**Risk factors for a first episode of primary uveitis in the UK and proportion of cases that experience recurrence following this first episode**

F. Malalana\*, J. L. Ireland, G.L. Pinchbeck, C.M. McGowan

Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Leahurst campus, Neston, UK

\* Corresponding author email: f.malalana@liverpool.ac.uk

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No competing interests have been declared

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**Authorship**

F. Malalana contributed to study design, data analysis and interpretation, preparation and approval of the manuscript. J.L. Ireland contributed to study design, data analysis and interpretation, preparation and approval of the manuscript G. L. Pinchbeck contributed to study design, data analysis and interpretation, preparation and approval of the manuscript. C. M. McGowan contributed to study design, data collection, analysis and interpretation, preparation and approval of the manuscript. F. Malalana has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Risk factors for a first episode of primary uveitis in the UK and proportion of cases that experience recurrence following this first episode**

**Summary**

**Background:** risk factors for a first episode of primary uveitis in horses have not been determined. In addition, disease progression and the proportion of horses that develop recurrence following the original episode is not known.

**Objectives:** to determine risk factors for the development of a first episode of primary uveitis in horses in the UK and to document the proportion of cases that experience recurrence following this first episode.

**Study design:** prospective case-control longitudinal study.

**Methods:** horses with a first episode of primary uveitis between July 2014 and August 2018 were recruited to the study. For each case, two controls were selected. A questionnaire was completed for each horse and multivariable logistic regression analysis carried out to identify associations between horse and management-level variables and the risk of uveitis. Each case was then followed longitudinally to determine the rate of recurrence of uveitis.

**Results:** 23 cases and 46 controls were recruited to the study. Being close to a pig farm (OR 27.8, CI 1.31-592.06) and a recent history of flooding of the pasture (OR 15.43, CI 2.80-84.98) were associated with increased risk of uveitis. Being in the same owner’s possession for a longer amount of time had a protective effect (OR 0.79, CI 0.68-0.93). Horses recovered uneventfully following treatment and showed no evidence of recurrence in 59.1% of the cases (n=13). In five horses (22.7%) the initial episode of uveitis could not be controlled and required surgical therapy. Recurrence was observed in four horses (18.2%).

**Main limitations:** Small sample size. Recall bias from owners for some of the data. Possibility of selection bias.

**Conclusions:** clinicians can use this information to identify horses with increased risk of uveitis and provide advice to the owners of these horses. The proportion of cases that experience recurrence appears low in the UK.

**Introduction**

Uveitis refers to inflammation of the uveal tract (iris, ciliary body and choroid) of the eye [1]. Uveitis can be classified as primary (endogenous) or secondary to injury, insult or abnormality, either ocular or systemic [1]. This inflammation can be acute in onset, chronic (unresolved) or recurrent (equine recurrent uveitis; ERU). ERU has been classified into three distinctive clinical forms: (1) classic; (2) insidious and (3) posterior [2]. Classic ERU is characterised by episodes of active intraocular inflammation followed by periods of quiescence with each inflammatory phase frequently showing increased severity. Insidious ERU is the form most commonly seen in the Appaloosa and is characterised by persistent, low grade inflammation, with very few external signs but with a cumulative destructive effect. Posterior uveitis affects mainly the vitreous, choroid and retina and is the most common form seen in Warmbloods and in horses in continental Europe [2]. ERU generally develops after an initial episode of primary uveitis but not every case of initial uveitis will develop into ERU [1]. The reasons why some cases of primary uveitis go on to become recurrent in nature are not clear and probably include immunological, genetic and microbial factors. In addition, there have been no epidemiological studies carried out to determine the number of horses in which their initial episode becomes a recurrent condition.

Likewise, no clear risk factors have been associated with the initial development of primary uveitis although an association has been reported in some cases with the recent administration of sulphonamides or vaccination in a number of reports in human ophthalmology [3, 4]. One study found a higher prevalence of ERU in geldings compared to mares and stallions [5]. However, this finding has not been shown in other studies [6, 7] and therefore may be a reflection of the general sex distribution in that particular horse population rather than a true sex-specific distribution. Anecdotally, the prevalence of ERU is believed to be higher in areas of continental Europe prone to flooding [8]. An increased risk of development of ERU has also been associated with certain breeds and other genetic factors [9-13].

The aims of this study were to:

1. Determine the risk factors for the development of a first episode of primary uveitis in horses in the UK
2. Document the proportion of cases that experience recurrence following this first episode

**Materials and methods**

*Study design*

A prospective case-control study was conducted to identify associations between horse and management-level variables and uveitis. Prior to data collection, the study was approved by the University of Liverpool ethics committee (VREC150). Horses reported by referring veterinarians or those admitted to the Philip Leverhulme Equine Hospital with a first episode of primary, spontaneous (i.e. with no identified trigger) uveitis between July 2014 and August 2018 were recruited to the study. For each case, two controls were selected.

Each case was then followed longitudinally for the duration of the study to determine the proportion of cases that experience recurrence following this first episode (Supplementary Item 1).

*Case and control definition and selection*

All referring veterinary practices involved in recruitment of cases for the study were contacted and briefed on the details of the study. These practices were visited by the author and all veterinarians in these practices received training to help identify and correctly diagnose horses with primary uveitis and to discuss appropriate treatment options as previously described [1]. After this training had taken place, cases of primary uveitis diagnosed following an ocular examination by these trained veterinarians were recruited onto the study. Cases were identified and included in the study if they were showing signs consistent with acute primary uveitis. These included ocular pain, blepharospasm, lacrimation, chemosis, corneal changes (oedema, vascularisation, cellular infiltrate, keratic precipitates), aqueous flare, hypopyon, hyphaema, miosis and iris colour changes, vitritis and retinal inflammation [1]. Horses with a known cause for the uveitis (for example, secondary to trauma or systemic disease) or those with reflex uveitis associated with another ocular condition were excluded. Likewise, horses were excluded if they had suffered previous episodes of uveitis in the past or if they had signs consistent with prior events of intraocular inflammation. After being notified of a case and, if the owner was willing to participate, they were contacted by the author by telephone to complete a questionnaire as soon as possible after the case was first diagnosed. This questionnaire was designed to gather data on signalment, history, management and observed clinical signs of the affected horses (Supplementary item 2). Control horses were also recruited to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease. For each case, two control horses were selected. These two horses were from a related geographical location to the case (registered with the same veterinary practice) but different premises. The controls were chosen as the next two appointments for the referring veterinarian that had referred the matching uveitis case whose owners were willing to take part in the study. Once enrolled in the study, one of the authors (FM) visited the premises where the control horses were stabled within 7 days to carry out a detail ophthalmic examination including direct and indirect ophthalmoscopy. Horses with evidence of prior ocular damage that might be attributable to uveitis would have been removed from the study however, none of the controls had any history of previous ocular disease and ophthalmic examination was unremarkable in all cases.

*Follow up data*

The referring veterinarians were contacted every 6 months to ascertain whether the cases had been attended for repeat episodes of uveitis since the initial enrolment. A recurrence was defined as a new episode of uveitis at least six weeks after cessation of clinical signs from the original episode as long as the appropriate therapy for this original episode had been instigated. Re-appearance of signs within six weeks of an episode was not considered a recurrence but rather a continuation of an incompletely treated event [14]. In addition, the owner of these horses were also contacted every 6 months to determine whether any perceived recurrence or episode of ocular disease had occurred for which veterinary advice had not been obtained.

*Data analysis*

Data were managed in Microsoft Excel1. IBM SPSS Statistics for windows version 24.0 was used for the statistical analysis2.

Associations between signalment, history, management and observed clinical signs were examined with logistic regression analysis. Continuous variables were assessed for linearity. Variables with p≤ 0.25 in the univariable analysis were included in the multivariable logistic regression models which were constructed using a backward step-wise elimination procedure. Prior to multivariable analysis, all variables were assessed for correlation using Spearman's rank correlation coefficients. Where Spearman's rank correlation coefficient was >0.8 the most statistically significant or biologically plausible variable was selected. The goodness of fit of the final models was assessed using the Hosmer-Lemeshow test statistic and the area under the receiver operating characteristic (ROC) curve. The distribution and outlier values of the standardized residuals (difference between the model predicted and actual outcome values) from each model were also assessed. The final models were repeated excluding observations with standardised residual values of <-2.0 or >2.0. Statistical significance was set at a value of p<0.05.

The normality of continuous data was analysed with a Kolmogorov-Smirnov test. Continuous data are described as mean and standard deviation for normally distributed data and as median and interquartile range (IQR) for skewed data. Categorical data are described as proportions with 95% confidence intervals (CI).

Time to event analysis was used to construct a Kaplan-Meier plot of cumulative probability of non-recurrence.

**Results**

During the period between July 2014 and August 2018 23 cases were recruited to the study (Table 1). In addition, 46 control horses were obtained for comparison (Supplementary item 3).

*Univariable and multivariable analysis*

Univariable analyses identified a large number of variables that were significantly associated with a first episode of uveitis and are shown in Supplementary item 4. The final multivariable logistic regression model is shown in Table 2. For every year that horses had been in their owner’s possession they were less likely to suffer a first episode of primary uveitis. In contrast, being close to a pig farm or a history of flooding of the field where the horses spent time turned out within the previous 12 months were associated with increased odds of a horse suffering a first episode of primary uveitis.

*Follow up data*

One horse was lost to follow up. Follow up time ranged from 8 to 63 months (median 41 months, IQR 26). Thirteen of the 22 horses for which follow up was available resolved uneventfully following treatment and showed no further episodes of uveitis (59.1%, CI 38.7-76.7). In five horses (22.7%, CI 10.1- 43.4) the initial episode could not be controlled. Three of these horses required enucleation of the affected eye (horses 6, 12 and 14); another one underwent pars plana vitrectomy (horse 13) and the fifth horse had a cyclosporine implant placed (horse 17).

Recurrence in the same eye occurred in four horses (18.2%, CI 7.3-38.5) (Table 3). One horse had a single recurrence three months after the initial episode, but no further episodes after that (horse 16). Another horse also had a recurrence episode three months initial presentation; this horse had a cyclosporine implant placed and did not show any further episodes of uveitis (horse 11). The third horse suffered five further episodes of intraocular inflammation (3, 5, 8, 10 and 18 months after the first event) before the affected eye was eventually enucleated (horse 18). The fourth horse suffered three episodes of recurrence (12, 15 and 33 months after the first episode) (horse 15). A Kaplan-Meier estimation of non-recurrence is shown in Figure 1.

**Discussion**

This is the first study carried out to determine potential risk factors associated with the development of primary spontaneous uveitis. Two variables, a history of recent flooding of the field where the horse is turned out and being in close proximity to a pig farm, were found to be associated with an increase in the risk of uveitis, although some of these associations may be due to selection bias in the design of the study. In addition, due to the wide confidence intervals these results should be interpreted with caution. In the case of flooding, this would have occurred within the previous 12 months of the first episode of uveitis and the horses would have spent time turned out in that field following the flooding event although not necessarily at the time of the flood. It is important to note also that no attempt was made to measure what exactly constitutes close proximity to a pig farm other than the horse owners’ perception, and this variable also included when pigs lived on the same premises as the horse. These two variables may be linked by the presence of *Leptospira* spp. Leptospires are spirochete bacteria present in virtually all mammalian species examined and endemic in geographic regions with a mild climate and in high precipitation and flood-prone areas [15-17]. Increases in the prevalence of uveitis after flooding were noted as early as the beginning of the 20th century in France and other regions of Europe [8]. As a recent example, an epidemic peak of human leptospirosis was associated with flooding in the Czech Republic [18]. With regards to pigs, they, together with other domestic farm species and other mammalian hosts such as hedgehogs and badgers, can act as reservoir to *Leptospira* species [18, 19]. Most cases of *Leptospira*-induced uveitis in Europe are associated with *Leptospira kirschneri* serovar Grippotyphosa [20- 23]. However, it is believed that minimal levels of the Grippotyphosa serovar exist in the UK wildlife or in domestic animal populations [14]. Specifically in pigs, a study looking at leptospiral titres in pigs due for export showed a prevalence of only 0.04% to Grippotyphosa [24]. In this study no link was found between the risk for primary uveitis and the presence of other domestic species, such as cattle, next to or on the horse’s home premises. Once again, previous studies have shown no evidence of the Grippotyphosa serovar in cattle in the UK [25]. Grippotyphosa typically uses voles and other small rodents as their host and rats are believed to be the reservoir host to other serovars [18]. Our questionnaire also asked specifically for the presence of wildlife in the field or rodents such as rats and mice in the stabling areas but these were not significant in the final model. Being pastured may also affect the prevalence of leptospirosis although reports have shown conflicting results [26, 27]. In our study, increases in time spent by the horse turned out in the field were not associated with an increased risk of primary uveitis. It is important to note that this study did not assess whether these horses had been exposed to *Leptospira*. In addition, a recent study suggested that the role of *Leptospira* spp. in cases of uveitis in the UK is modest [28] so the significance of these risk factors in relation *Leptospira* infection has to be interpreted with caution.

Length of time horses had been in the current owner’s possession also was significantly associated with the risk of primary uveitis in the final model. In this case, however, the longer the horse had been in the owner’s possession, the lower the risk of suffering a first episode of primary uveitis. The reasons for this are not clear and may simply represent the fact that owners of horses affected by uveitis may choose to simply get rid of the horse instead of spending time and money dealing with a potentially recurrent disease that may affect the horse’s performance over time. This theory is thwarted, however, by the fact that only first episodes of primary uveitis were considered for recruitment to the study. There is, of course, the possibility that perhaps some of these horses had been sold after suffering a previous episode of intraocular inflammation that had not caused permanent ocular changes in the affected eye and for which the new owner had not been informed, and what was considered a first episode was in fact a recurrence. However, no evidence of previous episodes of uveitis was noted during the initial ophthalmic exam in any of the horses in the study. Another explanation may be that as the duration of ownership increases the horse may develop immunity to a potential microbial initial triggering factor for the primary uveitis present in the premises; however, duration of time in the current premises was not retained in the final model as a protective factor.

A study in Germany showed a clear correlation between the age of a horse and the occurrence of uveitis [5]. Our study did not show age to be a risk factor. It is important to note that whilst the German study referred specifically to ERU our study focused on a first single episode of uveitis. Is it likely that the cumulative damage caused by repeated bouts of uveitis in cases of ERU increases with the horse’s age. This same study also found differences in breeds and sex. Thoroughbred horses were less frequently affected than Warmbloods and ponies, whereas geldings were more often affected than mares and stallions. In our study neither breed nor sex were retained as risk factors in the final model.

Two other factors have been associated with an increased risk of uveitis in human studies: recent administration of sulphonamides and recent vaccination [3, 4]. Vaccination against tuberculosis, influenza, MMR (measles, mumps, and rubella), Hepatitis B, HPV (human papillomavirus) and varicella has been associated with a limited number of cases of human autoimmune uveitis [29]. In this study, neither administration of any recent medication nor vaccination were shown to increase the risk of primary uveitis in the horses in our population.

Uveitis is frequently described as a common cause of recurrent ocular inflammation in horses and there is extensive literature in ERU. However, there have been no studies determining the proportion of cases that go on to become recurrent from a first original episode of primary uveitis. In this study, recurrence occurred in four out of 22 cases for which follow up was available. However, defining what constitutes a recurrence is not that straightforward [14]. Often eyes are medicated with the appropriate therapy; the uveitis appears to improve clinically and all medication is then ceased shortly after resolution of the clinical signs. A few days or weeks after discontinuation of the medication the eye may become inflamed again. In these cases, determining whether we are dealing with a single episode of unresolved uveitis or uveitis of recurrent behaviour is difficult. We therefore elected to define recurrence as inflammation that occurs at least six weeks after cessation of signs as long as appropriate therapy for the initial event had been instigated by the primary veterinarian. With this definition five horses were classified as having a severe, non-resolving single episode that required surgical management for their control.

In three of the four horses that showed recurrence, this occurred three months after the initial episode, perhaps suggesting that the first three months following the original episode are critical, and close monitoring and potentially continued anti-inflammatory therapy during this period may be advisable. All first recurrent events occurred within 12 months after the original episode, so we can presume that a horse may not go on to develop the recurrent form of the disease once it has had a relapse-free year from the first event, although due to the small numbers in this study this has to be interpreted with caution. However, once a horse has shown recurrence the interval between subsequent episodes can vary enormously, from two months to up to 18 months in our study.

This study has some limitations. Despite the long duration of the study (over four years), only 23 cases of primary uveitis were recruited to the study. This may be a representation of the lower perceived prevalence of primary uveitis in the UK compared to other parts of the world. More likely, it was also affected by lack of reporting of these cases by referring veterinarians, on whom we relied heavily for the provision of cases. Because of this small number, all the results have to be interpreted with caution. Likewise, these findings referred to a population of horses geographically restricted to the North-West of England and North Wales so any extrapolation to another equine population has to be carried out with caution. The time between the diagnosis of primary uveitis and completion of the questionnaire was kept a short as possible, but any delays may have affected the accuracy of the data provided by the owners. In addition, some of the questions related to events that happened in the weeks leading to the recruitment of the horse to the study and completion of the questionnaire so it is possible that some of the information provided by owners may not be accurate. All the cases and controls included in the study were reported by a referring veterinarian so the risk of a selection bias exists. In addition, and despite the training received by the referring veterinarians prior to commencement of the study, there is the possibility that some cases may have been misdiagnosed.

In summary, this study has identified factors associated with increased risk of primary uveitis in horses living in the North-West of England and North Wales. Horses living close to a pig farm and those being turned out in areas that have flooded recently may be at increased risk of developing uveitis. Clinicians can use this information to identify the horses at increased risk and provide advice to the owners of these horses, but any extrapolation to populations of horses living outside this area of the UK has to be done with caution. Within this dataset, approximately 22% of episodes were not controlled with medical therapy requiring further surgical therapy and approximately 18% of cases went on to become recurrent following an initial episode of primary uveitis. While larger studies are warranted, this provides information which can inform discussions on prognosis with owners of affected horses.

**Manufacturers’ addresses**

1Microsoft Corporation, Redmond, Washington, USA

2IBM Corporation, Armonk, New York, USA

**Table 1:** Details of horses with a first episode of uveitis in the North West of England enrolled in the study (n=23), including signalment and time of enrolment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Horse**  | **Age (years)** | **Sex** | **Breed** | **Date of enrolment** |
|  |
| 1 | 12 | Gelding | Arab | July 2014 |
| 2 | 8 | Mare | Warmblood | July 2014 |
| 3 | 23 | Mare | Pony | August 2014 |
| 4 | 14 | Gelding | Warmblood | August 2014 |
| 5 | 2 | Mare | Welsh Section D | August 2014 |
| 6 | 14 | Gelding | French Trotter | February 2015 |
| 7 | 7 | Gelding | Welsh Section D | March 2015 |
| 8 | 16 | Gelding | Warmblood | August 2015 |
| 9 | 22 | Gelding | Donkey | August 2015 |
| 10 | 14 | Mare | Appaloosa | September 2015 |
| 11 | 7 | Gelding | Warmblood | July 2015 |
| 12 | 2 | Stallion | Cob | November 2015 |
| 13 | 5 | Gelding | Lusitano | December 2015 |
| 14 | 14 | Gelding | Thoroughbred cross | December 2015 |
| 15 | 13 | Gelding | Warmblood | March 2016 |
| 16 | 17 | Gelding | Irish Sports | April 2016 |
| 17 | 2 | Mare | Irish Sports | August 2016 |
| 18 | 19 | Mare | Cob | November 2016 |
| 19 | 7 | Mare | Cob | February 2017 |
| 20 | 10 | Gelding | Thoroughbred cross | August 2017 |
| 21 | 7 | Gelding | Warmblood | September 2017 |
| 22 | 19 | Mare | Thoroughbred | September 2017 |
| 23 | 18 | Mare | Arab | August 2018 |

**Table 2:** Multivariable logistic regression model of risk factors for a first episode of primary uveitis in 23 horses in the North West of England.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Category** | **Odds ratio** | **95% CI** | **P value** |
|  |
| Time in owner’s possession (years) | Continuous | 0.79 | 0.68 – 0.93 | 0.004 |
| Recent flooding field | Yes | 15.44 | 2.80 – 84.98 | 0.002 |
| Pig farm | Yes | 27.80 | 1.31 – 592.06 | 0.03 |

**Table 3:** Details of horses with a first episode of uveitis in the North West of England enrolled in the study that went on to show recurrence (n=4), including time to initial recurrence and any further recurrent episodes, follow up time and final outcome.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Horse**  | **Initial recurrence** (months from original episode) | **Further recurrent episodes** (months from original episode) | **Follow up time**(months)  | **Final outcome** |
|  |
| 11 | 3 |  | 51 | Cyclosporine implant placed |
| 15 | 12 | 15 and 33 | 41 | No further episodes |
| 16 | 3 |  | 44 | No further episodes |
| 18 | 3 | 5, 8, 10 and 18 | 30 | Enucleation |

**Figure 1:** Kaplan-Meier estimate of non-recurrence for a cohort of horses reported with a first episode of uveitis in the North-West of England.



**Supplementary items:**

Supplementary Item 1: flow chart of subjects through study

Supplementary Item 2: copy of questionnaire

Supplementary Item 3: details of controls

Supplementary Item 4: results of univariable logistic analysis

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