Disease and pharmacologic risk factors for first and subsequent episodes of equine laminitis: A cohort study of free-text electronic medical records

Claire E. Welsh[a,*], Marco Duz[b], Timothy D.H. Parkin[a], John F Marshall[a]VALIDHTML

[a] Equine Clinical Sciences Division, Weipers Centre Equine Hospital, School of Veterinary Medicine, University of Glasgow, UK

[b] School of Veterinary Medicine and Science, University of Nottingham, UK

Abstract
Electronic medical records from first opinion equine veterinary practice may represent a unique resource for epidemiologic research. The appropriateness of this resource for risk factor analyses was explored as part of an investigation into clinical and pharmacologic risk factors for laminitis. Amalgamated medical records from seven UK practices were subjected to text mining to identify laminitis episodes, systemic or intra-synovial corticosteroid prescription, diseases known to affect laminitis risk and clinical signs or syndromes likely to lead to corticosteroid use. Cox proportional hazard models and Prentice, Williams, Peterson models for repeated events were used to estimate associations with time to first, or subsequent laminitis episodes, respectively. Over seventy percent of horses that were diagnosed with laminitis suffered at least one recurrence. Risk factors for first and subsequent laminitis episodes were found to vary. Corticosteroid use (prednisolone only) was only significantly associated with subsequent, and not initial laminitis episodes. Electronic medical record use for such analyses is plausible and offers important advantages over more traditional data sources. It does, however, pose challenges and limitations that must be taken into account, and requires a conceptual change to disease diagnosis which should be considered carefully.

Abbreviations

AIC, Akaike information criterion; EMR, electronic medical records; EMS, equine metabolic syndrome; PPID, pituitary pars intermedia dysfunction; PWP, Prentice, Williams, Peterson model; RAO, recurrent airway obstruction; LRT, likelihood ratio test

Keywords

Horse; Corticosteroid; Laminitis; Survival

1. Introduction

Laminitis is a painful, prevalent, multifactorial condition of ungulates. In the domestic horse, compromised welfare due to the pain and immobility associated with laminitis often leads to euthanasia (Slater, 2014, Wylie et al., 2013a and Wylie et al., 2013b). Many studies have identified significant risk factors for laminitis, but have not always been in agreement (Hunt, 1993, Polzer and Slater, 1997, Slater et al., 1995, Wylie et al., 2013a and Wylie et al., 2013b). Administration of certain systemic corticosteroids has been presumed to pose a risk of laminitis, but this potentially putative risk factor has not been well studied in the general horse population (Bailey and Elliott, 2007, Bailey, 2010, French et al., 2000, Katz and Bailey, 2012 and McCluskey and Kavenagh, 2004). Given financial constraints and ethical implications, previous studies have often been of limited sample size, thus reducing the power of the analyses to detect significant relationships of small effect size. In addition, the recurrent nature of laminitis has not been fully taken into account. It is possible that the initial case of laminitis is associated with different risk factors compared to subsequent episodes.

The use of electronic medical records (EMR) in first-opinion equine veterinary medicine in the UK is widespread. Although amalgamation of records between practices for epidemiologic research purposes is somewhat rare at present, sharing of such data will become more common in future (Johns and Adams, 2015 and Wylie et al., 2014). This resource can offer huge sample sizes, and could be more easily extrapolated to the general horse population compared with other study types. It may, however, suffer from problems not usually encountered in prospective studies, due to record accuracy and completeness, for example. In first-opinion practice, diagnoses and case management decisions are often informed by less than the full battery of gold-standard tests available for each condition. Indeed, veterinarians in practice are often required to treat horses according to tentative diagnoses reached by pattern recognition alone, or with minimal investigation, due to financial, time, or practical constraints. In addition, free-text medical records vary greatly in verbosity between individuals, cases and practices. EMR offer a true historical account of the decisions made in the treatment of individual animals, whether those decisions were well-founded or otherwise. As such, EMR are a very different data-type compared with experimental data, where exhaustive exclusion criteria can be universally applied. EMR likely contain a wealth of useful, accurate information, but may require a lower sensitivity of case identification to be of used.

The aims of this study were to use a large database of first-opinion electronic medical records to analyse the relationships between known medical risk factors for the first, and subsequent episodes of laminitis. Our hypotheses were that (a) systemic corticosteroid administration is significantly and independently associated with laminitis risk, and (b) significant risk factors for initial and subsequent laminitis episodes will vary.

Ethical approval for this study was granted by the Research Ethics Committee, School of Veterinary Medicine, University of Glasgow.

2. Materials and methods

2.1. Data source

EMR from a convenience sample of seven first-opinion equine veterinary practices around the UK were collected and amalgamated into a single anonymised dataset (Table 1). These data spanned twenty-six years (1987–2013, n = 70481 records), and contained the following database; unique numeric identifier per horse, date of birth, date of entry into the system (date of veterinary record), breed and sex. Free-text notes detailing the reason for the consultation, clinical findings, presumptive or definitive diagnosis, treatment, and prescription information were available for each record. Age was calculated as the date of record minus the date of birth, and ages less than 0 or greater than 40 years (due to erroneous date records in 16% of records) were removed. Age was subsequently categorised as follows: under 1 year, 1–4 years, 4–8 years, 8–13 years and above 13 years. Sex was converted in to three categories: female, male, and unknown sex. Breeds were converted initially into ten categories; Arab/Arab cross, Cob/Cob cross, Draught/Draught cross, Native/Native cross, pony/pony cross, Thoroughbred/Thoroughbred cross, Warmblood/Warmblood cross, Welsh/Welsh cross, unknown and other breed. Horses were followed from their first record in the dataset, to their first or subsequent laminitis episodes, or until they died, were lost from follow up or the study period ended. Censoring was assumed to be uninformative. All analyses were conducted in R statistical environment (R Core Team, 2015). Statistical significance was set at 0.05 and all testing was two-tailed.

Table 1.
Description of the convenience sample of first-opinion equine veterinary practices throughout the UK that contributed data to the current study between 1987 and 2013.

Practice	Number of full time veterinarians	Location	Cover own out-of-hours	RCVS Accredited[a]	Species seen	Number of branches	Number of records
1	11	Scotland	Yes	Yes	Mixed	2	2893

2	21	Central England	Yes	Yes	Equine only	1	38705
3	17	Northern England	Yes	Yes	Mixed	5	1442
4	14	Central England	Yes	No	Mixed	4	14339
5	11	Southern England	Yes	No	Equine only	1	5565
6	4	Northern England	Yes	Yes	Large species	1	5052
7	8	Northern England	Yes	No	Mixed	2	2485

[a] Accreditation of the practice by the Royal College of Veterinary Surgeons, URL: http://www.rcvs.org.uk/practice-standards-scheme/.

2.2. Text mining

Text mining was employed to convert free text records into numeric variables. Commercially available text mining software (SimStat and WordStat, Provalis Research Ltd., Canada) was used to construct dictionaries of words or phrases designed to mine free text records for instances of systemic or intra-synovial corticosteroid administration (triamcinolone acetonide, dexamethasone, prednisolone and methylprednisolone) and laminitis, and for records of syndromes known to be related to laminitis, or known to be a common indication for systemic or intra-synovial corticosteroid use (Table 2). These syndromes were decided upon a priori after discussion with experienced equine veterinarians, and examination of a proportion of EMR containing corticosteroid administration. The iterative mining process used was similar to that published in Lam et al., 2007; and validated for use in veterinary data by Anholt et al. (Anholt et al., 2014a, Anholt et al., 2014b and Lam et al., 2007). Negated terms were excluded where possible (e.g. 'not Cushing's disease'). A 'case' of laminitis or disease was thereby defined as a record containing at least one non-negative word or phrase pertaining to that condition.

Table 2.
Examples of the words and phrases used to categorise electronic medical records (EMR) from a convenience-sampled UK horse cohort between 1987 and 2013. Where possible common negations were excluded, and all terms were validated through assessment of the term in context.

Category	Examples of words/phrases used for case detection (excluding misspellings)
Laminitis	Laminitis, founder, laminitic
Triamcinolone	Adcortyl, Triamcinolone, Kenalog, Vetalog
Recurrent Airway Obstruction (RAO)	RAO, heaves, Chronic Obstructive Pulmonary Disease (COPD)
Respiratory	Bronchospasm, bronchoconstriction, cough, dyspnoea, pneumonia, wheeze
Dermatologic	Abrasion, alopecia, blepharitis, bursitis, cellulitis, Chorioptes, dermatitis, eczema, folliculitis, furunculosis, lymphangitis, pyoderma, sweet itch, thrombophlebitis
Equine Metabolic Syndrome (EMS)	EMS, metabolic syndrome, peripheral Cushing's
Pituitary Pars	Cushing's disease, PPID, hyperadrenocorticism, Pergolide, Prascend

Intermedia Dysfunction (PPID)	
Prednisolone	Prednicare, Prednidale, Prednisolone, Preds
Methylprednisolone	Depomedrone, Methylprednisolone
Dexamethasone	Colvasone, Dexamethasone, Dexadresson, Dexafort, Duphacort
Gastrointestinal	Colic, colitis, diarrhoea, enteritis, enterocolitis, scour
Systemic	Abortion, allergy, anaphylaxis, autoimmune, bacteraemia, dystocia, endometritis, endotoxaemia, hepatitis, mastitis, Pemphigus, peritonitis, placentitis, pyelonephritis, pyrexia, sepsis, toxaemia, urticaria, vasculitis
Orthopaedic	Osteoarthritis, epiphysitis, kissing spines, osteomyelitis, sesamoiditis, spavin, spondylosis, tendonitis
Neurological	Ataxia, encephalopathy, hemiplegia, meningitis, Wobblers syndrome

2.3. Outcomes

Two outcomes were assessed in this study, thus two models were built. The first episode of laminitis per horse was the initial outcome examined (Model 1). Subsequent episodes of laminitis were examined as a secondary outcome (Model 2). Horses were at risk of a subsequent episode of laminitis 60 days following the previous episode. A hypothesised causal web for the association of all factors involved in these analyses is shown in Fig. 1.

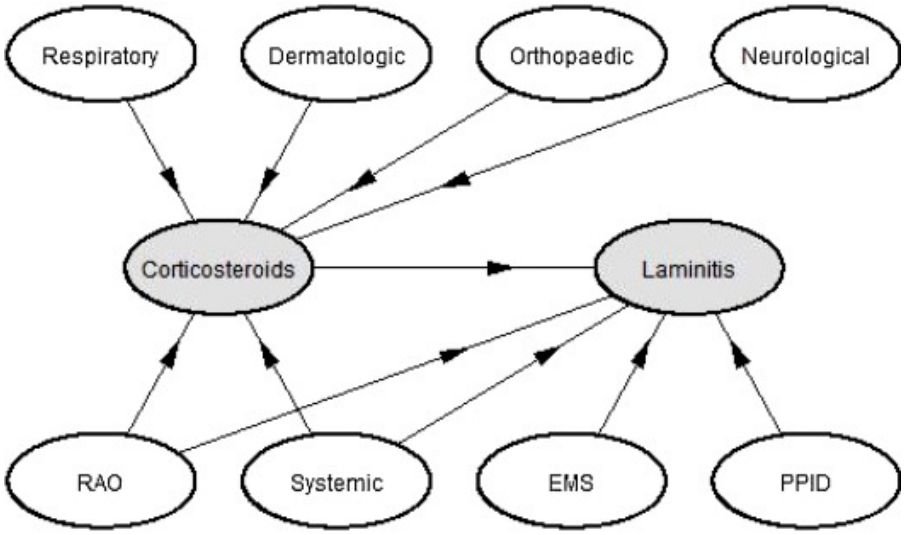

Fig. 1.
Proposed causal web: possible relationships between reasons for corticosteroid administration, chronic diseases and laminitis.

2.4. Survival analyses

2.4.1. First laminitis episode (Model 1)

Univariable Cox proportional hazard models were used to estimate the association between horse characteristics, disease and corticosteroid administration, and time to first laminitis episode. A random (frailty) effect was included to account for clustering within practices, and models were stratified according to age group at the time of entry to the dataset. Variables were retained for consideration if the Wald p-value for the coefficient was <0.2. The assumption of proportional hazards was tested for each variable by visual inspection of scaled Schoenfeld residuals plots. The breed variable was re-categorised to leave only statistically significant levels, with others subsumed into the 'Unknown/other breed' category. Collinearity between potential risk factors was assessed with Cramer's V, and where associations exceeded 0.4, the variable with the higher univariable AIC was considered for exclusion from further analyses (Rosner and Rosner, 2006).

A forward stepwise manual multivariable model-building procedure was then carried out, by sequential inclusion of significant variables in order of ascending AIC. Variables were retained if coefficient Wald p-values or the likelihood ratio test (LRT) p-value for inclusion of the variable was <0.05. All pairwise interactions between retained variables were assessed for LRT significance, and were included in the final model in order of ascending AIC. Variables not included were subsequently forced back into the model to assess the proportion change in existing coefficients. Variables were considered for retention if they led to a change in any existing coefficients of more than 30%. The power of the model to detect a postulated hazard ratio of 1.3 for the effect of corticosteroid prescription (excluding methylprednisolone) on laminitis risk at significance level 0.05 was 81%, 96% and 64% for triamcinolone, dexamethasone and prednisolone, respectively.

2.4.2. Subsequent laminitis episodes (Model 2)

To investigate the secondary outcome, only 46 horses had more than 6 episodes of laminitis, so analysis of subsequent laminitis episodes was restricted to the second–sixth episodes (n = 37888 records, 3358 horses). Recurrent airway obstruction (RAO), pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome (EMS) were considered lifelong risk factors for laminitis, therefore all time-points following detection of these conditions in an individual were considered positive for that condition, irrespective of future diagnoses. For analysis of the time to subsequent laminitis episode (second–sixth), a recurrent-events extension to the Cox proportional hazards model was employed. The Prentice, Williams, Peterson (PWP) model allows for ordered recurrent events,

and adjusts for clustering and the non-independence of events within individuals (Prentice et al., 1981). A frailty term was included to account for clustering within practices, and models were stratified by age group. Univariable and multivariable model building procedures proceeded as above. Proportional hazards assumptions for three syndromes were violated; the risk of time to subsequent laminitis episode of PPID, colic and dermatologic syndromes was not static over time (and tended to increase in all cases), therefore interaction terms with time were added to account for these time-varying covariates.

3. Results

3.1. Population characteristics

Table 3 reports the variables considered for models of association with time to laminitis episode. Dexamethasone was the corticosteroid prescribed to the greatest number of horses (2204, 3.1%), and gastrointestinal syndromes affected the largest number of horses of all the disease syndromes studied (7760, 11%). Laminitis was detected in medical records of 4081 (5.8%) horses (Table 4). Of these, 72% (2965 horses) had more than one laminitis episode. The median (IQR) time between first and second episodes of laminitis was 363 days (133–865). Table 5 gives a description of the outcomes tested, including their event rates.

Table 3.
Baseline characteristics of a convenience sample of UK horses attended by seven first-opinion UK veterinary practices between 1987 and 2013.

Characteristic		Number of horses	Percentage (n = 70481)	Number of laminitis-positive horses (%)
Sex	Female	26019	36.9	1682 (6.4)
	Male	37975	53.9	2101 (5.5)
	Unknown	6487	9.2	298 (4.6)
Practice	1	2893	4.1	168 (5.8)
	2	38705	54.9	2681 (6.9)
	3	1442	2.0	82 (5.7)
	4	14339	20.3	261 (1.8)
	5	5565	7.9	296 (5.3)
	6	5052	7.2	417 (8.3)
	7	2485	3.5	176 (7.1)
Breed	Other/unknown	59681	84.7	3854 (6.5)
	Arab	954	1.4	65 (6.8)
	Cob	2132	3.0	110 (5.2)
	Draught	1049	1.5	38 (3.6)
	Native	2218	3.1	227 (10.2)
	Pony	1415	2.0	115 (8.1)
	Welsh	3032	4.3	305 (10.1)
Corticosteroids	Triamcinolone	1234	1.8	38 (3.1)
	Dexamethasone	2204	3.1	90 (4.1)
	Methylprednisolone	306	0.4	11 (3.6)

	Prednisolone	895	1.3	108 (12.1)
Disease syndrome	Gastrointestinal	7760	11.0	450 (5.8)
	Equine Metabolic Syndrome	143	0.2	82 (57.3)
	Pituitary Pars Intermedia Dysfunction	2070	2.9	601 (29.0)
	Recurrent Airway Obstruction	1228	1.7	65 (5.3)
	Respiratory	3773	5.4	243 (6.4)
	Orthopaedic	1839	2.6	193 (10.5)
	Neurological	631	0.9	65 (10.3)
	Dermatologic	4473	6.3	323 (7.2)
	Systemic	2778	3.9	251 (9.0)

Table 4.
Number of laminitis episodes recorded per horse between 1987 and 2013 at a convenience sample of seven UK first-opinion equine veterinary practices.

Total number of laminitis episodes	Number of horses	Percentage of horses (n = 70481)
0	66400	94.21
1	1116	1.58
2	2553	3.62
3	79	0.11
4	208	0.30
5	30	0.04
6	49	0.07
7	8	0.01
8	21	0.03
9	4	0.01
10	3	<0.01
11	1	<0.01
12	3	<0.01
13	1	<0.01
14	1	<0.01
15	1	<0.01
16	1	<0.01
17	0	0
18	1	<0.01
19	0	0
20	1	<0.01

Table 5.
Description of the outcomes assessed in the current study of first and subsequent laminitis episodes in a UK horse cohort between 1987 and 2013.

Outcome	Number of horses (%)	Number of events	Range of events	Median follow-up time (days) (IQR)	Total time	Event rate per 1000 horse years (95% CI)
First laminitis episode	3977 (5.7)	3977	NA	901 (84–3480)	23597.4 years	168.5 (163.8–173.4)
All laminitis	3977 (5.7)	8168	0–20	1188 (87–4343)	50783.2	160.8 (157.7–164.1)

episodes					years	

IQR Inter-quartile range; CI confidence interval.

3.2. First laminitis episode (Model 1)

Table 6 reports significant associations between risk factors and the time to first laminitis episode. Compared to unknown/other breeds, Arabs, cobs, Native breeds, ponies and Welsh breeds were associated with time to first laminitis episode. Of all syndromes studied, only neurological syndromes were not associated with time to first laminitis episode. Administration of systemic corticosteroids was not significantly associated with time to the first laminitis episode. A number of significant interaction terms were included in the final model for first laminitis episode (see Table 6). Triamcinolone prescription was not significant in a univariable model (p-value 0.84), and no methylprednisolone was prescribed during the time from study entry to first laminitis episode for any horse. Dexamethasone and prednisolone prescription were significant in univariable models (p-values < 0.01), but were dropped from the multivariable model after inclusion of disease and signalment variables.

Table 6.
Association between potential risk factors and time to first laminitis episode in a veterinary-attended UK horse cohort between 1987 and 2013. Hazard ratios are derived from Model 1, a multivariable Cox survival analysis of time to first laminitis episode.

Characteristic		Number of horses	Hazard Ratio	95% Confidence Interval	Wald *p*-value
Breed	Unknown/other	59681	1 (REF)		
	Arab	954	1.80	1.37–2.34	<0.01
	Cob	2132	1.36	1.10–1.69	<0.01
	Draught	1049	0.94	0.66–1.33	0.72
	Native	2218	2.46	2.10–2.87	<0.01
	Pony	1415	1.77	1.43–2.20	<0.01
	Welsh	3032	2.56	2.23–2.94	<0.01
Disease syndrome	Pituitary Pars Intermedia Dysfunction (PPID)	2070	11.18	9.26–13.51	<0.01
	Equine Metabolic Syndrome (EMS)	143	8.06	5.79–11.20	<0.01
	Gastrointestinal	7760	2.57	2.22–2.98	<0.01
	Orthopaedic	1839	1.85	1.59–2.16	<0.01
	Dermatologic	4473	3.70	3.03–4.52	<0.01
	Systemic	2778	1.35	1.19–1.53	<0.01
	Respiratory	3773	1.17	1.04–1.32	<0.01
	Recurrent Airway Obstruction (RAO)	1228	1.44	1.21–1.70	<0.01
Sex	Female	26019	1 (REF)		<0.01
	Male	37975	0.88	0.82–0.94	<0.01
	Unknown	6487	0.65	0.55–0.76	<0.01
PPID: time			0.99	0.99–0.99	<0.01*
Colic: time			0.99	0.99–0.99	<0.01*

Dermatologic: time			0.99	0.99–0.99	<0.01*
Breed: dermatologic	Other/unknown: Dermatologic		1 (REF)		<0.01*
	Arab: Dermatologic		0.28	0.11–0.69	<0.01
	Cob: Dermatologic		0.51	0.27–0.95	<0.01
	Draught: Dermatologic		0.27	0.10–0.78	<0.01
	Native: Dermatologic		0.45	0.25–0.82	<0.01
	Pony: Dermatologic		0.17	0.04–0.71	<0.01
	Welsh: Dermatologic		0.22	0.12–0.40	<0.01
PPID: EMS			0.35	0.21–0.57	<0.01*
PPID: Orthopaedic			0.51	0.35–0.72	<0.01*
EMS: dermatologic			0.31	0.12–0.78	<0.01*

REF referent level.

*
p-values from likelihood-ratio tests comparing models with and without interaction term.

3.3. Subsequent laminitis episodes (Model 2)

Table 7 contains all variables significantly associated with the risk of second–sixth laminitis episode in a multivariable PWP model. Horse breed and sex were not associated with subsequent laminitis episodes. Prednisolone prescription was associated with 5.3 times the hazard of subsequent laminitis episodes, and unlike the first laminitis episode, neurological syndromes were associated with an increased hazard also. RAO was associated with a reduced hazard of subsequent laminitis episodes, in contrast to its increased hazard ratio for first laminitis episode. Methylprednisolone prescription was not associated with subsequent laminitis at the univariable stage. All other excluded variables were significant at univariable modelling stage, then dropped at the multivariable modelling stage.

Table 7.
Association between risk factors and time to subsequent laminitis episode (second–sixth episodes, n = 3358 horses) in horses receiving veterinary attention from a convenience sample of UK veterinary practices between 1987 and 2013. Results of Model 2, a multivariable Prentice, Williams Peterson model of time to second–sixth laminitis episode.

Characteristic	Number of Horses	Hazard Ratio	95% Confidence Interval	Wald *p*-value
Pituitary Pars Intermedia Dysfunction (PPID)	721	1.63	1.31–2.03	<0.01
Orthopaedic	256	5.33	3.48–8.18	<0.01
Respiratory	383	3.10	2.08–4.62	<0.01
Systemic	358	2.69	1.84–3.93	<0.01
Prednisolone	156	5.25	2.59–10.63	<0.01
Neurological	83	7.20	3.11–16.67	<0.01

Recurrent Airway Obstruction (RAO)	294	0.62	0.45–0.85	<0.01
PPID: Respiratory		4.53	1.50–13.69	<0.01*
PPID: RAO		2.75	1.23–6.12	0.02*
Systemic: RAO		7.02	1.68–29.38	<0.01*

*p-values from likelihood-ratio tests comparing models with and without interaction term.

4. Discussion

Risk factors for the first (Model 1) and subsequent (Model 2) episodes of laminitis were found to differ in this population. Breed, sex, EMS, colic and dermatologic syndromes were significantly associated with the first episode of laminitis, but not subsequent episodes. Similarly, prednisolone prescription and neurological syndromes were significantly associated with subsequent laminitis episodes, but not with a horse's first episode. Risk factors found to affect both first, and subsequent laminitis episodes were PPID, orthopaedic, systemic, and respiratory syndromes. Many of the clinical syndromes studied were hypothesized to only affect laminitis risk through the intermediary variable of corticosteroid prescription (Fig. 1), however this was not supported by the final models reported here. This finding may indicate that laminitis has more potential aetiological origins than first thought, and that corticosteroid use is less important.

Recurrence of laminitis was common in this population, with 72% of laminitic horses experiencing at least one recurrence of the condition. Laminitis is clinically subdivided into acute and chronic forms, the former of which can be recurrent and cause no permanent anatomic changes, and the latter of which is defined by irreversible hoof changes and worsening prognosis (Hunt, 1993, Katz and Bailey, 2012 and Slater et al., 1995). Detection of these subdivisions requires radiography, and progression from acute to chronic stage occurs at unpredictable times, if at all. In the majority of cases, the stage of laminitis was not reported in EMR, therefore this subdivision was not available for inclusion in the modelling procedures.

EMR represent an important data resource for veterinary epidemiology. Embedded systematic clinical nomenclature systems are not yet a feature of most practice management software systems, thus all disease and treatment information (excluding auto-generated prescriptions and billing) is contained in free-text. The largest source of error in the use of this information arises through the necessity to apply text-mining or machine learning technologies to categorise records, as manual classification would be too cumbersome and thereby negate the sample-size benefits of EMR. Record categorisation is unlikely to reach 100% sensitivity and specificity because of the variation in nomenclature, phraseology,

spelling accuracy and verbosity of EMR. However, with judicious use of powerful software, and an iterative, diligent approach, diagnostic accuracy of the text-mining process for medical data has been shown to be highly accurate, especially in the case of pharmacology (Anholt et al., 2014a, Anholt et al., 2014b and Roque et al., 2011). The second large source of potential error in the use of EMR from first-opinion practice arises from the variable, reactive nature of primary veterinary care. Whereas in prospective, experimental studies, inclusion criteria can and must be exhaustive, retrospective 'real-world' data will likely never reflect such completeness. The role of the veterinarian is to deliver the most likely diagnosis possible, given financial and practical constraints, and to offer the most appropriate care for that individual. In reality, diagnoses are commonly arrived at without a full, referral-level battery of appropriate tests. Treatment and management regimens vary greatly, even given seemingly identical clinical scenarios. EMR therefore represent historical accounts of the true course of clinical events, and when the general veterinary-attended population is the population of interest, study of the decisions made in the 'real world' may be more applicable than experimental data. This study was based upon data from a convenience sample of practices, which may have led to a reduction in the generalizability of results, however, given that each practice offered primary care to the general horse population, this reduction should be small.

The EMR used in this study had some limitations. In very many cases, the diagnostic criteria employed to make clinical decisions were missing, partial, or unclear. Application of stringent diagnostic inclusion criteria was therefore not possible if the data were to be used to greatest effect. The diagnoses included in this study were therefore taken as rote, either from non-negative terminology inclusions, or prescription of medications that were very likely to indicate disease diagnosis (e.g. Pergolide use as an indicator of PPID). In addition, many of the diseases studied are unchallenging to diagnose in a primary care setting, simply by pattern recognition of the combination of history and clinical signs presented, thus lending confidence to included diagnoses. We cannot, however be certain of the accuracy of this method, without retrospectively obtaining definitive diagnoses, which were not possible given data anonymization and ethical considerations. Different practices, and veterinarians working 'in the field' as opposed to a hospital setting, will have employed differing diagnostic modalities in laminitis case investigation. We posit, however, that a diagnosis of laminitis made through clinical examination with or without radiography alone is likely to be sufficiently accurate (given that this will be the basis for treatment in a great many animals) to allow case identification in this study. Therefore, although other diagnostic investigations would offer more information on the disease

course, the diagnosis without such information is valid and worthy of inclusion. Most clinical scenarios were grouped into 'syndromes' for use here, to enable inclusion of clinical signs likely to lead to corticosteroid administration before definitive diagnoses were reached. Given these differences, apparent disease prevalence reported here cannot be directly compared to other studies. No husbandry or environmental details were included in EMR, therefore known laminitis risk factors related to, for example, grain overload, could not be included in the models. Some errors were detected in either the date of veterinary care episode, or date of birth of some horses (16% of records). It was not possible to identify which dates were erroneous, therefore calculated ages with spurious values were set as missing. We had no reason to believe that date errors would systematically over or underestimate horse ages, and had no way of retrospectively validating dates resulting in appropriate ages, therefore age was included in the analyses, but conclusions drawn from it must be interpreted cautiously. Horses were anonymised and given a unique numeric identifier before analyses proceeded. Given that registration at multiple veterinary practices is possible, some duplication or truncation of medical histories may have occurred, but given the geographic spread of the practices involved this was thought likely to be minimal. For similar reasons, laminitis or other disease diagnoses (or corticosteroid administration) may have occurred prior to an animal's inclusion in these data. All horses were considered at risk of laminitis, provided it was more than sixty days since their last episode. This time period was chosen as it was thought likely that a horse suffering an active episode of laminitis would receive veterinary products or attention at least once in a two-month period. There are no previous studies from which to validate this assumption, however, therefore it may be an over or underestimate. EMS, PPID and RAO are lifelong conditions known to increase laminitis risk (McCue et al., 2015, Menzies-Gow, 2015 and Tadros and Frank, 2013). Horses with these diagnoses may, therefore, have been under greater scrutiny for signs of laminitis, and apparent prevalence may therefore have been inflated in these animals. Changes over the study period in the prevalence of diagnosis of each condition should not have materially affected the estimates of strength of association with laminitis due to the nature of survival analysis.

The clinical syndromes tested for association with laminitis in this study represent many of the clinical scenarios encountered in primary practice, that are either known or thought to pose an increased risk of laminitis (e.g. endometritis), or are indications for the use of corticosteroids. Without inclusion of the possible causes of corticosteroid use, spurious associations between drug use and laminitis may have been generated. Despite the inclusive, general terms

used to categorise EMR, inclusion of disease syndromes led to corticosteroid use dropping out of significance in most multivariable models. Respiratory syndromes and RAO were included as separate risk factors in this study. Corticosteroids are often administered to ease inflammation-related respiratory clinical signs in the absence of definitive diagnoses. Respiratory signs such as cough, dyspnoea and wheezing can be associated with multiple diseases. RAO represents a specific clinical entity, which theoretically poses a lifelong risk of laminitis due to its corticosteroid-based treatments, or possibly due to the effects systemic inflammation (Cornelisse and Robinson, 2013 and Menzies-Gow, 2015). RAO was included separately so that, as with PPID and EMS, diagnosis of these conditions would render an animal permanently categorised as suffering from that condition, unlike other transient, curable respiratory conditions. The Cramer's V statistic for association between respiratory and RAO categories was 0.09 (data not shown), indicating sufficiently low association to include both as independent predictors.

Four corticosteroid drugs were included in these analyses, due to their commonness in practice and their systemic or intra-synovial routes of administration. These four drugs have been found to exert different effects upon equine tissues, have different pharmacologic properties, and could therefore be supposed to have different associations (if any) with laminitis risk (Cornelisse and Robinson, 2013 and McIlwraith, 2010). Specific drug formulations were not always included in EMR, and accurate doses and anatomic sites of administration were vanishingly rare. Most horses in the primary care setting are not weighed regularly, and drug dosing tends to be calculated based on the veterinarian's best guess of an animal's weight. Therefore, given the paucity of accurate information available, drug dose was not included in these analyses. Only the use of prednisolone remained in the multivariable Model 2 after accounting for significant signalment and clinical parameters, and despite a relatively low model power (64%). This suggests that triamcinolone, dexamethasone and methylprednisolone, used as they were in this population over the study period, do not pose a risk of laminitis induction or recurrence. The reason for this difference is unclear, however it may relate to the differences in route of administration; prednisolone is often administered orally in tablet form (Peroni et al., 2002), whereas the other corticosteroids are more commonly delivered via intra-muscular injection. A course of prednisolone tablets would therefore represent a single prescription, but a much longer exposure time (through multiple doses) compared to single injections. Although the potency of triamcinolone and dexamethasone may be greater than the equivalent dose of prednisolone (Johnson et al., 2002), given this postulated difference in exposure

time, the risk of laminitis following prednisolone administration would be magnified. It is possible that the 'true' magnitude of effect of triamcinolone and dexamethasone on laminitis risk is significant (i.e. over 1), but this study would have been underpowered to detect associations of less than 1.3 using the Cox proportional hazard model.

Clinical risk factors for initial laminitis episodes were found to differ from those for subsequent episodes. Only PPID, orthopaedic, systemic and respiratory syndromes were found to be associated with time to laminitis episode in both scenarios. Interestingly, RAO appeared to be associated with an increased risk of the initial laminitis episode, but a reduced risk of subsequent episodes. The reason for this disparity is not known. Breed and sex were important risk factors for initial laminitis episode, but not for subsequent episodes. Both breed and sex have previously been associated with laminitis risk (Alford et al., 2001, Bamford et al., 2014 and Wylie et al., 2014), as have the endocrinopathies PPID and EMS (Donaldson et al., 2004, Johnson et al., 2002, Wylie et al., 2013a and Wylie et al., 2013b). Many significant interaction terms were included in both final multivariable models. These terms were not shared between both models, but all included either PPID, EMS or RAO, which were included as lifelong diagnoses after the initial diagnostic record. All main effects remained statistically significant despite the inclusion of interactions. Interplay between clinical risk factors for laminitis is therefore very complex. Categories of clinical signs included as predictors in these analyses were intended to capture potential associations between underlying (unknown) disease processes and laminitis, to avoid spurious associations of drug administration with the outcome. Therefore, greater emphasis should be placed on interpreting the presence or absence of corticosteroid administration predictors in final models, rather than the presence, or magnitude of clinical sign risk factors. The only truly putative risk factor with a significant laminitis risk association in these models was prednisolone administration. This corticosteroid should therefore be avoided in horses with pre-existing laminitis risks or those who have already suffered from the disease. Good management may lower the risk of EMS (through maintenance of appropriate weight), dermatologic syndromes (via avoidance of injuries leading to cellulitis, for example), or colic, but for the most part, these clinical conditions are unavoidable. It was beyond the scope of this study to assess the effects and appropriateness of treatment of the conditions included on laminitis risk, but future research may be able to ascertain which treatment regimens can modify the disease course and offer hope of avoiding future laminitis episodes. Similarly, we did not include information on the treatment of laminitis (e.g. orthopaedic shoeing, corrective farriery, nutritional adjustment,

rest periods etc.) as it was beyond the scope of this study, and in many cases was not recorded. Many of these factors could have modified the likelihood and time to subsequent laminitis episodes following the first diagnosis, however there was no reason to presume systematic differences in laminitis treatment between the categories of independent variables included.

The use of equine first-opinion EMR for studies of this type is feasible, and offers advantages over smaller scale, prospective studies, or those involving only referral populations. It does, however, pose additional challenges and has some limitations which need to be addressed and taken into account if study validity is to be accepted. Data errors can be a feature of any study, but are difficult or impossible to rectify. The variable nature of medical records also means that useful information is often missing, either systematically (like horse weights), or idiosyncratically. Studies focusing on prescription information may offer the most accuracy in terms of sensitivity of categorisation, due to the automated nature of prescribing and billing, but will likely always suffer from a lack of dosing information in this species until weighing horses accurately becomes easy and commonplace. Despite these limitations, EMR can be used to better understand veterinary decision-making, and to help untangle complicated disease systems that require large sample sizes for their estimation.

Acknowledgments
The authors are grateful to the practices and owners that contributed data to this study. CW is funded by the British Veterinary Association – Animal Welfare Foundation (grant number: Norman Hayward Fund_2014_1_JM).

References
Alford et al., 2001
P. Alford, S. Geller, B. Richrdson, M. Slater, C. Honnas, J. Foreman, J. Robinson, M. Messer, M. Roberts, D. Goble, D. Hood, M. Chaffin
A multicenter, matched case-control study of risk factors for equine laminitis
Prev. Vet. Med., 49 (2001), pp. 209–222 http://dx.doi.org/10.1016/S0167-5877(01)00188-X

Anholt et al., 2014a
R.M. Anholt, J. Berezowski, I. Jamal, C. Ribble, C. Stephen
Mining free-text medical records for companion animal enteric syndrome surveillance
Prev. Vet. Med., 113 (2014), pp. 417–422
http://dx.doi.org/10.1016/j.prevetmed.2014.01.017

Anholt et al., 2014b
R.M. Anholt, J. Berezowski, C.S. Ribble, M.L. Russell, C. Stephen
Using informatics and the electronic medical record to describe antimicrobial use in the clinical management of diarrhea cases at 12 companion animal practices
PLoS One, 9 (2014), pp. 1–8 http://dx.doi.org/10.1371/journal.pone.0103190

Bailey and Elliott, 2007
S.R. Bailey, J. Elliott
The corticosteroid laminitis story: 2. Science of if, when and how
Equine Vet. J., 39 (2007), pp. 7–11
http://dx.doi.org/10.2746/042516407X166035

Bailey, 2010
S.R. Bailey
Corticosteroid-associated laminitis
Vet. Clin. North Am. Equine Pract., 26 (2010), pp. 277–285
http://dx.doi.org/10.1016/j.cveq.2010.04.001

Bamford et al., 2014
N.J. Bamford, S.J. Potter, P. a. Harris, S.R. Bailey
Breed differences in insulin sensitivity and insulinemic responses to oral glucose in horses and ponies of moderate body condition score
Domest. Anim. Endocrinol., 47 (2014), pp. 101–107
http://dx.doi.org/10.1016/j.domaniend.2013.11.001

Cornelisse and Robinson, 2013
C.J. Cornelisse, N.E. Robinson
Glucocorticoid therapy and the risk of equine laminitis
Equine Vet. Educ. (2013), pp. 39–46 http://dx.doi.org/10.1111/j.2042-3292.2011.00320.x

Donaldson et al., 2004
M.T. Donaldson, A.J.R. Jorgensen, J. Beech
Evaluation of suspected pituitary pars intermedia dysfunction in horses with laminitis
J. Am. Vet. Med. Assoc., 224 (2004), pp. 1123–1127
http://dx.doi.org/10.2460/javma.2004.224.1123

French et al., 2000

K. French, C.C. Pollitt, M.a. Pass
Pharmacokinetics and metabolic effects of triamcinolone acetonide and their possible relationships to glucocorticoid-induced laminitis in horses
J. Vet. Pharmacol. Ther. (2000), pp. 287–292 http://dx.doi.org/10.1046/j.1365-2885.2000.00288.x

Hunt, 1993
R.J. Hunt
A retrospective evaluation of laminitis in horses
Equine Vet. J., 25 (1993), pp. 61–64

Johns and Adams, 2015
I.C. Johns, E.-L. Adams
Trends in antimicrobial resistance in equine bacterial isolates: 1999–2012
Vet. Rec., 35 (5) (2015), pp. 367–375 http://dx.doi.org/10.1136/vr.102708

View Record in Scopus
Johnson et al., 2002
P.J. Johnson, S.H. Slight, V.K. Ganjam, J.M. Kreeger
Glucocorticoids and laminitis in the horse
Vet. Clin. North Am. Equine Pract., 18 (2002), pp. 219–236
http://dx.doi.org/10.1016/S0749-0739(02)00015-9

Katz and Bailey, 2012
L.M. Katz, S.R. Bailey
A review of recent advances and current hypotheses on the pathogenesis of acute laminitis
Equine Vet. J., 44 (2012), pp. 752–761 http://dx.doi.org/10.1111/j.2042-3306.2012.00664.x

Lam et al., 2007
K. Lam, T. Parkin, C. Riggs, K. Morgan
Use of free text clinical records in identifying syndromes and analysing health data
Vet. Rec., 161 (2007), pp. 547–551 http://dx.doi.org/10.1136/vr.161.16.547

McCluskey and Kavenagh, 2004
M.J. McCluskey, P.B. Kavenagh
Clinical use of triamcinolone acetonide in the horse (205 cases) and the incidence of glucocorticoid-induced laminitis associated with its use

Equine Vet. Educ., 16 (2004), pp. 86–89 http://dx.doi.org/10.1111/j.2042-3292.2004.tb00272.x

McCue et al., 2015
M.E. McCue, R.J. Geor, N. Schultz
Equine metabolic syndrome: a complex disease influenced by genetics and the environment
J. Equine Vet. Sci., 35 (2015), pp. 367–375
http://dx.doi.org/10.1016/j.jevs.2015.03.004

McIlwraith, 2010
C.W. McIlwraith
The use of intra-articular corticosteroids in the horse: what is known on a scientific basis?
Equine Vet. J., 42 (2010), pp. 563–571 http://dx.doi.org/10.1111/j.2042-3306.2010.00095.x

Menzies-Gow, 2015
N.J. Menzies-Gow
I have decided to treat my RAO case with systemic corticosteroids: should I screen it for laminitis risk?
Equine Vet Educ., 27 (2015), pp. 332–333 http://dx.doi.org/10.1111/eve.12352

Peroni et al., 2002
D.L. Peroni, S. Stanley, N.E. Robinson
Prednisone per os is likely to have limited efficacy in horses
Equine Vet. J., 34 (2002), pp. 283–287

Polzer and Slater, 1997
J. Polzer, M.R. Slater
Age, breed, sex and seasonality as risk factors for equine laminitis
Prev. Vet. Med., 29 (1997), pp. 179–184 http://dx.doi.org/10.1016/S0167-5877(96)01086-0

Prentice et al., 1981
R.L. Prentice, B.J. Williams, A.V. Peterson
On the regression analysis of multivariate failure time data
Biometrika, 68 (1981), pp. 373–379

R Core Team, 2015

R Core Team
R: A Language and Environment for Statistical Computing
R Foundation for Statistical Computing (2015) [WWW Document]. URL http://www.r-project.org/

Roque et al., 2011
F.S. Roque, P.B. Jensen, H. Schmock, M. Dalgaard, M. Andreatta, T. Hansen, K. Søeby, S. Bredkjær, A. Juul, T. Werge, L.J. Jensen, S. Brunak
Using electronic patient records to discover disease correlations and stratify patient cohorts
PLoS Comput. Biol., 7 (2011), p. e1002141
http://dx.doi.org/10.1371/journal.pcbi.1002141

Rosner and Rosner, 2006
B. Rosner, R. Rosner
Fundamentals of Biostatistics
(6th ed.)Cengage Learning, Inc. (2006)

Slater et al., 1995
M.R. Slater, D.M. Hood, G.K. Carter
Descriptive epidemiological study of equine laminitis
Equine Vet. J., 27 (1995), pp. 364–367 http://dx.doi.org/10.1111/j.2042-3306.1995.tb04071.x

Slater, 2014
J. Slater
Equine disease surveillance
Vet. Rec., 175 (2014), pp. 271–272 http://dx.doi.org/10.1136/vr.g4982

Tadros and Frank, 2013
E.M. Tadros, N. Frank
Endocrine disorders and laminitis
Equine Vet. Educ., 25 (2013), pp. 152–162 http://dx.doi.org/10.1111/j.2042-3292.2011.00327.x

Wylie et al., 2013a
C.E. Wylie, S.N. Collins, K.L.P. Verheyen, J.R. Newton
A cohort study of equine laminitis in Great Britain 2009–2011: estimation of disease frequency and description of clinical signs in 577 cases
Equine Vet. J., 45 (2013), pp. 681–687 http://dx.doi.org/10.1111/evj.12047

Wylie et al., 2013b
C.E. Wylie, S.N. Collins, K.L.P. Verheyen, J.R. Newton
Risk factors for equine laminitis: a case-control study conducted in veterinary-registered horses and ponies in Great Britain between 2009 and 2011
Vet. J., 198 (2013), pp. 57–69 http://dx.doi.org/10.1016/j.tvjl.2013.08.028

Wylie et al., 2014
C.E. Wylie, J.R. Newton, a. P. Bathe, R.J. Payne
Prevalence of supporting limb laminitis in a UK equine practice and referral hospital setting between 2005 and 2013: implications for future epidemiological studies
Vet. Rec., 176 (2014), p. 72 http://dx.doi.org/10.1136/vr.102426