxomatosis is a highly contagious, frequently fatal viral disease affecting both wild and domesticated European rabbits across many areas of the world. Here we used electronic health records (EHRs) collected from pet rabbits attending a sentinel voluntary network of 191 veterinary practices across Great Britain (GB) between March 2014 and June 2019 to identify new features of this disease's epidemiology. From a total of 89,408 rabbit consultations, text mining verified by domain experts identified 207 (0.23 %) cases where myxomatosis was the only differential diagnosis recorded by the attending practitioner. Cases occurred in all months but February and were distributed across the country. Consistent with studies in wild rabbits, the majority of cases occurred between August and November. However, there was also evidence for considerable variation between years. A nested case control study identified important risk factors for myxomatosis within this pet animal population including season, sex, age, vaccination status and distance to likely wild rabbit habitats. Female entire rabbits were twice as likely to be a case (odds ratio (OR) 1.98, 95 % confidence interval (CI) 1.26–3.13, p = 0.003), suggesting a novel role for behaviour in driving transmission from wild to domesticated rabbits. Vaccination had the largest protective effect with vaccinated rabbits being 8.3 times less likely to be a case than unvaccinated rabbits (OR = 0.12, 95 % CI 0.06-0.21, p = < 0.001).

Using a health informatics approach, we add new understanding to seasonal patterns of myxomatosis, confirming existing risk factors and identifying new ones that together can inform targeted health messages to rabbit owners and veterinary practitioners aimed at reducing the impact of this preventable disease. The surveillance of disease in pet rabbit sentinels also provides novel insight to disease in wild sympatric rabbit populations where infection is maintained.

1. Introduction

Myxomatosis is an important disease affecting rabbits globally caused by myxoma virus (MYXV), a member of the poxvirus family (Bertagnoli and Marchandeau, 2015; MacLachlan and Dubovi, 2017). More rarely the virus has also been shown to infect brown hares (*Lepus europaeus*) (Barlow et al., 2014) and most recently, Iberian hares (*Lepus granatensis*) (García-Bocanegra et al., 2019).

Myxoma virus induces a benign disease in its natural host, American *Sylvilagus* rabbits. However, the disease can be severe and is often fatal in the European rabbit (*Oryctolagus cuniculus*; 'rabbits' and variants of, hereafter), as well as derived pet, experimental and farmed species (Bertagnoli and Marchandeau, 2015). The virus causes profound disease in most susceptible animals, starting around four days post-infection with characteristic clinical signs including blepharoconjunctivitis and swelling of the face, ears and anogenital region (Meredith, 2013). Affected rabbits become febrile and extremely lethargic, the vast majority dying within 48 h of the onset of clinical signs (MacLachlan and Dubovi, 2017). Classically secondary tumour-like lesions can develop, that can vary in extent and form between viral strains, and from which the virus takes its name (Marlier et al., 1999; Simpson et al., 2017).

The significance of myxomatosis lies not just in the disease of pet and farmed animals, but also in its ecological impact on wild rabbits where natural infections of naïve animals can decimate populations (Kerr, 2012; Kerr and Best, 1998). This led to the use of the virus in the early 1950s in Australia and parts of Europe as a biological control agent of wild rabbit populations (Kerr et al., 2015). Declines in rabbit populations have ecological and economic implications, impacting predator species and grassland ecological communities, as well as the rural economy (Flowerdew et al., 1992). The virus was first reported in

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the UK in 1953 (Bartrip, 2008). Subsequently, the virus and the rabbit have undergone co-evolution leading to the emergence of more resistant rabbits, and viruses of altered virulence (Alves et al., 2019; Best and Kerr, 2000; Ross et al., 1989).

Rabbits become infected with MYXV following close contact with diseased animals. However, transmission is more likely if an individual is bitten by infected rabbit fleas (*Spilopsyllus cuniculi*) (Lockley, 1954; Ross et al., 1989; Sobey and Conolly, 1971) and mosquitos (Brugman et al., 2015; Service, 1971). The disease in wild rabbits is most prevalent in the UK between late summer and early winter (August-January), with a secondary winter-spring peak (February- April) driven primarily by the timing and success of the main rabbit breeding season, the proportion of susceptible rabbits, and other causes of mortality (Ross et al., 1989). Effective control of the disease in pet rabbits is typically achieved by reducing contact with vectors and wild rabbits, as well as by vaccination (Meredith, 2013). Several attenuated or recombinant virus vaccines have been available and generally offer good protection of vaccinated animals (Spibey et al., 2012). Vaccine uptake however has been limited, with approximately 50 % of UK veterinary-visiting pet rabbits lacking a recorded vaccination history (Sánchez-Vizcaíno et al., 2018).

Despite the importance of this virus to pet, farmed and wild rabbits, there is little known about its overall ecology and risk factors for infection. Here we take a novel approach based on health record data to explore host, vaccine and seasonal factors affecting presumptive myxomatosis cases in a primarily pet rabbit population seen in a sentinel network of veterinary practices from across GB.

2. Materials and methods

2.1. Data extraction and inclusion criteria

Electronic health records (EHRs) were collected between March 2014 and June 2019 from SAVSNET, the Small Animal Veterinary Surveillance Network, a sentinel network of 191 volunteer veterinary practices using compatible practice management software and recruited based on convenience across Great Britain. In participating practices, data are collected from each booked consultation (where an owner has made an appointment to see a veterinary surgeon or nurse). Owners are given the option to opt out at the time of their consultation, thereby excluding their data. For those that participate, data are collected on a consultation-by-consultation basis and can include information about the animal (e.g. species, breed, sex, neuter status, age, owner's postcode, insurance and microchipping status), as well as a free-text clinical narrative that had been pre-processed to remove most inadvertent personal identifiers, treatments given, and the vaccination history. SAVSNET has received ethical approval from the University of Liverpool Research Ethics Committee (RETH000964). For a full description of SAVSNET, see Sánchez-Vizcaíno et al. (2017).

To explore the seasonality and risk factors for myxomatosis, clinical narratives were first screened using a Python regular expression to identify those consultations referencing the word myxomatosis and identified term variants and misspellings, whilst reducing common false positives such as documented myxomatosis vaccination. The final regex was

```
? < !(\svac|ivac|vacc|cine|\s[vr]hd|\snob|ster))\smyx[oi]\s?(?!-
?_?/?\s?\+?(rhd|vhd|rhv|vac|a02|a01|a1\d|and))
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Retrieved narratives were subsequently read by the authors (BH or AR) to identify those involving rabbits with lesions recorded in the clinical narrative that, in the opinion of the attending practitioner, were extremely likely to be caused by myxomatosis, and where no other differential diagnoses were recorded: this was the case definition.

In order to determine risk factors associated with myxomatosis, we conducted a retrospective case-control study; control rabbit consultations (1 case: 5 controls) were randomly chosen from the entire database of rabbit consultations excluding those that were detected by the regular expression.

2.2. Animal data

For each case and control, the date of consultation, the owner's postcode, and the rabbit's sex, date of birth, neuter status and vaccination history were retrieved from their health record. Manual reading of clinical narratives was used to classify other relevant clinical or outcome data such as clinical signs and euthanasia. Many cases had incomplete information regarding breed, which was therefore excluded from the analyses.

The date of the most recent recorded myxomatosis vaccination was used to categorise each animal into those vaccinated between 8 and 365 days ago (likely protected based on duration of immunity experiments), those vaccinated less than 8 days ago (likely not protected), and those vaccinated more than 365 days ago (beyond approved duration of immunity), as well as those with no recorded myxomatosis vaccination.

Owner postcodes were used to calculate both Nomenclature of Territorial Units for Statistics (NUTS) 1 codes (European Commission, 2016), and latitude and longitude (Anon, 2019). Latitudes were further divided into equal quintiles, with Lat1 being the most southerly. For each quintile the number of myxomatosis cases per 1000 total rabbit consultations was calculated for each month. Data on the degree of urbanisation for each postcode were also obtained using a 10-fold score for England and Wales (Biddy and Brindley, 2013) and a 7-fold score for Scotland (Scottish Government, 2019). Regions 1 and 2 in Scotland, and A, B and C in England and Wales were classified as urban locations ($>$ 10,000 population) with the remaining classified as rural ($<=$ 10,000 population) (Government Statistical Service, 2018).

Finally, we looked to explore the proximity of wild and pet rabbits. Since discrete population density estimates and occurrence data do not exist for wild rabbits across most of Britain (Mathews et al., 2018), we therefore calculated the Euclidean distance between individual points (i.e. case / control) and the nearest patch of suitable wild rabbit habitat. Suitable habitats were identified *a priori* and extracted from the CORINE Land Cover (CLC) 2018 Version 20 raster (European Environment Agency, 2019). These included *pastures* (CORINE code 2.3.1), *complex cultivation patterns* (2.4.2), *land principally occupied by agriculture with significant areas of natural vegetation* (2.4.3), *broad-leaved forest* (3.1.1), *mixed forest* (3.1.3), and *natural grassland* (3.2.1)(Gibb, 1990; Hulbert et al., 1996; Trout et al., 2000). The minimum distance between individual points and the nearest patch of suitable habitat was calculated using ArcGIS (Redlands, 2011).

2.3. Statistical analysis

Univariable logistic regression was conducted utilising case control status as a binary dependent variable. Every explanatory variable (Table 1) was explored, with a likelihood ratio test (LRT chi-squared test) being used to assess fit compared to a null model. Continuous explanatory variables were assessed to ascertain presence (or absence) of a clear linear relationship with the dependent variable. Explanatory variables with an LRT of $p \leq 0.2$ were included in an initial multivariable logistic regression model. Interactions between sex and neuter status were included in the initial multivariable logistic regression model. A backwards selection process was utilised in order to produce a model fit with the lowest Akaike information criterion (AIC) possible. Multicollinearity in the final multivariable model, assessed via the Variance Inflation Factor (VIF), was not found to be present. No two-way explanatory variable interactions beyond sex and neuter status were found to improve final multivariable model fit. All analyses were carried out using R version 3.4.4 (R Core Team, 2015).

Table 1
Univariable logistic regression investigating ten variables as potential predictors of myxomatosis cases in rabbits from 191 veterinary practices throughout GB. Significant variables are shown in bold. Total cases = 177. Total controls = 1170 controls. [a] Standard error, [b] Odds Ratio, [c] 95 % Confidence Interval.

Variable	Category	Case N (%)	Control N (%)	beta	SE [a]	OR [b] (95% CI) [c]	p value
Region (NUTS1)	UKJ (Intercept) (South East)	40 (22.6)	289 (24.7)	−1.98	0.17		
	UKC (North East)	11 (6.2)	107 (9.1)	−0.3	0.36	0.74 (0.35–1.45)	0.41
	UKD (North West)	13 (7.3)	81 (6.9)	0.15	0.34	1.16 (0.57–2.22)	0.67
	UKE (Yorkshire & Humber)	28 (15.8)	127 (10.9)	0.47	0.27	1.59 (0.93–2.69)	0.08
	UKF (East Midlands)	14 (7.9)	68 (5.8)	0.4	0.34	1.49 (0.74–2.83)	0.24
	UKG (West Midlands)	7 (4.0)	89 (7.6)	−0.57	0.43	0.57 (0.23–1.24)	0.19
	UKH (East of England)	44 (24.9)	178 (15.2)	0.58	0.24	1.79 (1.12–2.86)	0.02
	UKI (Greater London)	1 (0.6)	5 (0.4)	0.37	1.11	1.45 (0.07–9.26)	0.74
	UKK (South West)	10 (5.6)	144 12.3()	−0.69	0.37	0.5 (0.23-0.99)	0.06
	UKL (Wales)	3 (1.7)	43 (3.7)	−0.68	0.62	0.5 (0.12–1.47)	0.27
	UKM (Scotland)	6 (3.4)	39 (3.3)	0.11	0.47	1.11 (0.4–2.62)	0.82
Sex	Male (Intercept)	75 (42.4)	664 (56.7)	−2.18	0.12		
	Female	102 (57.6)	507 (43.3)	0.58	0.16	1.78 (1.29–2.45)	< 0.001
Neutered	Entire (Intercept)	140 (79.1)	538 (46.0)	−1.35	0.09		
	Neutered	37 (20.9)	632 (54.0)	−1.49	0.19	0.23 (0.15-0.33)	< 0.001
Microchipped	No (Intercept)	175 (98.9)	1070 (91.4)	−1.81	0.08		
	Yes	2 (1.1)	100 (8.6)	−2.1	0.72	0.12 (0.02-0.39)	0.004
Land type	Urban (Intercept)	119 (67.2)	868 (74.2)	−1.99	0.1		
	Missing	2 (1.1)	8 (0.7)	0.6	0.8	1.82 (0.27–7.38)	0.45
	Rural	56 (31.6)	294 (25.1)	0.33	0.18	1.39 (0.98–1.95)	0.06
Vaccination status	No vaccine recorded (Intercept)	155 (87.6)	453 (38.7)	−1.07	0.09		
	Vaccinated < 7days (not protected)	5 (2.8)	304 (26.0)	−3.04	0.46	0.05 (0.02-0.11)	< 0.001
	Vaccinated 8–365 days (protected)	13 (7.3)	356 (30.4)	−2.24	0.3	0.11 (0.06-0.18)	< 0.001
	Vaccinated > 365 days (out of date)	4 (2.3)	57 (4.9)	−1.58	0.53	0.21 (0.06-0.51)	0.003
Sex and neuter	Male entire (Intercept)	53 (29.9)	280 (23.9)	−1.66	0.15		
	Female entire	87 (49.2)	258 (22.1)	0.58	0.19	1.78 (1.22–2.62)	0.003
	Female neutered	15 (8.5)	249 (21.3)	−1.14	0.31	0.32 (0.17-0.56)	< 0.001
	Male neutered	22 (12.4)	383 (32.7)	−1.19	0.27	0.3 (0.18-0.5)	< 0.001
Season	Quarter 1; Jan-March (Intercept)	6 (3.4)	288 (24.6)	−3.87	0.41		
	Quarter 2; April - June	17 (9.6)	322 (27.5)	0.93	0.48	2.53 (1.04–7.1)	0.05
	Quarter 3; July – Sep	88 (49.7)	292 (25.0)	2.67	0.43	14.47 (6.76–37.59)	< 0.001
	Quarter 4; Oct - Dec	66 (37.3)	268 (22.9)	2.47	0.43	11.82 (5.46–30.94)	< 0.001
		median [range]	median [range]				
Age	Age at consultation			−1.95	0.09		
		2.0 [0.0–10.7]	3.3 [0.0–13.0]	−0.42	0.09		< 0.001
Distance to habitat	Distance to habitat			−1.91	0.08		
		0.17 [0.0–4.26]	0.27 [0.0–5.85]	−0.27	0.11		0.01

3. Results

When applied to the full SAVSNET database of 89,408 rabbit consultations, the final regex identified a total of 1551 consultations Fig. 1). Manual reading identified 212 consultations (13.7 %) that satisfied the case definition of active and highly likely myxomatosis. These 212 consultations included 12 consultations from six rabbits that had each visited the veterinary practice twice within a 10-day period and were considered to be suffering from the same episode of disease; only the first consultation was kept for each. In 14 consultations, more than one animal was involved (2–3); only single cases were included for each of these. Manual reading of the controls identified one additional case that contained a spelling variation not detected by the regex (myxamatosis); this animal was redefined as a case giving a final data set of 207 cases and 1224 controls. Of the cases, 68.8 % mentioned swelling of the eyes, 45.7 % inflammation of the genitals and, 20.9 % inflammation of the ears, 59.4 % were euthanised at first presentation, 18.8 % had euthanasia recommended, and in 21.7 % of cases animals were sent home.

Case or control animals lacking either a valid age (n = 35), where postcode could not be mapped (n = 46) or that were in Northern Ireland (n = 1) were excluded from statistical analyses, leaving a final dataset of 177 cases and 1170 controls. Descriptive statistics for all categories are shown in Table 1, which also highlights the six of eight predictor variables that were significant in the univariable analyses.

Temporally, there was clear evidence of both annual seasonality and yearly variation (Fig. 2. Data here were expressed as a proportion of the total number of cases per 1000 rabbit consultations collected by

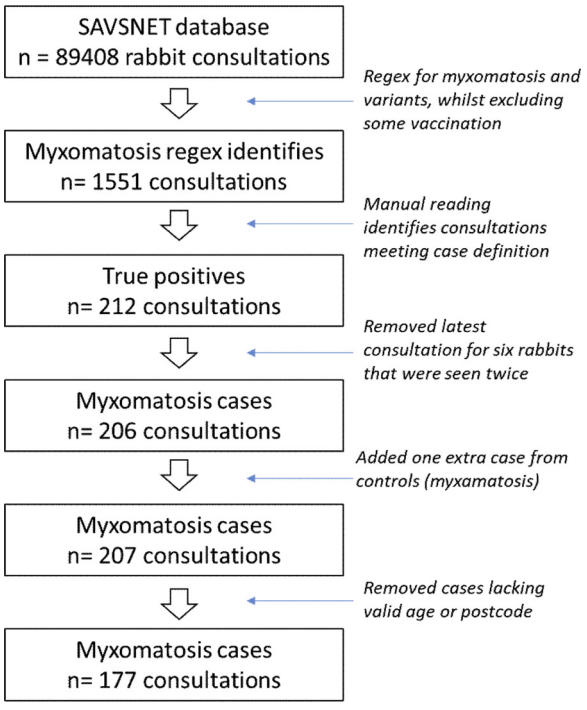

Fig. 1. Criteria used to extract the consultations and episodes of myxomatosis from the SAVSNET database for use in the final analyses.

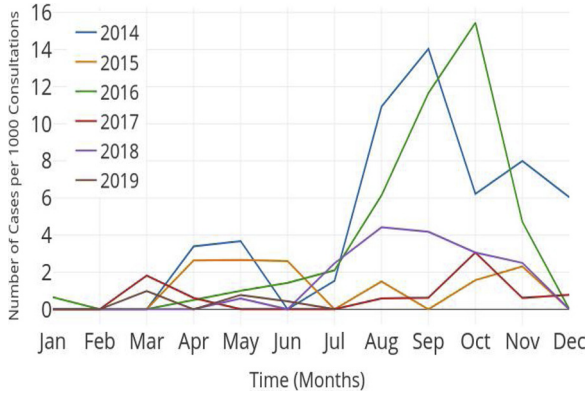

Fig. 2. Seasonal and annual variation of myxomatosis in Great Britain between 2014 and 2019; cases are expressed per 1000 total rabbit consultations per month.

SAVSNET, taking into account that these numbers have grown annually as the number of practices participating in SAVNSET have grown from 4667 to 20,555 rabbit consultations per year in 2014 and 2019 respectively. Apart from 2015, myxomatosis cases peaked between August and November. The seasonal peak was highest in 2014 and 2016, moderate in 2018 and lowest in 2015 and 2017. For 2014 and 2015, a second generally smaller peak was also evident between April and June. Geographically, cases were dispersed across GB showing a broadly similar seasonality across all latitudes Fig. 3).

Results of multivariable analysis are shown in Table 2. The highest odds were modelled in Eastern England (UKH) but none reached significance. Vaccination within 365 days had a profound negative impact on risk, whereas all yearly quarters were associated with an increased risk compared to quarter 1 (January – March), particularly high in quarter 3 (July-September) and 4 (October-December). Sex and neuter status appeared to have a complex pattern of interaction: compared to male entire rabbits, male neutered rabbits were at a reduced risk and female entire rabbits at increased risk. Each year of additional age was associated with a reduction in myxomatosis risk (Fig. 4a). Although predictions of rural and urban status were not part of the final model, increasing distance from owner postcode to predicted rabbit-suitable habitats was also associated with a reducing probability of disease (Fig. 4b).

4. Discussion

Myxomatosis is an important disease of rabbits at many levels. As well as its impact on pet animal health and welfare, it has profound implications on the ecology of wild rabbit populations globally, has been used as a model to describe host and pathogen co-evolution, and is a rare example of introducing infectious agents to control animal populations (Villafuerte et al., 2017). Despite this there have been few

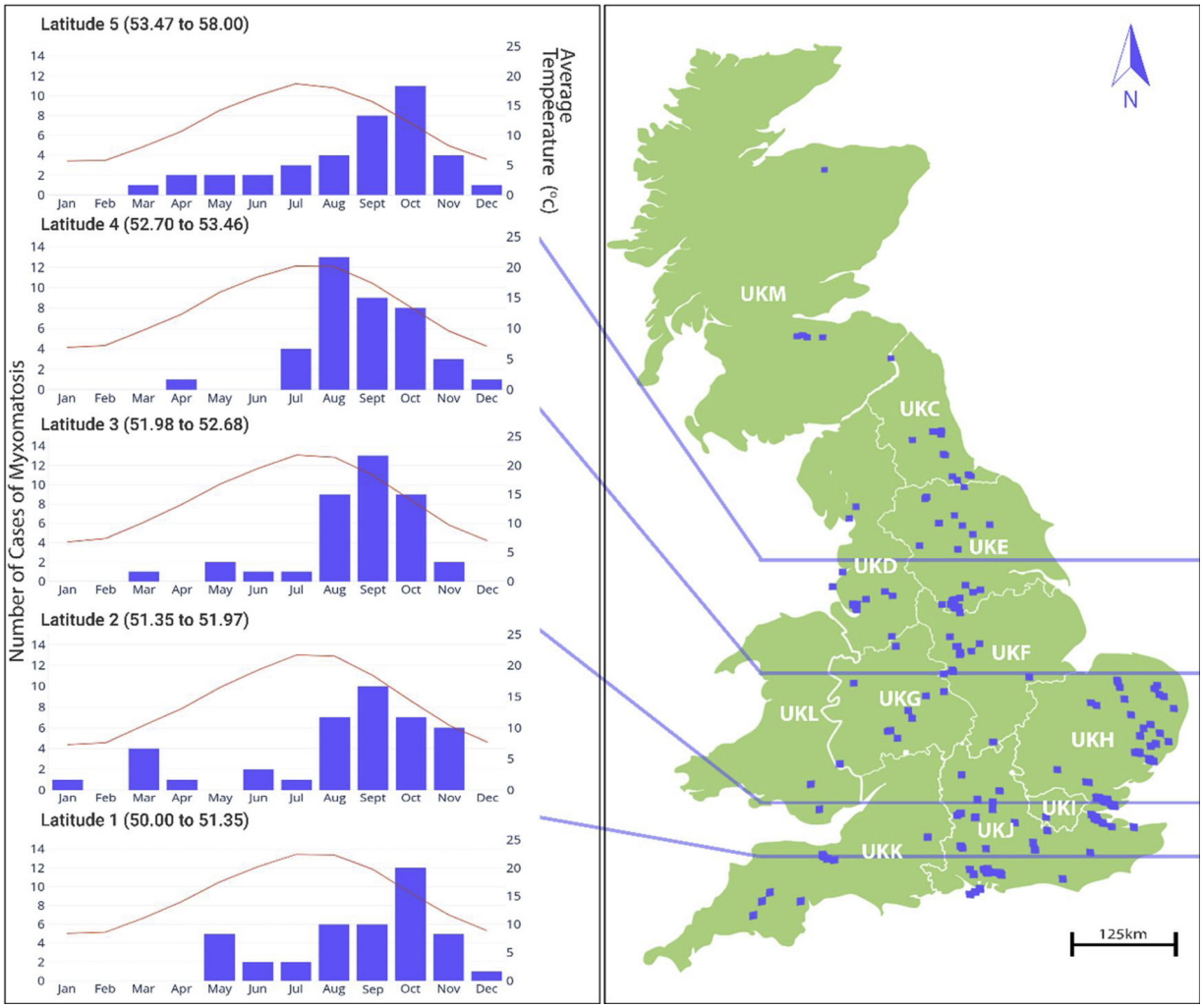

Fig. 3. Location and seasonality of the 177 myxomatosis cases used within the final statistical analyses within each UK NUTS1 region of GB. To explore the impact of latitude on disease seasonality, number of cases per month and mean monthly temperature are indicated for quintiles of cases at increasing latitudes.

Table 2
Finalised multivariable logistic regression model identifying significant (p-values ≤0.05) predictors of myxomatosis cases in rabbits from 191 veterinary practices throughout GB. Significant variables are indicated in bold. [a] Standard error, [b] Odds Ratio, [c] 95 % Confidence interval.

Variable	Category	beta	SE [a]	OR [b] (95% CI) [c]	p value
	Intercept	−3.27	0.5		
Categorical variables					
Region of GB (NUTS1)	UKJ (South east)	–	–	–	–
	UKC (North East)	−0.78	0.4	0.46 (0.2-0.99)	0.055
	UKD (North West)	−0.12	0.4	0.89 (0.39–1.93)	0.774
	UKE (Yorkshire & Humber)	0.14	0.32	1.15 (0.61–2.16)	0.667
	UKF (East Midlands)	0.3	0.4	1.35 (0.61–2.92)	0.449
	UKG (West Midlands)	−0.76	0.5	0.47 (0.17–1.19)	0.127
	UKH (East of England)	0.56	0.29	1.75 (0.98–3.12)	0.057
	UKI (Greater London)	−0.47	1.18	0.63 (0.03–4.93)	0.693
	UKK (South West)	−0.62	0.42	0.54 (0.23–1.19)	0.140
	UKL (Wales)	−0.87	0.68	0.42 (0.09–1.42)	0.204
	UKM (Scotland)	0.11	0.56	1.12 (0.35–3.18)	0.841
Vaccine	No vaccine recorded	–	–	–	–
	Vaccinated < 7days AR1	−3.07	0.48	0.05 (0.02-0.11)	< 0.001
	Vaccinated 8 to 365 days	−2.13	0.32	0.12 (0.06-0.21)	< 0.001
	Vaccinated > 365 days	−0.98	0.57	0.38 (0.11–1.04)	0.086
Season	Quarter 1; Jan-March	–	–	–	–
	Quarter 2; April - June	1.07	0.5	2.9 (1.14–8.4)	0.033
	Quarter 3; July - Sept	2.71	0.45	15 (6.68–40.29)	< 0.001
	Quarter 4; Oct- Dec	2.63	0.46	13.88 (6.12–37.58)	< 0.001
Sex and neuter status	Male entire	–	–	–	–
	Female entire	0.68	0.23	1.98 (1.26–3.13)	0.003
	Female neutered	−0.33	0.35	0.72 (0.35–1.41)	0.347
	Male neutered	−0.64	0.3	0.53 (0.29-0.94)	0.034
Continuous variables					
Age	–	−0.36	0.11	0.7 (0.56-0.86)	< 0.001
Distance to habitat	–	−0.26	0.12	0.77 (0.6-0.97)	0.035

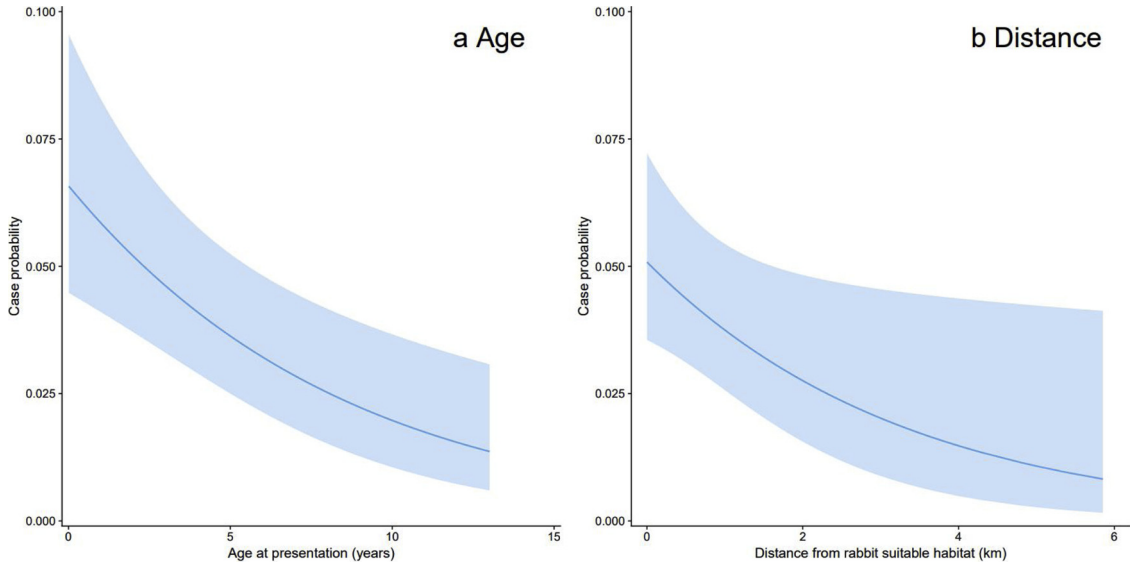

Fig. 4. Results of final multivariable modelling on myxomatosis risk, showing the impact of a) age and b) distance to putative wild rabbit habitat.

opportunities to describe its epidemiology in pet rabbits. Here we have taken a new approach using EHRs to describe the seasonality and risk factors of myxomatosis in a large population of primarily pet rabbits attending a sentinel network of veterinary practices across GB.

The majority of myxomatosis cases occurred between August and October, demonstrating considerable seasonal variation in the number of cases recorded. This is broadly consistent with previous studies of wild rabbit populations (Ross et al., 1989) and suggests that the disease has a similar ecology within both populations, with frequent opportunities for transmission between wild and pet populations. Our observation that as the distance between a pet rabbit owner's postcode and potential wild rabbit habitat reduces the risk of myxomatosis significantly increases, gives further support to the suggestion that wild rabbits are an important source of infection to pet animals. The seasonality of myxomatosis cases in wild populations has been attributed to the complex interplay between seasonal fluctuations of the rabbit population, particular that of naïve juvenile rabbits, that reach highest numbers in the population in the late summer and autumn (Mead-Briggs et al., 1975), and become most susceptible to myxomatosis as their maternally-derived antibodies begin to wane (Ross et al., 1989). This is at a time of year when it seems most likely pet rabbits would be housed outside leading to greater chance of infection with MYXV from infected wild rabbits.

Although MYXV can be transmitted in the absence of vectors, its transmission is known to be enhanced in wild rabbit populations that are also exposed to blood feeding external vectors, often with subtle

changes in the timing of disease (Shepherd and Edmonds, 1978). The main vectors of myxomatosis in wild rabbits are generally considered to be the European rabbit flea (Lockley, 1954) and to a lesser extent other biting insects such as *Anopheles* spp. mosquitos (Brugman et al., 2015; Muirhead-Thomson, 1956; Service, 1971). However, flea seasonality as measured in GB wild rabbit populations is out of step with that of the main peaks of myxomatosis. Flea counts on rabbits peak between January and April, and are lowest in the autumn when the disease peaks (Mead-Briggs et al., 1975), suggesting that flea burdens alone are not sufficient to drive the main autumnal peaks of disease in wild rabbits (Ross et al., 1989).

In pet rabbits, very little is published on flea populations, with most companion animal research in the UK being conducted on cats and dogs (Beresford-Jones, 1981). Certainly, pet rabbits can be infested with fleas (Meredith and Lord, 2014). However, this may be relatively rare in veterinary-visiting rabbits (lower than 1% of consults with rabbits recording the presence of fleas; authors' unpublished data), considerably lower than in both dogs, cats (Singleton et al., 2019) and wild rabbits, where most animals are infested (Shepherd and Edmonds, 1978; Sobey and Conolly, 1971). Indeed pet rabbits frequently benefit from ectoparasiticide treatments to control such vectors (Singleton et al., 2018). One survey of pet rabbits showed the most common flea found on German pet rabbits was the cat flea (*Ctenocephalides felis*), and less frequently *Hystrichopsylla talpae* (the mole flea) and *Spilopsyllus cuniculi* (Visser et al., 2001). Although a very small study, these results still highlight the potential exposure of pet rabbits to parasites from both domesticated and wild species (Meredith and Lord, 2014). Further studies are required to more fully understand the biology of individual flea species on pet rabbits and to understand the extent to which the cat flea is involved in myxomatosis transmission.

Although myxomatosis cases peaked in late summer to autumn, cases were observed in this population in all months except February. There was also some evidence for a second peak in cases between May and June in some years, similar to that described for wild rabbit populations (Ross et al., 1989). Whether this is due to higher levels of rabbit fleas likely to be present on wild rabbits at this time of year (Mead-Briggs et al., 1975), other known vectors such as *A. maculipennis* (Brugman et al., 2015; Service, 1971), or other ecological and behavioural factors that impact on contact between wild and pet rabbits is unknown.

In addition to showing seasonal variation, the number of myxomatosis cases in pet rabbits showed a biennial distribution, with more cases in 2014, 2016 and 2018 compared to the 2015 and 2017. Annual variation in disease prevalence has been previously described in field studies of wild rabbits and likely reflects complex interplays between the size of the susceptible population surviving an epidemic and the presence of other diseases (Ross et al., 1989). As SAVSNET collects further data, it will be interesting to see if this annual pattern continues and whether the cycles observed in pet animals are similar to those in nearby wild rabbit populations.

As with other studies, an animal's sex also had a significant impact on their risk of infection (Ross et al., 1989). This was most apparent for entire (i.e. non-neutered) female rabbits, which were almost twice as likely to have myxomatosis in our study population. However, in comparison, the risk is reversed in wild rabbits, with males that show a greater tendency to roam, being most at risk (Ross et al., 1989). Roaming is likely to be a less-prominent feature of pet rabbit behaviour as they are usually housed under some degree of confinement (Meredith and Lord, 2014). This apparent inconsistency in risk between sexes in wild and pet rabbits could be explained if sexually active female pet rabbits attracted infected wild rabbits, especially males, thereby increasing opportunities for transmission, and is supported by our observation that neutered female pet rabbits were not at a greater risk compared to entire males. A recent study in GB suggested neutering of rabbits was less common than for cats and dogs, with less than half of rabbits being recorded as neutered (45.8 %); neutering was also less common in female rabbits (40.3 %) than male rabbits (50.0 %) (Sánchez-Vizcaíno et al., 2017). Further studies aimed at understanding those features of entire female rabbits and their care that place them at heightened risk for myxomatosis will help identify targeted health interventions aimed at reducing this risk.

In our case control study, vaccination also had a significant impact on the odds of myxomatosis within this population. Rabbits between seven and 365 days of myxomatosis vaccination were almost 10 times less likely to present as a case. Vaccination remains one of the primary methods of protecting pet animals from this significant disease (Spibey et al., 2012). Whilst a large part of this effect is likely to be immune driven, the fact that rabbits within seven days of vaccination, before the onset of vaccine immunity, are also less likely to become a case, suggests that in these animals, owner behaviours such as keeping recently vaccinated rabbits quarantined might also play a role in their protection. Pet rabbits are less frequently vaccinated than domestic cats and dogs. In one study, although over 99 % of vaccinated rabbits were vaccinated against myxomatosis, only 48.4 % of rabbits actually had a record of ever receiving a vaccination, compared to 73.1 % of cats and 81.5 % of dogs (Sánchez-Vizcaíno et al., 2018). It is clear that increasing the proportion of vaccinated rabbits is likely to be the simplest and most effective way of reducing the prevalence of myxomatosis in the domestic rabbit population.

The majority of myxomatosis cases identified in our study were euthanased at first presentation. Of remaining animals, most were either never seen again, suggesting they may have died at home, or were euthanased within a few days of presenting (authors' unpublished data). This highlights the severe nature of disease in these rabbits and suggests a clear belief by the attending veterinary practitioners that many myxomatosis infections both severely compromise the welfare of the patient, and will turn out to be fatal. MYXV is used as a classic research model to understand the co-evolution of pathogen virulence and host resistance. Whilst the most virulent strains of MYXV exhibit a mortality rate of > 99 %, other strains show lower virulence with mortality rates of < 50 %, even in rabbits that have not been selected for resistance (Best and Kerr, 2000; Marlier et al., 1999). Individual wild rabbits also show varying susceptibility as animals that survive infection reproduce leading to a gradual evolution of genetic resistance (Alves et al., 2019; Kerr, 2012; Kerr et al., 2015). There is little known about the virulence of MYXV strains that pet rabbits are exposed to, nor to the potential for different breeds or lineages of pet rabbits to show varying susceptibility/resistance to myxomatosis. In the current study, there was evidence that two rabbits survived in the long term after first being identified as a case; one was vaccinated (< 365 days) and the other having no recorded vaccines. In the future as data volumes increase, it is possible the health informatics approach taken here could identify markers of individual cases where outcomes may be more favourable, such that euthanasia can be postponed and replaced by more supportive therapy.

Although EHRs can provide new insight into disease, their use inevitably has certain limitations. Despite having a highly efficient system for extracting cases of myxomatosis from the SAVSNET database, some true cases of myxomatosis were likely missed either because they were not recorded, or because they were recorded in a way that was not picked up by the regular expression used. As such, the level of disease reported here is likely to be an underestimate of the true incidence of myxomatosis during the study period. In contrast, the case definition adopted herein was almost entirely based on presenting clinical signs – in no cases did we see evidence of specific confirmatory laboratory tests being used. Whilst the clinical signs of myxomatosis in rabbits are generally extreme and striking, it is possible that some of the rabbits considered here to meet the case definition did not have myxomatosis. Clearly, the data available for analysis is restricted to animals that presented to SAVSNET-participating practices, who are recruited largely by convenience. Therefore, the results presented here may not be generalisable to the entire population of rabbits attending veterinary

practices in GB. National coverage of SAVSNET data is variable such that areas of the country that lack cases should not be used to indicate lack of risk as these are also frequently areas from which SAVSNET receives more limited data. As SAVSNET grows it is hoped that some of these coverage issues will be addressed.

In conclusion, although previous literature has explored factors associated with myxomatosis, they have typically been within wild populations. Here, we have taken a novel approach using health records at scale to contribute to a scarce literature on the epidemiology of myxomatosis, a highly significant disease in pet and wild animals. We confirm the seasonality of this disease and the importance of vaccination for its control, as well as for the first time identifying the heightened risk for entire female pet rabbits, possibly driven by behaviour. All of these factors can be used as the basis of targeted health messages for veterinary practitioners and rabbit owners. Using EHRs is a cost-effective way of providing longitudinal disease data and can shed new insight into diseases of both managed animals, and, for diseases like myxomatosis, wild animals, where infection likely passes between the two populations.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prevetmed.2020.104924.

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