Horse and Management Level Risk Factors for Specific Types of Equine Colic

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

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ABSTRACT

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Colic is one of the most common causes of mortality in horses and is a significant disease in terms of equine welfare and economic cost. The aim of this study was to identify horse- and management-level risk factors for specific types of equine colic. Knowledge of factors that increase or decrease the risk of different types of colic can improve our understanding of the pathogenesis of these conditions, assist early identification of cases and can allow preventive strategies to be devised if the identified risk factors are alterable.

The seasonality of specific types of colic occurring at the University of Liverpool over a 10 year period (January 1995 – December 2004) was explored using a novel model-based approach. A regression model with either a latent variable or with a linear trend identified 6- and 12- month cyclical patterns for all colics, all medically and surgically treated colics, epiploic foramen entrapment (EFE), equine grass sickness and large colon displacement / torsion. A 12-month cyclical pattern only was identified for the large colon impaction group. No seasonal pattern was identified in the pedunculated lipoma group. The patterns identified in this study appeared to coincide with times of management change or periods when horses are more likely to be intensively managed. These findings generate hypotheses for disease causality in further epidemiological studies.

Two prospective case-control studies were conducted to identify risk factors for EFE. Data were collected from 109 cases and 301 control horses based in UK, Ireland and USA in the matched case-control study. Controls were matched to cases on clinic and time, to control for horse and management differences between different geographic regions. A concurrent unmatched case-control study was conducted in the UK over a 24 month period to explore the seasonal pattern identified for this type of colic. Data were collected from 77 cases and 216 controls in the latter study. Crib-biting / windsucking behaviour was associated with the largest risk of EFE in both studies. A history of colic in the previous 12 months and increasing height were also significantly associated with increased risk of EFE in both studies. A variety of behavioural features of horses were also found to alter the risk of EFE. The results of these studies have indicated that horses at risk of EFE may have some underlying gastrointestinal dysfunction and have identified areas for further research.

Prospective matched and unmatched case-control studies were also conducted to identify risk factors for idiopathic focal eosinophilic enteritis (IFEE). Data were collected from 31 cases and 93 controls in the matched case-control study and 18 cases and 216 controls in the unmatched case-control study. Both studies identified younger horses and horses with current or recent access to a stream / pond or stagnant water to be at increased risk of IFEE. Horses with a history of colic in the previous 12 months and those who had not been treated for tapeworms in the previous 12 months placed horses at increased risk of IFEE in the matched and unmatched studies respectively. There was also an association between the number of horses currently resident on the premises or those who had access to the current pasture and risk of IFEE.

Work described in this thesis has characterised a seasonal incidence of specific types of colic in a UK hospital population. In addition it has identified risk factors for colic due to EFE and IFEE in horses in the UK, Ireland and the USA. Knowledge of these risk factors can assist identification of horses that are at high-risk for these specific forms of colic. In addition some of the identified risk factors are modifiable and this information could potentially be used to devise disease prevention strategies for high-risk individuals. The findings from these studies provide a further understanding of the pathogenesis of specific types of colic and have identified areas that require further research.

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CHAPTER 1

Introduction

Material forming part of this introduction has been published during the writing of this thesis:

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INTRODUCTION

Colic is a term used to describe abdominal pain which, in the horse, is usually gastrointestinal in origin. It has been recognised as a disease of the horse for centuries and is significant in terms of equine welfare and economics. Overall, estimated case fatality rates as a result of colic vary from 6.7-15.6% depending on the population studied and the type of lesion (Kaneene *et al.* 1997; Tinker *et al.* 1997b; Mair 2004). Colic is reported to be the single most common cause of death in some horse populations, representing over a quarter of all deaths in one study (Tinker *et al.* 1997b). In the USA, the annual cost of colic has been estimated at $115.3 million, losses due to death accounting for 66% of this figure (Traub-Dargatz *et al.* 2001). In a survey conducted with horse owners in the UK, colic was ranked as the third most important disease of horses after grass sickness and laminitis (Mellor *et al.* 2001).

Epidemiological studies investigating risk factors for colic

There are many anecdotal reports of what may cause colic, and ways in which it may be prevented, in the veterinary and equestrian literature. However, until recently, there has been little scientific evidence to substantiate or refute these theories. Recent epidemiological studies have shown that colic, like most non-communicable diseases, is complex and multi-factorial in nature (Reeves 1997). In many cases of colic, the exact gastrointestinal dysfunction or lesion is unknown; spasmodic/gas colic or colic of unknown cause was diagnosed in 69–72% of cases seen within the general equine population and only 7–9% of cases in two of these studies were surgical in nature (Proudman 1992; Hudson *et al.* 2001; Mair 2004). The reported incidence of colic in different horse populations varies from 3.5-10.6 colic episodes per 100 horses per year (Kaneene *et al.* 1997; Tinker *et al.* 1997b; Hillyer *et al.* 2001; Traub-Dargatz *et al.* 2001). Within a horse population, incidence rates can vary considerably, influenced by variables between and within horse establishments (Tinker *et al.* 1997b).

Identification of risk factors for colic is important in furthering our understanding of disease causality. Knowledge of these risk factors may also assist diagnosis of the underlying cause of colic; this is particularly relevant in lesions requiring surgical correction where prompt diagnosis and treatment is critical. In addition, identification of modifiable risk factors may potentially enable disease-prevention strategies to be developed.

Epidemiological studies investigating risk factors for colic in general or specific types of colic are both important. Because the underlying gastrointestinal dysfunction is usually unknown, studies investigating risk factors for colic overall are more representative of the general equine population. However, risk factors may be different for specific types of colic and studies looking at colic of any cause could miss some disease-specific findings (Reeves *et al.* 1996; Hudson *et al.* 2001).

A summary of the epidemiological studies that have investigated risk factors for colic in general and for specific types of colic are shown in Tables 1 and 2 respectively. A number of different study designs, including case-control, cohort and longitudinal have been used to investigate risk factors for colic in general. Case-control studies provide the most efficient means of investigating diseases that are relatively rare (Schlesselman 1982) making them particularly relevant to the study of specific types of colic. Some of the studies listed in both tables used other hospital cases as 'controls' (e.g. other horses with colic or horses undergoing investigation for other medical conditions). The use of horses with other types of colic in particular may introduce a number of inherent biases due to the fact these horses may have been exposed to risk factors that predispose to these different forms of colic. This choice of controls may also explain some of the conflicting results found between various studies.

Horse-level risk factors

A variety of horse-level factors may put an individual at increased or decreased risk of suffering from colic. Measures to limit exposure to such risk factors are difficult to conceive, but knowledge of these factors can assist in the diagnosis of certain types of colic. Horse owners or carers may also be more likely to observe for signs of colic, identifying the disease at an earlier stage, in individuals known to be at significantly increased risk of developing colic.

Gender

Some types of colic may be gender-specific in nature (e.g. inguinal herniation in stallions) but overall there is no clear association between gender and colic. Whereas some studies have reported geldings to be at increased risk of suffering colic associated with pedunculated lipomas (Blickslager *et al.* 1992; Edwards and Proudman 1994), others have reported geldings to be at reduced risk of developing colic of any cause (Kaneene *et al.* 1997) or have found no significant association between gender and incidence of colic (Reeves *et al.* 1989; Reeves *et al.* 1996; Tinker *et al.* 1997a; Cohen *et al.* 1999; Traub-Dargatz *et al.* 2001). Associations between gender and risk of colic may be confounded by other factors such as use of horse and associated management practices. Foaling (Kaneene *et al.* 1997) or the 60-150 day period after foaling (White 1997) have been associated with increased risk of colic in mares.

Age

Studies investigating the association between age and colic have yielded different results. Foals <6 months old were found to be at decreased risk of suffering from colic in one study (Traub-Dargatz *et al.* 2001), whereas horses aged 2-10 years (Tinker *et al.* 1997a), >8 years (Cohen and Peloso 1996), >10 years (Cohen *et al.* 1999) or those of increasing age in a linear form (Kaneene *et al.* 1997) have been reported to be risk factors for colic in other studies. The conflicting results from these studies may be explained by differences in study population, choice of controls and even definition of colic. Several studies have consistently identified older horses and ponies to be at increased risk of suffering from colic associated with pedunculated lipomas (Blickslager *et al.* 1992; Edwards and Proudman 1994; Freeman and Schaeffer 2001).

Breed

The association between breed of horse and colic also varies between studies. Thoroughbreds were more likely to develop colic in studies by Traub-Dargatz *et al.* (2001) and Tinker *et al.* (1997a). The latter study also identified Arab horses to be at reduced risk of colic whereas other studies (Cohen *et al.* 1995; Cohen and Peloso 1996; Reeves *et al.* 1996; Cohen *et al.* 1999) found Arab horses to be at significantly increased risk. Some studies have identified no association between breed and colic (Kaneene *et al.* 1997).

Crib-biting / windsucking behaviour

Crib-biting / windsucking behaviour has not been investigated as a risk factor for colic in general. However, horses exhibiting crib-biting /windsucking behaviour have been identified to be at significantly increased risk of suffering from simple colonic obstruction and distension (SCOD) colic (Hillyer *et al.* 2002) and epiploic foramen entrapment (EFE) (Archer *et al.* 2004a).

History of previous colic

Horses with a history of colic have been identified to be at increased risk of suffering further episodes in several studies (Cohen *et al.* 1995; Reeves *et al.* 1996; Tinker *et al.* 1997a; Cohen *et al.* 1999). In a study by Traub-Dargatz *et al.* (2001) 43.5% of horses suffering from colic were reported to have had colic previously, 11% of these within 1 year of the primary colic event. Horses previously suffering colic have also been significantly associated with SCOD colic (Hillyer *et al.* 2002).

Management-level risk factors

Colic may be more prevalent in certain months of the year in some equine populations (Proudman 1992; Tinker *et al.* 1997b; Hillyer *et al.* 2001; Traub-Dargatz *et al.* 2001). Despite anecdotal suggestions that weather-related factors may be associated with the development of colic, there is no scientific proof of this (Gonclaves *et al.* 2002). The patterns of colic found in the former studies may be associated with management factors common to certain times of the year rather than weather factors alone. To date, no studies have investigated the temporal patterns of colic using time-series methodology. In this thesis we present a novel, model-based approach to investigate the seasonality of colic and identify seasonal patterns that may be associated with certain management-level risk factors (Chapter 2).

Parasite control

Parasites are a well-documented cause of colic in the horse. Migrating larvae of *Strongylus vulgaris* were once thought to cause up to 90% of all colic episodes in the horse (White 1997) but the availability of modern anthelmintics has resulted in reports of *S. vulgaris*-associated colic now being rare. More recently, the tapeworm

Anoplocephala perfoliata has been implicated as a cause of colic. Proudman *et al.* (1998) demonstrated a strong association between intensity of infection with *A. perfoliata* and ileal impaction and spasmodic colic, and this finding has been supported by a further epidemiological study in the south-eastern USA (Little and Blikslager 2002). Uhlinger (1990) demonstrated the importance of parasites as a cause of colic in an intervention study conducted over a 5 year period. The incidence of colic in their study population was most effectively reduced by anthelmintic schedules with the highest efficacy.

Epidemiological studies relating parasite infestation and anthelmintic control with colic have yielded conflicting results (Cohen 2003). Some studies have identified no association of colic with the type of anthelmintic administered or the parasite control programme (Cohen *et al.* 1995; Hillyer *et al.* 2001; Traub-Dargatz *et al.* 2001). Other studies have identified horses to be at decreased risk of colic if they were on a regular anthelmintic programme (Cohen *et al.* 1999) or if they had been de-wormed recently (Uhlinger 1990; Reeves *et al.* 1996; Hudson *et al.* 2001). Failure to administer a pyrantel salt in the three months prior to admission has been reported to be a risk factor for development of ileal impaction (Little and Blikslager 2002) and non-administration of moxidectin/ivermectin anthelmintic in the previous 12 months was associated with SCOD in another study (Hillyer *et al.* 2002) although the precise reasons for this were unclear. Cohen *et al.* (1999) reported increased risk of colic in the seven day period following anthelmintic administration. Reduced risk of colic in these studies may be explained by strategies that prevent large numbers of parasites accumulating in the gastrointestinal tract. Recent anthelmintic administration may increase the risk of colic if large numbers of intestinal parasites are already established due to the intestinal inflammation that results when these parasites are killed.

Feed types and feeding practices

Traub-Dargatz *et al.* (2001) reported no association between colic and the types of dried forage fed or the frequency of feeding forage. In contrast, horses with a history of being fed coastal Bermuda grass hay in the USA were found to be significantly more likely to have had a previous episode of colic or suffer from recurrent colic in one study (Cohen and Peloso 1996) whereas Hudson *et al.* (2001) reported feeding hay from round bales and feeding hay other than alfalfa, coastal or Bermuda types to increase the risk of colic. Feeding less easily digested, more complex or varied diets with a high proportion of forage in the form of either hay or pasture placed horses at decreased risk of colic in another study (Tinker *et al.* 1997a). In the USA, feeding of coastal Bermuda grass hay has also been identified as a risk factor for development of ileal impactions (Little and Blickslager 2002) and a history of being fed alfalfa hay placed horses at increased risk of enterolithiasis in a separate study (Cohen *et al.* 2000).

Two studies reported no association between colic and feeding a particular type of concentrate (Cohen *et al.* 1999; Traub-Dargatz *et al.* 2001) whereas feeding of >2.7 kg oats/day was significantly associated with colic in another study (Hudson *et al.* 2001). Tinker *et al.* (1997a) found increasing concentrate intakes to be associated with an increasing risk of colic, this risk increasing 6-fold in horses being fed the greatest quantities of concentrate (>5 kg/day) compared to horses on pasture receiving no concentrates. In this study, feeding whole grain decreased the risk of colic and feeding of more processed feeds such as pellets or sweet feeds increased the risk. In comparison, colic risk was increased in horses fed whole-grain corn but when all non-roughage concentrate feeds were combined, colic risk was found to decrease with increased intake of concentrates (Reeves *et al.* 1996). However this association was considered more likely to be a result of confounding by physical exercise, which could not be controlled for in the analysis of the latter study.

A number of feeding practices have been identified as risk factors for colic. These include: feeding a new batch of hay in the preceding two weeks (Hudson *et al.* 2001), a change in the type of hay fed (Cohen *et al.* 1999), more than 1 change/year of hay (Tinker *et al.* 1997a), a recent change in type or amount of grain or concentrate fed (Tinker *et al.* 1997a; Hudson *et al.* 2001) and diet change in the two week period prior to examination (Cohen *et al.* 1995; Cohen *et al.* 1999). Hillyer *et al.* (2002) found that horses were at increased risk of SCOD colic in the 14 days after an increase in the amount of concentrate fed. The evidence from these studies demonstrates that dietary change is an important and consistently identified risk factor for colic.

Exercise

Cohen *et al.* (1999) reported an increased risk of colic in horses being exercised at least once a week compared to those turned out with no ridden exercise even when other confounding factors such as diet were taken into account. Hillyer *et al.* (2001) suggested that the incidence of colic may have been associated with stage of training or level of activity in horses on National Hunt or Flat racing premises based on the seasonal pattern of colic in these two groups. However, this study did not control for factors such as nutrition, transport and use, which confound the relationship between exercise and colic. An increased risk of SCOD colic was also associated with a recent change in a regular exercise programme (either a decrease in frequency / duration or any change in intensity), particularly in the week following change (Hillyer *et al.* 2002). This effect remained significant when feeding and housing practices were taken into account in the final multivariable model.

Stabling and access to pasture

Horses that spend 100% of their time in the stable have been reported to be at increased risk of colic when compared to horses that spend no time in a stable (Hudson *et al.* 2001). However, mild episodes of colic may be more likely to be detected in stabled horses compared to those turned out at pasture for long periods of time (Kaneene *et al.* 1997) and stabled horses may experience other management factors that predispose to colic. In addition, horses that are predominantly stabled may have less opportunity for exercise. Cohen *et al.* (1995; 1999) identified a change in stabling within the previous two weeks to be associated with increased risk of colic, although these studies did not examine which particular stabling changes predisposed horses to colic. Increased number of hours spent in the stable was also associated with increased risk of SCOD, particularly in the 14 days following change in housing (Hillyer *et al.* 2002).

Decreased exposure to pasture (classified as either a decrease in acreage or time at pasture) was a significant risk factor for colic in one study (Hudson *et al.* 2001). Traub-Dargatz *et al.* (2001) reported no association between colic and type of pasture, pasture quality, percentage of pasture with edible vegetation or stocking density. In contrast, a stocking density of <0.5 horses/acre was associated with significantly increased risk of chronic intermittent colic in another study (Cohen and Peloso, 1996). The latter study took into account factors such as nutrition and parasite control and this finding was considered to be due to owner factors, such as closer observation for colic / increased likelihood of seeking veterinary attention or other management factors that were not measured.

Access to water

Horses with access to ponds have been shown to be at decreased risk of suffering colic (Cohen *et al.* 1995). This is in agreement with the findings of Kaneene *et al.* (1997) where provision of water to groups of horses from sources other than buckets, troughs or tanks was associated with decreased risk. Hudson *et al.* (2001) found no significant association between the type of watering practice and colic but none of the horses in their study had access to water denied for longer than 4 hours. An increased risk of colic was identified in another study in horses without access to water in outdoor enclosures (Reeves *et al.* 1996).

Transport

The association between colic and transport is inconsistent; Cohen *et al.* (1995) did not find any association whereas White (1997) reported increased risk of colic following transport. Hillyer *et al.* (2002) reported that transport in the previous 24 hours was associated with a large increase in risk for SCOD (Odds Ratio [OR] 17.48, 95% confidence interval [95% CI] 2.16-141.35). This finding was considered to be related to transport itself or representative of simultaneous management changes such as change in premises, physical constraint and deprivation of water and feed which were either non-significant when measured alone or could not be measured.

Dental prophylaxis

Cohen *et al.* (1995) did not identify any association between frequency of dental prophylaxis and colic although both cases (horses with colic) and their controls received dental care making this comparison difficult. Horses that had their teeth checked or treated fewer times per year were found to be at increased risk of SCOD in the study by Hillyer *et al.* (2002).

Vaccination

In the USA, Tinker *et al.* (1997a) identified an increased risk of colic in horses following Potomac horse fever vaccination particularly up to 14 days following vaccination. No association between colic and vaccination has been found in other studies and this relationship was considered more likely to be a marker for good healthcare, rather than a cause of colic, by the authors of the latter study.

Premises / owner factors and use of horse

Horses whose owners provide their care have been shown to be at decreased risk of colic or recurrence of colic compared to horses cared for by a non-owner (Reeves *et al.* 1996; Hillyer *et al.* 2001). Owners may provide better health care for their horses or this finding may be related to other factors such as density of horses on the premises or their exercise level (Cohen 2003). Traub-Dargatz *et al.* (2001) reported no association between the gender of the person making health care decisions on the operation or the relationship of the person implementing health care to the owner of the operation. The latter study, and a study by Reeves *et al.* (1996) did not find any association between colic and use of the horse. In contrast, horses used for eventing, showing, or horses in training, particularly flat-trained racehorses, have been shown to be at increased risk in some studies (Kaneene *et al.* 1997; Tinker *et al.* 1997a: Hillyer *et al.* 2001). However, in these studies confounding factors such as age, breed and type of horse, nutrition, exercise and transport were not all taken into account when considering use of horse as a risk factor for colic. Use of horse may be significant when specific types of colic are considered e.g. strangulating obstructions of the large colon in brood mares (Reeves *et al.* 1996). Mild episodes of colic may also be missed on premises where horses spend most of their time at pasture and are not used for any activities (Kaneene *et al.* 1997).

In conclusion, a number of horse- and management-level factors have been identified as risk factors for colic. Whilst some risk factors are consistently reported, other risk factors vary between studies or are contradictory. Some of these variations may be explained by differences between study populations, case definition, study design, including selection of controls, and methods of analysis.

Epiploic foramen entrapment

The epiploic foramen (foramen of Winslow or foramen omentale) is a 4-6 cm slit-like opening located in the right dorsal abdomen that separates the omental bursa from the abdominal cavity (Figure 1). Its borders are formed by the base of the caudate process of the liver, the portal vein and the gastropancreatic fold (Freeman 2005). Strangulating obstruction is the usual sequel to herniation of intestine into the foramen and small intestine is most frequently involved (Figure 2). Rarely the caecum (Scheidmann 1989) or large colon (Foerner *et al.* 1993; Steenhaut *et al.* 1993) may become entrapped.

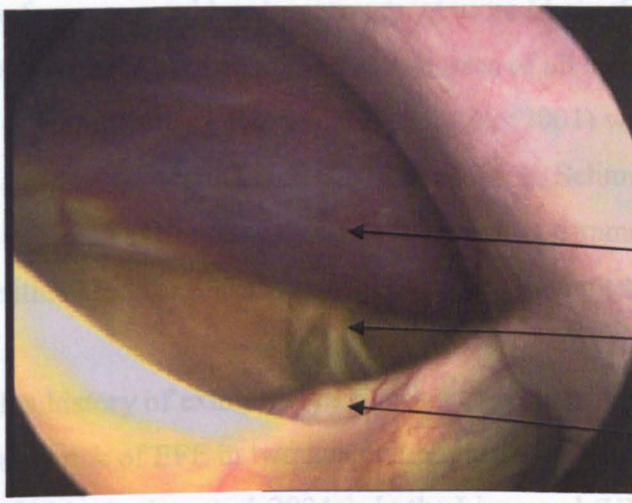


Figure 1. Image of the epiploic foramen taken during laparoscopic examination of the right dorsal abdomen (Picture courtesy of Tim Phillips).

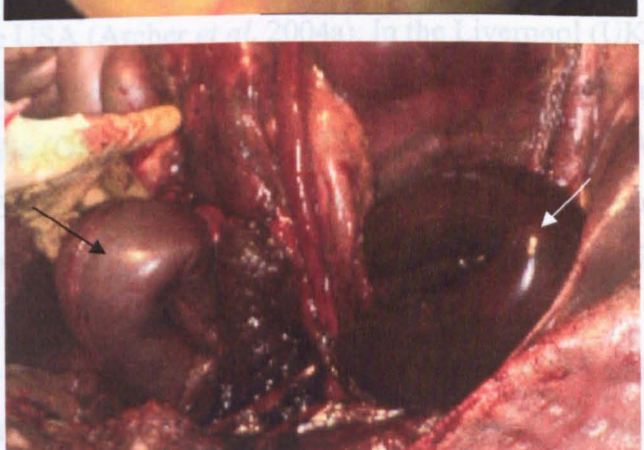


Figure 2. Small intestine most frequently becomes entrapped in the epiploic foramen. Ileum can be seen entering the foramen (black arrow) resulting in loop of ileum / distal jejunum becoming strangulated (white arrow).

Entrapment of intestine in the epiploic foramen (EFE) has been reported in the veterinary literature in horses and cattle (Deprez *et al.* 2006). EFE is rare in cattle whereas it is one of the most common causes of small intestinal strangulation in the horse, representing 2-8% of colic cases that undergo surgery and 5-23% of all strangulating lesions of the small intestine (Freeman 2005). Short-term (defined as time from surgery to discharge from the clinic) survival rates for horses that have undergone surgical correction of EFE vary from 63-88%. EFE has been identified as a risk factor for reduced long-term survival in horses undergoing colic surgery (Proudman *et al.* 2002), found in part to be due to lower total plasma protein levels and longer duration of surgery in these horses (Proudman *et al.* 2005) making investigation of the epidemiology of this condition important.

Few studies have investigated the epidemiology of EFE. Historically, it was suggested that increasing age predisposed to this condition due to the fact that atrophy of the right lobe of the liver occurs more commonly in older horses and subsequent enlargement of the epiploic foramen would make entrapment more likely (Freeman and Schaeffer 2001). However, EFE has been reported in horses of all ages, including foals, and this hypothesis was refuted by Freeman and Schaeffer (2001) who found no evidence that increasing age was associated with EFE. In addition, Schmid (1998) found no correlation between age and the width of the epiploic foramen in an anatomic study of 15 horses euthanased for reasons unrelated to the gastrointestinal tract.

Horses with a history of exhibiting crib-biting or windsucking behaviour were found to be at increased risk of EFE in two hospital populations, one based in the UK and the other in the USA (Archer *et al.* 2004a). In the Liverpool (UK) population, horses with EFE were 8.2 times more likely to exhibit this behaviour compared to horses with other types of colic (OR 8.2, 95% CI 4.5-15.1). In the Ilinois (USA) population horses with EFE were 34.7 times more likely to exhibit this behaviour compared to horses with other forms of strangulating small intestinal lesions (OR 34.7, 95% CI 6.2-194.6).

In addition to windsucking / crib-biting behaviour, breed and season were also found to be risk factors for EFE in the Liverpool population. Thoroughbred or Thoroughbred-cross horses were associated with increased risk of developing EFE and significantly more cases of EFE occurred during the months of December, January and February compared to other months (Archer *et al.* 2004b). In Germany, Scheidemann (1989) has reported that, in one clinic population, more cases of EFE occurred between December and April compared to other months of the year.

The studies investigating risk factors for EFE so far have all used other colic cases as controls. This may introduce bias due to the fact that the control population may not be representative of the population from where the cases came and they may have been exposed to risk factors predisposing them to other forms of colic. To date no studies have investigated risk factors for EFE using a population of healthy horses as controls nor have any management-level risk factors or other horse-level factors been investigated.

Equine idiopathic focal eosinophilic enteritis

Eosinophilic gastrointestinal disorders (EGID) encompass a variety of diseases that feature eosinophilic leukocyte (eosinophil) accumulation at a number different anatomic sites in the gastro-intestinal tract. These include eosinophilic oesophagitis, gastritis, gastroenteritis, enteritis and colitis. These disorders have been identified in multiple species including: humans (Shanahan 2003; Uenishi *et al.* 2003), dogs (Quigley and Hendry 1981), cats (Hendrick 1981; Griffin and Meunier 1990), horses (Rooney and Robertson 1996) and cattle (Cebra *et al.* 1998). In humans, primary EGID are defined as disorders that primarily affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia e.g. drug reactions, parasite infections and malignancy (Rothenberg 2004). In all species, primary EGID are relatively uncommon. However, in humans, a mini-epidemic of these diseases (particularly eosinophilic oesophagitis) has been noted over the last decade (Bates 2000).

Eosinophilic infiltration of the gastro-intestinal tract may be one manifestation of a more diffuse infiltrative eosinophilic disease affecting multiple organs. Such 'hypereosinophilic syndromes' have been identified in many species (Hendrick 1981; German *et al.* 2002). In the horse, a syndrome of multi-systemic, eosinophilic epitheliotrophic disease of unknown aetiology affects multiple organs, including the skin and gastro-intestinal tract (Nimmo-Wilkie *et al.* 1985; Gibson and Alders 1987). Eosinophilic infiltration may, however, be confined to the gastro-intestinal tract with variable regions affected. Clinical signs of diffuse eosinophilic enteritis and colitis include weight loss, hypoalbuminaemia and diarrhoea, consistent with diffuse infiltrative intestinal disease (Pass and Bolton 1982; Lindberg 1984; Roberts 2000) and occasionally colic associated with recurrent colonic impactions (Bassage *et al.* 1997).

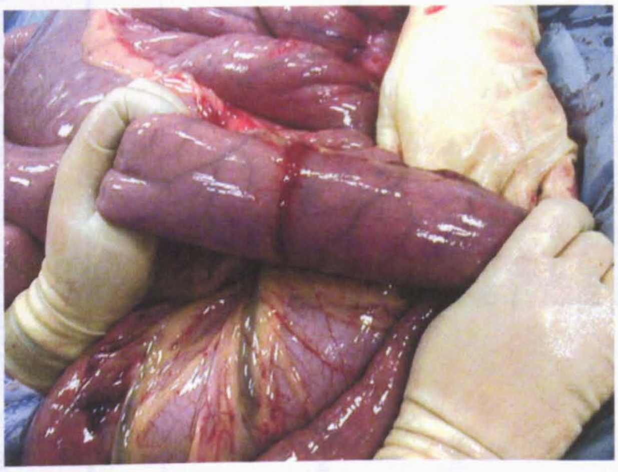
Focal eosinophilic lesions of the small intestine and colon have been identified in the horse secondary to localised infiltration by the fungus *Pythium* sp. (Allison and Gillis 1990) and encapsulated nematodes (Cohen *et al.* 1992). More recently focal, idiopathic disorders of the small intestine (idiopathic focal eosinophilic enteritis; IFEE) and large colon, confirmed or suspected to be eosinophilic in nature, have been reported in the horse (Table 3). In the lesions examined histologically no aetiologic cause could be determined; although Eimeria parasites were noted on histological examination of intestine from one horse in the study by Scott *et al.* (1999) and one horse in the study by Archer *et al.* (2006a), these parasites were not found in the other lesions and were presumed to be incidental findings (Hirayama *et al.* 2002).

Affected horses present with signs of acute colic due to obstruction of ingesta at the site of visibly striking focal or circumferential lesions of the small intestine (Figures 3a & 3b) or colon (Figure 4) and appear to carry a better prognosis than horses with the diffuse form of the condition. It is interesting to note that prior to the late 1990's, these distinct, focal lesions of unknown aetiology were not reported in the literature. The reason for this is unknown but is not considered to be due to lack of recognition by surgeons due to the fact that experienced surgeons have not encountered these visibly striking lesions until the last 6-8 years (G.B. Edwards, personal communication). Depending on their location in the gastrointestinal tract, these lesions have been variously termed as inflammatory bowel disease (Scott *et al.* 1999), segmental eosinophilic colitis (Edwards *et al.* 2000), idiopathic focal eosinophilic enteritis (Southwood *et al.* 2000; Archer *et al.* 2006a), idiopathic eosinophilic enteritis (Stanar *et al.* 2002), multifocal eosinophilic enteritis (Swain *et al.* 2003) and circumferential mural bands in the small intestine causing simple obstructive colic (Perez Olmos *et al.* 2006).

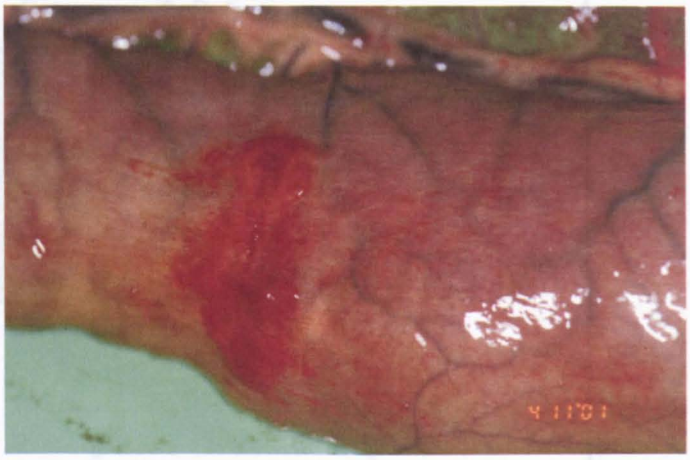
It has been suggested that histopathological diagnosis of idiopathic focal eosinophilic lesions (Figure 5) should be based on two criteria: i.) eosinophils constitute the overwhelming majority of the inflammatory cells and ii.) the number of eosinophils should greatly exceed the low numbers of this cell that are universally present in the intestinal mucosa and submucosa of both normal horses, and of horses with a range of other intestinal lesions (Meschter *et al.* 1986; Packer *et al.* 2005; Archer *et al.* 2006a). It is important to note that not all of the lesions detailed in Table 3 underwent histopathological examination. Based on the accumulated evidence in these studies, focal plaques and CMB are most likely to be associated with marked accumulation of eosinophils. The only reports of focal, circumferential lesions which did not contain marked number of eosinophils are reported in the paper by Archer et al. (2006). It is possible that the predominantly fibrous nature of three lesions mentioned in this paper may have represented the same disease but at a later stage, based on observations that eosinophils have the potential to induce fibrosis in human and guinea-pig tissues (Pincus *et al.* 1987; Noguchi *et al.* 1992) and early fibroplasia has been noted histologically in other cases of IFEE.

The precise role of the eosinophil in the gastrointestinal tract of the horse is unknown but traditionally its principle function has been thought to be phagocytosis of immune complexes after some type of chemotactic stimulus (Hubert 2006). A number of factors including arachidonic acid metabolites, platelet activating factor (PAF), tumour necrosis factor (TNF), eotaxin and interleukins (IL-3, IL-5) are known to play a role in the recruitment and survival of eosinophils (Rothenberg 2004; Hubert 2006). In humans the aetiology of primary EGID is considered to be a result of the interplay between genetic and environmental factors based on observations that this condition may be familial, it may be strongly associated with allergies and atopies, the severity of the disease may be reversed by institution of an allergen-free diet and mast cell degranulation is commonly found in tissue specimens (Rothenberg 2004; Khan 2005). This situation may be different in the horse given that Mäkinen *et al.* (2005) found the lesions to be dominated by eosinophils and macrophages with T cells as the main lymphocyte population and an absence of mast cells. The latter finding was considered to make a potential immediate hypersensitivity or typical IgE-mediated anti-helminth reaction unlikely (Proudman and Kipar 2006).

The histological features of the focal eosinophilic lesions identified in the small intestine and colon are similar (Archer *et al.* 2006a) so it may be reasonable to speculate that similar causes may be involved in the pathogenesis of these distinct lesions. It has been suggested that the anatomic location of the lesions in the small intestine relative to the local vasculature may be relevant to the pathogenesis of the disease (Scott *et al.* 1999) but this has not been consistently found in other studies. In addition there do not appear to be any horse- or management-lèvel factors in the studies detailed in Table 3 that are common to affected horses. To my knowledge no epidemiological investigations have been undertaken to investigate this apparently emerging condition. Knowledge of risk factors for this condition would provide us with a greater understanding of the pathogenesis of these unusual lesions.



(a)



(b)

Figures 3a & 3b . Circumferential (a) and plaque-like (b) idiopathic focal eosinophilic enteritis lesions. Ingesta has become impacted at each site resulting in distension of small intestine proximally (to the right of the lesion in both images).

Figure 4. Focal idiopathic, eosinophilic lesion affecting the large colon.

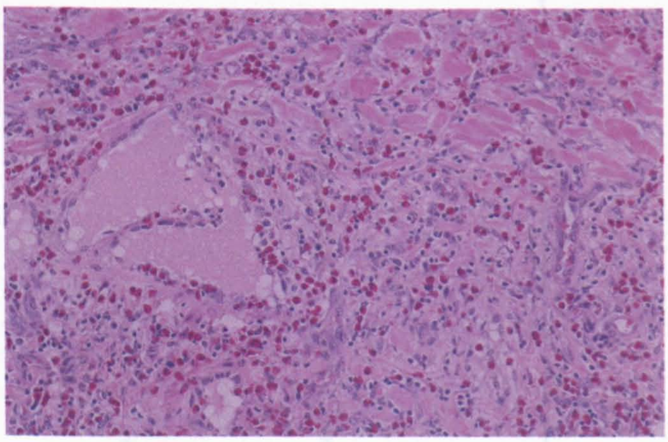


Figure 5. Photomicrograph of small intestinal submucosa with intense infiltration by eosinophils. In addition dilated lymphatics, fibroplasia and capillary proliferation are evident (Haematoxylin and eosin [HE] x 250).

Table 1. A summary of published studies that have investigated risk factors for colic of any type. The table details the population studied, the design of the **study and factors that increased or decreased the risk of colic in these populations. Case-control studies marked with an * indicate that other horses with colic were used as controls.**

Author	***Population studied***	***Study design***	***Analysis***	***Factors identified***
Reeves *et al.* (1989)	Single veterinary teaching hospital population (USA)	Case–control* study	Chi-squared test	Age Breed Gender
Cohen *et al.* (1995)	Horses in Texas (USA)	Case-control study	Logistic regression	History of previous colic History of previous abdominal surgery Recent change in diet
Cohen & Peloso (1996)	Horses in Texas (USA)	Case-control study	Logistic regression	Age Breed History of abdominal surgery Feeding coastal grass hay Recent change in stabling Recent change in diet Density of horses on farm
Reeves *et al.* (1996)	Five veterinary teaching hospital populations (USA)	Case-control* study	Logistic regression	Age Breed Outdoor access & water supply Use of daily worming product Amount of concentrate / whole grain Person responsible for daily care Previous history of colic
Kaneene *et al.* (1997)	Horses in Michigan (USA)	Cohort study	Logistic regression	Gender Foaling De-worming Age Use of horse Water source

Tinker et al. (1997a)	*Horses in Virginia and* Maryland (USA)	*Cohort study*	*Logistic regression*	*Age* Previous history of colic Change in concentrate and hay feeding Concentrate intake Feeding of whole grain Potomac horse fever vaccination
Cohen *et al.* (1999)	Horses in Texas (USA)	Matched case control study	Conditional logistic regression	Breed Age Recent change in diet & type of hay Previous episode of colic History of previous colic surgery Recent change in weather conditions and housing Recent administration of anthelmintic Failure to receive regular de-worming Regular exercise
Hillyer *et al.* (2001)	Thoroughbred training premises in UK during 1997	Cross-sectional study	Relative risk analysis & Logistic regression	Season No. of horses on premises Premises type Carer
Hudson *et al.* (2001)	Horses in Texas (USA)	Matched case-control study	Conditional logistic regression	Breed Recent change in batch of hay Decreased exposure to pasture Recent change in type of grain / concentrate Quantity of oats fed daily Feeding hay from round bales Recent anthelmintic administration
Traub-Dargatz *et al.* (2001)	Horses in 28 states (USA)	Cohort study	Incidence rates, Mantel-Haenzel test Death loss economic calculations	Breed Age Rotation of anthelmintics Parasite testing practices

Table 2. Previous studies investigating factors associated with occurrence of specific types of colic. The table details the colic type studied, the study **population, study design and the factors associated with increased or decreased risk of colic. Case-control studies marked with an * indicate that other horses with colic were used as controls.**

Author	*Colic type investigated*	*Study population*	*Study design*	*Factors identified*
Blickslager *et al.* (1992)	Pedunculated lipoma	Single equine hospital population (USA)	Case-control* study	Age Gender
Edwards & Proudman (1994)	Pedunculated lipoma	Single equine hospital population (UK)	Case-control* study	Age Gender Breed
Proudman *et al.* (1998)	Spasmodic colic & ileal impaction	Single equine hospital population (UK)	Matched case-control study	*A. perfoliata* infection
Hassel *et al.* (1999)	Enterolithiasis	Single equine hospital population (USA)	Case-control* study	Breed Gender
Cohen *et al.* (2000)	Enterolithiasis	Single equine hospital population (USA)	Matched case-control study	Breed Feeding alfalfa hay Duration of outdoor turnout
Freeman & Schaeffer (2001)	Epiploic foramen entrapment (EFE) and pedunculated lipoma	Single equine hospital population (USA)	Retrospective descriptive study	Increasing age (pedunculated lipoma)

Hillyer *et al.* (2002)	Simple colonic obstruction and distension colic	2 equine hospital populations (UK)	Matched case-control study	Crib-biting / windsucking behaviour No. hours stabled per day Change in regular exercise Ivermectin / moxidectin use in previous 12 months History of transport in previous 24 hours Resident on current premises <6 months History of previous colic episode No. of times teeth checked / treated per year
Little & Blickslager (2002)	Ileal impaction	Single equine hospital (USA)	Case-control* study	Feeding Coastal Bermuda hay Failure to administer a pyrantel salt within previous 3 months
Archer *et al.* (2004a)	Epiploic foramen entrapment	Two equine hospital populations (UK & USA)	Case-control* study	Crib-biting / windsucking behaviour
Archer *et al.* (2004b)	Epiploic foramen entrapment	Single equine hospital population (UK)	Case-control* study	Breed Crib-biting / windsucking behaviour Season
Garcia-Seco *et al.* (2005)	Pedunculated lipomas	Single equine hospital population (USA)	Case-control* study	Gender Saddlebred and Arabian breeds Age > 14 years
Stephen *et al.* (2004)	Primary small intestinal volvulus	Single equine hospital population (USA)	Case-control* study	No statistical difference between the signalment of cases compared to the hospital population

Table 3. A summary of reports of confirmed and suspected idiopathic focal eosinophilic lesions of the equine small intestine and colon. CMB = circumferential mural band

Study author(s)	*Study location*	*Number of cases*	*Location and visual appearance of the lesions*	*Histopathology*	*Post-operative outcome*
Scott *et al.* (1999)	USA	11	Oedematous / haemorrhagic sections of SI and colon in all cases; CMB present in 6 horses (4=SI, 2=colon)	Eosinophilic infiltration in all cases in varying proportions	100% short-term survival 91% alive at follow-up 1.5 – 7 years post-operatively
Edwards *et al.* (2000)	UK	22	Focal, segmental mural haemorrhagic lesions evident in the left dorsal colon	Histopathology performed in 11 cases; intense infiltration by eosinophils in all cases and variable degrees of mucosal necrosis	82% short-term survival Overall long-term survival of 73% 3 months – 7 years post-operatively
Southwood *et al.* (2000)	USA	6	2-4cm diameter intramural mass on the anti-mesenteric border of the jejunum in all 6 cases; 1 case had an additional CMB	Marked eosinophilic infiltration of the mucosa, submucosa, muscularis and serosa in all cases	83% alive at 5-60 months post-operatively
Stanar *et al.* (2002)	USA	1	2cm diameter nodular lesion in the mid-jejunum causing partial stricture at the site	Marked eosinophilic infiltration of the mucosa, submucosa and muscularis	Single case; alive 3 months post-operatively
Swain *et al.* (2003)	UK	1	3 intramural, circumferential, constricting lesions in the jejunum and ileum	Extensive transmural inflammation dominated by eosinophils	Single case; euthanased 15 hours post-operatively
Archer *et al.* (2006a)	UK	12	7 CMB, 2 plaques and 3 with plaques and CMB; all located in the small intestine	Severe, transmural enteritis; eosinophils the predominant inflammatory cell in all cases	83% short-term survival and overall long term survival of 58% upto 13 months postoperatively
Perez Olmos *et al.* (2006)	Ireland	28	All had CMB (one or multiple) located in the mid – distal jejunum	Histopathology performed in 2 cases; predominantly eosinophilic infiltration seen in both	100% survival reported 10-74 months post-operatively

THESIS AIMS AND OUTLINE

The aim of this thesis was to identify horse- and management-level risk factors for specific types of equine colic.

The first aim was to investigate whether certain forms of colic are seasonal and, if so, to identify the nature of these patterns in relation to time of the year. Case-control studies have identified particular months of the year as risk factors for equine grass sickness and epiploic foramen entrapment (EFE) but, to date, no studies have specifically investigated seasonal patterns in colic using time-series based methods. Knowledge of seasonal patterns could help to generate hypotheses about horse- and management-level factors that may be associated with particular types of colic. In Chapter 2, a novel modelling technique was used to explore the seasonality of specific types of colic occurring in a single UK equine hospital over a 10 year period.

To date there is limited information about risk factors for EFE and no studies have investigated the epidemiology of this type of colic using a population of healthy horses as controls. In Chapter 3 the results of a matched case-control study are presented. Cases of EFE were recruited onto this study from collaborating clinics based in the UK, Ireland and USA. Controls were matched to cases on clinic and time to control for horse and management factors that vary between geographical locations. In Chapter 4, the results of an unmatched case-control study that was conducted to explore particular management-level factors that may vary seasonally are presented. A subset of EFE cases recruited from 9 clinics located in the UK were used in this study. Controls were randomly selected from the client population of these clinics at monthly intervals during the 24 month recruitment period. We wished to test a number of hypotheses as risk factors for EFE including stabling and turnout routines, types of feed, feeding practices and behavioural features including whether horses exhibited certain forms of stereotypic behaviour.

The final aim of this thesis was to identify horse- and management-level risk factors for idiopathic focal eosinophilic enteritis (IFEE). To date no studies have investigated the epidemiology of this unusual and apparently emerging disease in horses. Identification of risk factors could assist our understanding of the pathogenesis of this condition. In Chapter 5 the results of concurrent matched and unmatched case-control studies are presented. Specifically we wished to test a number of hypotheses including parasite control, diet and recent changes in diet and pasture as potential risk factors for this condition.

CHAPTER TWO

Is equine colic seasonal? Novel application of a model based approach

This chapter has been published during the writing of this thesis:

Archer D.C., Pinchbeck G.L., Proudman C.J., Clough, H.E. (2006). Is colic seasonal? Novel application of a model based approach. *BMC Veterinary Research* **2**, 27

Abstract

Colic is an important cause of mortality and morbidity in domesticated horses yet many questions about this condition remain to be answered. One such question is: does season have an effect on the occurrence of colic? Time-series analysis provides a rigorous statistical approach to this question but until now, to our knowledge, it has not been used in this context. Traditional time-series modelling approaches have limited applicability in the case of relatively rare diseases, such as specific types of equine colic. In this paper we present a modelling approach that respects the discrete nature of the count data and, using a regression model with a correlated latent variable and one with a linear trend, we explored the seasonality of specific types of colic occurring at a UK referral hospital between January1995 - December 2004.

Six- and twelve-month cyclical patterns were identified for all colics, all medical colics, epiploic foramen entrapment (EFE), equine grass sickness (EGS), surgically treated and large colon displacement / torsion colic groups. A twelve-month cyclical pattern only was seen in the large colon impaction colic group. There was no evidence of any cyclical pattern in the pedunculated lipoma group. These results were consistent irrespective of whether we were using a model including latent correlation or trend. Problems were encountered in attempting to include both trend and latent serial dependence in models simultaneously; this is likely to be a consequence of a lack of power to separate these two effects in the presence of small counts, yet in reality the underlying physical effect is likely to be a combination of both.

The use of a regression model with either an autocorrelated latent variable or a linear trend has allowed us to establish formally a seasonal component to certain types of colic presented to a UK referral hospital over a 10 year period. These patterns appeared to coincide with either times of managemental change or periods when horses are more likely to be intensively managed. Further studies are required to identify the determinants of the observed seasonality. Importantly, this type of regression model has applications beyond the study of

equine colic and it may be useful in the investigation of seasonal patterns in other, relatively rare, conditions in all species.

Introduction

Analysis of temporal patterns in data (i.e. data that arises over time) constitutes an important area of statistics, with applications in a wide range of fields from economics to engineering (Diggle 1990). Consistent seasonal patterns in disease suggest the possibility of predictable behaviour, and in human medicine these have assisted rational planning of hospital resources in addition to providing clues regarding disease aetiology. The latter aspect is important in stimulating research to further the understanding of disease causality. Time-series analysis has been used in the human medical field to investigate a number of non-infectious conditions including asthma and aortic aneurysms (Upshur *et al.* 2005) and in veterinary epidemiology to investigate patterns in infectious diseases (Carter *et al.* 1986; Courtin *et al.* 2000; Ward 2002; Tinline and MacInnes 2004). However these statistical methods have received relatively little attention in the field of non-infectious veterinary diseases and, to our knowledge, have not previously been reported in the investigation of colic in the horse.

Colic is an important cause of mortality and morbidity in domesticated horses and has a complex, multifactorial nature (Kaneene *et al.* 1997; Reeves 1997; Tinker *et al.* 1997b; Mair 2004). Many questions about this condition remain to be answered including the effect of season on the occurrence of colic. Knowledge of a seasonal pattern (or indeed lack of evidence of a seasonal pattern) in the incidence of colic within a population could assist identification of risk factors for this disease. Such information could be used to devise preventative strategies, such as altered management practices, to potentially reduce its occurrence. Increased incidence of colic has been identified in certain months of the year in several different equine populations (Proudman 1992; Tinker *et al.* 1997b; Hanson *et al.* 1998; Hillyer *et al.* 2001; Traub-Dargatz et al. 2001) but the association between season and colic is unclear. This may, in part, be attributable to limitations in the statistical approaches that have previously been used to address this issue (Cohen 2003).

Many standard statistical approaches are built upon the assumption that observations are mutually independent. This assumption is likely to be inappropriate in the case of colic since many factors may be interdependent; observations in adjacent months might be more similar than those which occur months apart due to, for example, similarities in feed types and duration of stabling. Time-series methods provide a valid means of investigating seasonal patterns in colic. Traditional approaches, such as the Auto-regressive Integrated Moving Average (ARIMA) of Box and Jenkins (Box *et al.* 1994) offer a number of possibilities. However, this approach requires the number of observations at each time of interest to be large for the Normal distribution-based assumptions upon which it is based to remain valid. This method would not be suitable for diseases, such as admissions of colic cases to a hospital, in which the counts per month are relatively small (i.e. typically less than 30). In the latter situation, it is necessary to use a modelling approach that respects the discrete nature of the count data. One possibility lies in the use of a Poisson distribution to model count data within a framework broadly analogous to that of generalised linear modelling (Zeger 1988; Zeger and Qaqish 1988; McCullagh and Nelder 1989).

The aim of this study was to determine if there was any evidence of seasonality in horses presented to a UK referral hospital with particular types of colic. Using a Bayesian approach, we fitted a regression model which incorporated autocorrelation as a latent variable, to reflect the fact that, having taken account of seasonality and trend, any remaining serial dependence may operate over a shorter temporal scale and is likely to represent unmeasured influential covariates which themselves vary over time. In addition we fitted a model without latent correlation but with a linear trend. Based on current evidence in the literature, our *a priori* hypotheses were that equine grass sickness (EGS) and epiploic foramen entrapments (EFE) would demonstrate seasonality but that intestinal obstruction by pedunculated lipomas would be a random event without any evidence of seasonality. It was unclear if a seasonal effect would be seen in the other colic groups.

Materials and methods

Colic data

All cases of colic admitted to the Philip Leverhulme Equine Hospital, University of Liverpool between 1st January 1995 and 31st December 2004 were reviewed retrospectively. The numbers of colic cases occurring in each of the 120 months under investigation were recorded and aggregated as counts per month in the groups defined in Table 1.

Exploratory data analysis

For each colic type, the effect of increasing yearly case numbers was removed (de-trended) by subtracting an annual average to create a residual (Chatfield 2004). A box plot of these residuals by month was then generated. This allowed us to search for preliminary descriptive evidence of seasonality without the data being complicated by the presence of an annual trend (defined as an increase / decrease in the number of colic cases admitted over time for each 12 month period).

Regression model

Our chosen model for incorporating latent correlation was similar to the generalised linear model with Poisson response and logarithmic link function, which is commonly used to model independent count data (McCullagh and Nelder 1989) but has an added level of complexity in that dependence between observations in the series is explicitly incorporated via a latent variable. This is an example of a Bayesian Hierarchical model (see, for example Gelman *et al.* 2003). This approach allows us, having accounted for seasonality and trend, to determine whether any correlation between observations at successive time points, over a shorter scale than that indicated by cycles or trend, remains. Having accounted for these factors, we can then determine whether observations in two successive months are more (or less) similar than we might expect by chance.

The most general model incorporating cycles at both 6 and 12-month frequencies is as follows: Let N_t be the number of admissions in month t, and t indicate annual trend. The harmonic components at 6- and 12-month frequencies are used to represent the seasonal components, and α represent the dependence between latent variables in successive months. From an inferential point of view our interest concerns whether the 95% credible interval for α contains 0, which equates to no evidence of latent serial correlation.

$$
\begin{aligned}
&N_t \sim \text{Poisson}(\mu_t) \\
&\log(\mu_t) = \beta_0 + \beta_1 \sin\left(\frac{2\pi t}{12}\right) + \beta_2 \cos\left(\frac{2\pi t}{12}\right) + \beta_3 \sin\left(\frac{2\pi t}{6}\right) + \beta_4 \cos\left(\frac{2\pi t}{6}\right) + \beta_5 t + e_t \\
&e_t \sim N(\mu_t, \sigma_\tau^2) \\
&\mu_t = \alpha + e_{t-1}
\end{aligned}
$$

The model detailed above treats the unobserved variables as a latent, temporally varying process (here autoregressive of order 1 so that the latent variable in the current month is allowed to depend via a Normal distribution on the equivalent latent variable in the previous month; in principle in its most general form the structure could be of order q where $q \geq 1$).

The model was fitted within a Bayesian framework as described in Congdon (2001) using Markov Chain Monte Carlo (MCMC) methods within the software package WinBugs in combination with the R library "R2WinBUGS" (Sturtz *et al.* 2005). A 'burn-in' of 20,000 iterations was used and a sample of 100,000 realisations from the posterior distribution for each parameter was produced. The output chain for each parameter was thinned to every 10th observation to reduce correlation between samples in the posterior distribution. Vague prior distributions were adopted for each of the β parameters (reflecting a lack of prior belief concerning parameter values), and the prior distribution for α was Uniform on [-1, 1] (although we believe *a priori* that any latent dependence in models for data of this kind is likely to be positive, bounding the parameter in this way allows us to examine the evidence in favour of serial dependence being present via a 95% credible interval for α which excludes 0). Markov chain convergence was assessed by comparing two chains from divergent starting values and comparing traces, and in addition examining the $\hat{R}$ statistic provided by WinBUGS which is the "potential scale reduction factor" and for a convergent chain approaches the value 1. Final inference was therefore based upon 16,000 draws (from the two chains judged to be in equilibrium) from the posterior distribution for each parameter. In the case where the 95% credible interval for the sine component at a given frequency excluded 0 but the cosine component did not, or vice versa, both terms were retained due to the fact that the sine and cosine terms together uniquely determine the location and scale of the cycle. Analogous models were compared using the Deviance Information Criterion (DIC) (Spiegelhalter *et al.*

2002) which we present in Tables 3 and 4. The DIC penalises models which are over-complex so that a "good" model represents a balance between plausible explanation of the data and model parsimony; in broad terms, the smaller the DIC, the better the model. In each case, we select as optimal the model which both carries the smallest DIC value and is the simplest.

Within each selected "best" model for each colic, the posterior mean, posterior standard deviation and 95% credible interval for each parameter are given in Table 2. We only report in full parameter estimates for the model with serial dependence and without trend; as we have discussed the estimates of seasonal components in the models with trend but no serial dependence are identical save for sampling variation induced by the MCMC algorithm. Within a Bayesian framework we cannot make statements about the "statistical significance" of parameter estimates as the common concept of a p-value and associated concepts of statistical significance are founded upon frequentist, rather than Bayesian, arguments. Instead, as an initial screen, we judged those parameters for which the standard deviation was smaller than half of the mean to have a marked effect on the outcome of interest (mean number of colic cases observed). We also reported the posterior 95% credible interval: an equivalent approach in this case involves identifying parameters for which this interval does not contain the value 0.

For each colic type, an estimate of the model's seasonal component was calculated by exponentiating from the chosen "best" model the sum of the posterior means of the seasonal components on the log scale, thus representing a multiplicative term in a model for the original observations. This enabled us to produce a graphical representation of the cyclical patterns in each group in relation to months of the year (Figure 2).

Results

Exploratory data analysis

The total numbers of colic cases for each diagnostic category are shown in Table 1 and boxplots of detrended colic admissions by month for each colic group are presented in Figure 1. Total admissions of all colic cases to the hospital appeared to peak in the months of April / May and again in October / November / December. A similar pattern was also evident in the medically and surgically treated colic groups. There was a clear seasonal effect for EGS, with a pronounced peak in May and a suggestion of a secondary peak in October. Cases of EFE appeared to peak in the months of December/January. There did appear to be a possible seasonal component to cases of large colon displacements and torsions, with peaks in the spring and autumn months, whereas primary large colon impaction colics appeared to peak over the autumn and winter months. There was no graphical evidence of a seasonal effect in cases of pedunculated lipoma.

Table 1: Colic categories, case definitions and number of cases in each category admitted to the PLEH between January 1st 1995 and 31st December 2004.

Colic category	Case definition	Total number
All Colics	All confirmed cases of colic admitted to the hospital	2580
All Surgical Colics	Colic cases with surgical lesions confirmed at exploratory laparotomy or post-mortem examination	1612
All Medical Colics	All colic cases that resolved with medical treatment only	968
Pedunculated Lipoma	Obstruction of small intestine by a pedunculated lipoma diagnosed at exploratory laparotomy or post-mortem examination	231
Epiploic Foramen Entrapment	Entrapment of the small intestine in the epiploic foramen diagnosed at exploratory laparotomy or post-mortem examination	92
Equine Grass Sickness	Equine grass sickeness cases confirmed by histological examination of the ileum	109
Large colon displacements or torsions	Displacement or torsion of the large colon diagnosed by rectal examination, clinical signs and response to treatment; treated either surgically or medically or diagnosed at post-mortem examination	435
Large colon impactions	Primary large colon impactions confirmed by rectal examination and response to treatment (medically treated group) or at exploratory laparotomy	214

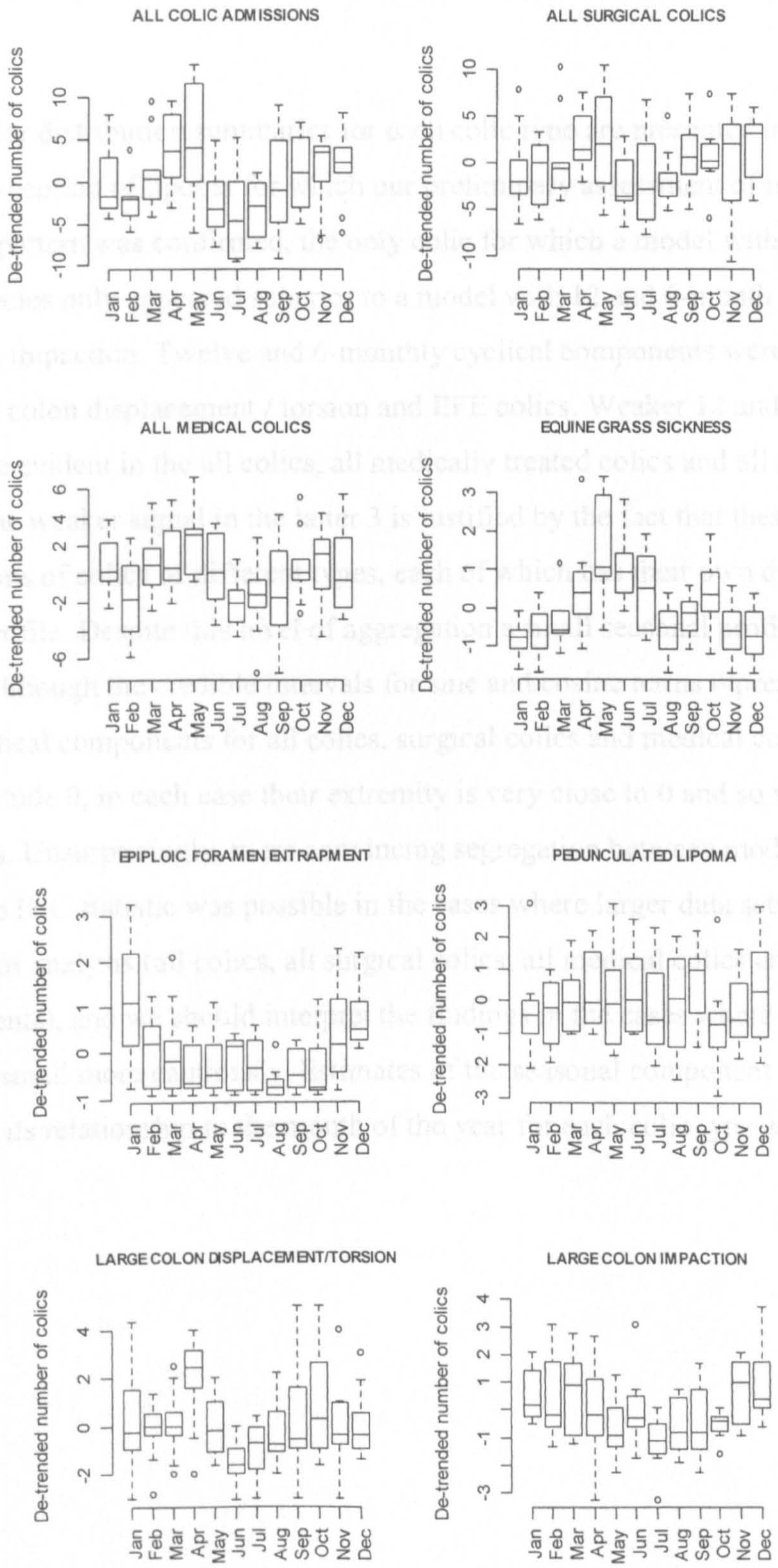


Figure 1. Boxplots of de-trended (annual average subtracted) colic admissions by month for each colic admitted to a UK referral hospital between January 1995 – December 2004.

Regression model with seasonal components, trend and an autocorrelated latent variable

The posterior distribution summaries for each colic type are presented in Table 2. With the exception of lipoma for which our preliminary assessment of no evidence of a seasonal pattern was confirmed, the only colic for which a model with twelve-monthly cycles only appeared superior to a model with 12 and 6-month cycles was large colon impaction. Twelve and 6-monthly cyclical components were identified for EGS, large colon displacement / torsion and EFE colics. Weaker 12 and 6-monthly cycles were evident in the all colics, all medically treated colics and all surgical colics groups. The weaker signal in the latter 3 is justified by the fact that these represent combinations of colics of different types, each of which has their own distinct seasonal profile. Despite this level of aggregation a small seasonal profile emerges. Note that although the credible intervals for sine and cosine terms representing12-month cyclical components for all colics, surgical colics and medical colics do not strictly exclude 0, in each case their extremity is very close to 0 and so we retained these terms. Unsurprisingly, more convincing segregation between models upon the basis of the DIC statistic was possible in the cases where larger data sets were available for analysis (all colics, all surgical colics, all medical colics and large colon displacements), and we should interpret the findings in the cases where counts per month are small more cautiously. Estimates of the seasonal component for the "best" model and its relationship to the month of the year for each colic type are shown in Figure 2.

Table 2: Parameter estimates from the regression models for each colic type

For compactness, $S_{12} = \sin\left(\frac{2\pi t}{12}\right)$, $C_{12} = \cos\left(\frac{2\pi t}{12}\right)$, $S_6 = \sin\left(\frac{2\pi t}{6}\right)$ and $C_6 = \cos\left(\frac{2\pi t}{6}\right)$.

Colic type	*Parameter*	*Posterior Mean*	*Posterior Standard Deviation*	*95% Credible Interval*
All Colics	Intercept	2.849	0.966	1.059, 4.737
	S_{12}	0.082	0.043	-0.002, 0.167
	C_{12}	0.029	0.043	-0.055, 0.113
	S_6	-0.132	0.033	-0.196, -0.067
	C_6	-0.007	0.033	-0.071, 0.058
	α	0.005	0.012	-0.018, 0.029
All Surgical	Intercept	2.159	1.089	-0.017, 4.156
	S_{12}	0.065	0.054	-0.042, 0.173
	C_{12}	0.034	0.055	-0.073, 0.142
	S_6	-0.114	0.042	-0.196, -0.032
	C_6	-0.037	0.041	-0.119, 0.044
	α	0.007	0.015	-0.024, 0.037
All Medical	Intercept	2.218	1.035	0.271, 4.225
	S_{12}	0.117	0.061	-0.001, 0.237
	C_{12}	0.021	0.059	-0.095, 0.136
	S_6	-0.167	0.051	-0.267, -0.067
	C_6	0.044	0.049	-0.054, 0.140
	α	0.004	0.014	-0.023, 0.031
Equine Grass Sickness	Intercept	-1.430	1.278	-3.750, 1.244
	S_{12}	-0.275	0.190	-0.655, 0.093
	C_{12}	-1.060	0.206	-1.481, -0.673
	S_6	-0.638	0.172	-0.980, -0.306
	C_6	0.041	0.163	-0.277, 0.357
	α	0.006	0.024	-0.042, 0.054
Epiploic Foramen Entrapment	Intercept	-0.698	1.029	-2.710, 1.456

	S_{12}	0.396	0.199	0.013, 0.794
	C_{12}	0.590	0.168	0.271, 0.929
	S_6	0.028	0.167	-0.302, 0.356
	C_6	0.404	0.169	0.077, 0.736
	α	0.002	0.020	-0.038, 0.041
Pedunculated Lipoma	Intercept	-0.253	1.123	-2.489, 1.872
	α	0.010	0.019	-0.028, 0.049
Large Colon Impaction	Intercept	0.057	0.957	-1.643, 1.999
	S_{12}	0.265	0.118	0.033, 0.497
	C_{12}	0.389	0.118	0.162, 0.622
	α	0.005	0.021	-0.038, 0.046
Large Colon Displacement / Torsion	Intercept	-0.275	1.112	-2.388, 2.065
	S_{12}	0.116	0.101	-0.084, 0.315
	C_{12}	0.166	0.110	-0.049, 0.383
	S_6	-0.234	0.090	-0.410, -0.058
	C_6	-0.256	0.090	-0.433, -0.080
	α	0.005	0.022	-0.039, 0.049

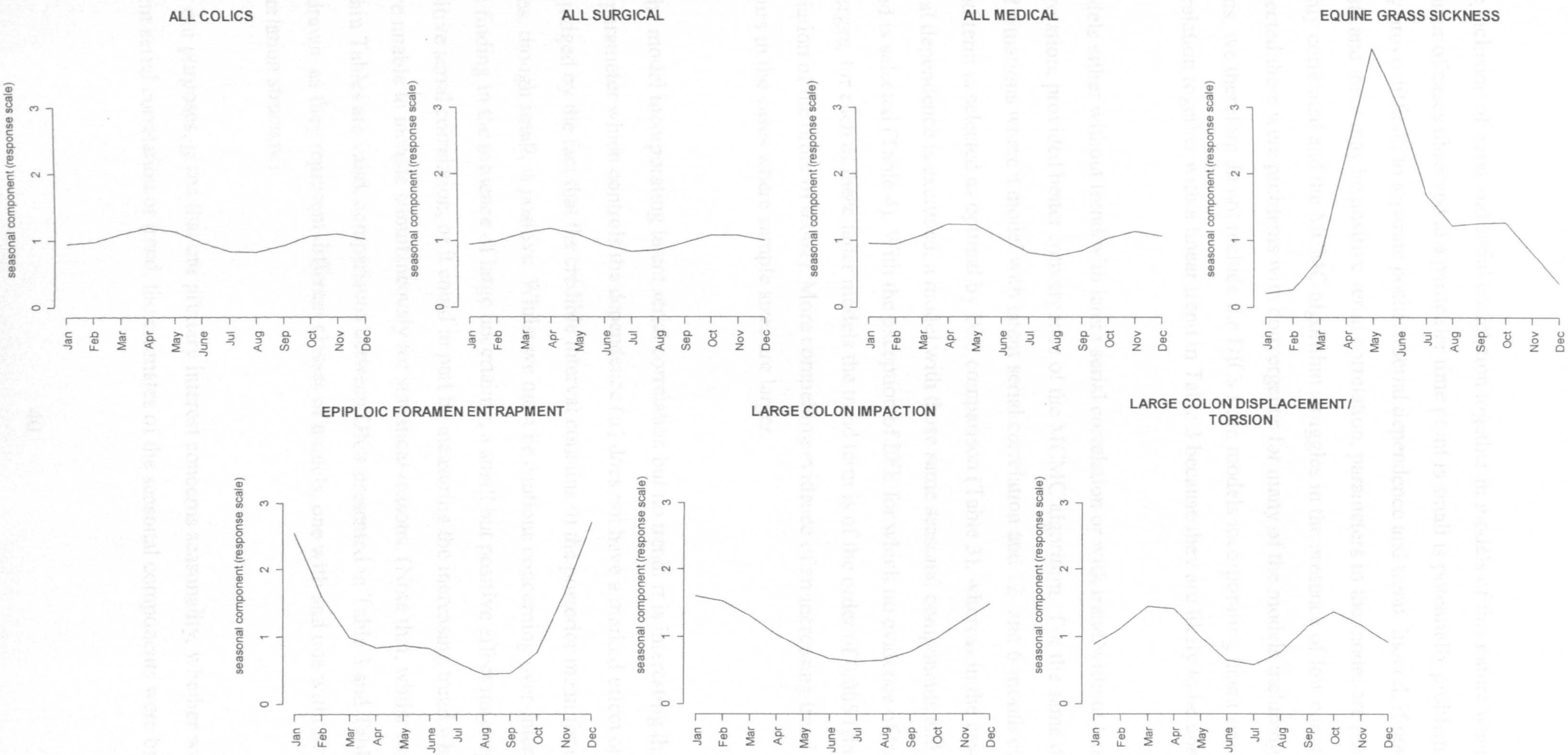


Figure 2. Estimate of model's seasonal component for each colic type. For each colic type an estimate of the model's seasonal component was extracted using the posterior mean of the parameter associated with each of the sine and cosine terms based on the frequencies detected for each group in Table 2. With the exception of the large colon impaction group (12 month cycles only) all models incorporated 12- and 6-monthly cycles.

The inclusion of trend and serial correlation together in models of this nature where the number of cases observed at a particular time point is small is potentially problematic, as it may prove difficult to separate positive serial dependence and trend. Indeed, if positive trend exists and there may be positive serial correlation, parameters in the model are potentially highly correlated and the MCMC algorithm struggles in the presence of low counts. As expected there were problems with convergence for many of the models including both terms; we therefore do not include the DICs from models incorporating latent serial correlation together with a linear trend in Table 3 because they are likely to be unreliable.

Models either without trend/with latent serial correlation or with trend/without latent serial correlation, provided better convergence of the MCMC algorithm. For the same data set we find situations where a model with latent serial correlation and 12- and 6-month cycles but no trend term is selected as optimal by DIC comparison (Table 3), whereas in the case where serial dependence is excluded, a model with those same seasonal components and a positive trend is selected (Table 4). With the exception of EFE for which no evidence of trend emerges, for each of these latter models the trend term is of the order of 0.005 (standard deviation of the order of 0.002). More compelling evidence of an increasing trend over time occurs in the cases where sample sizes are larger.

In the model incorporating latent serial correlation but no trend, it is interesting that although the parameter which controls the dependence (α) does not have a marked effect on the model (as judged by the fact that the credible interval contains 0) the posterior mean for α in all cases, though small, is positive. Whilst we must be cautious concerning over-interpretation of this finding in the presence of large uncertainty, a small but positive effect may represent positive serial correlation, or it could in part be measuring the increasing trend which we were unable to include simultaneously for statistical reasons. (Note that, whilst comparisons within Tables are valid, comparisons between DICs presented in Table 3 and Table 4 cannot be drawn, as they represent different classes of models, one with and one without a latent correlation structure).

For our purposes, given that our primary interest concerns seasonality, whether we included latent serial correlation or trend, the estimates of the seasonal components were broadly similar across models and this renders our findings regarding seasonality robust in the presence of these largely statistical effects.

Table 3: Deviance information criteria (DICs) for models with a latent autocorrelation structure. A lower DIC statistic can be considered to represent a better model.

Model	Total	Total surgical	Total medical	EFE	Grass sickness	Large colon impaction	Large colon displacement	Lipoma
No seasonality, no trend	756.83	718.59	607.42	282.14	339.02	414.80	483.27	**419.58**
12-month seasonality, no trend	754.20	720.39	604.86	261.33	280.39	**391.20**	481.77	421.54
12- and 6-month seasonality, no trend	**732.29**	**708.46**	**592.65**	**258.93**	**267.09**	394.47	**459.30**	425.44

Table 4: Deviance information criteria (DICs) for models without a latent autocorrelation structure but with trend (Poisson GLMs). A lower DIC statistic can be considered to represent a better model.

Model	Total	Total surgical	Total medical	EFE	Grass sickness	Large colon impaction	Large colon displacement	Lipoma
No seasonality, no trend	796.18	728.37	645.77	280.79	329.39	429.29	513.58	422.95
12-month seasonality, no trend	793.62	729.59	645.22	258.15	289.65	411.25	513.64	425.78
12- and 6-month seasonality, no trend	773.29	721.87	633.73	**255.35**	277.67	414.21	500.42	429.93
No seasonality, trend	740.80	704.58	613.87	282.11	324.70	422.58	480.01	**413.20**
12-month seasonality, trend	735.36	704.83	611.45	259.15	284.20	**403.98**	478.60	415.88
12- and 6-month seasonality, trend	**717.63**	**698.06**	**601.9**	256.60	**272.58**	407.02	**466.76**	419.74

Discussion

The aim of the present study was to investigate the seasonality of different types of colic presented at a UK equine referral hospital. Cohen (2003) stated the need for new statistical or epidemiological models that could address deficiencies in our knowledge regarding equine colic. This model provides a useful means of investigating temporal patterns in equine colic, and to our knowledge, this is the first report that uses time-series methods of analysis to explore seasonal patterns in equine colic.

Two studies in the UK have described an apparent peak in cases of colic of any cause in spring and autumn months (Proudman 1992; Hillyer *et al.* 2001). In the present study, similar patterns were evident in the all colic and all medically or surgically treated colic groups with small peaks evident around the months of March / April and October / November. Hillyer *et al.* (2001) suggested that the seasonal pattern of colic in the racehorse population under investigation in their study may have been associated with stage of training or level of activity. Increased risk of colic has been identified following change in diet and stabling in the preceding 2 weeks (Cohen *et al.* 1995; Cohen *et al.* 1999) and following decreased exposure to pasture (Hudson *et al.* 2001). Therefore, these patterns of colic may not be surprising given that, at these times of the year in the UK, changes in management practices such as turnout, stabling and exercise are more likely to occur.

This modelling approach confirmed our hypothesis that EGS would exhibit seasonality, as demonstrated by other workers using different approaches. Although EGS may occur at any time of the year, the peak incidence of this condition in the UK is reported in the months of spring and summer, and the month of May in particular (Doxey *et al.* 1991; Wood *et al.* 1998). In the present study, EGS exhibited significant 12- and 6- month cyclical components, cases peaking in the month of May with a secondary less pronounced peak in the month of October. Risk factors for EGS that have been identified in epidemiological studies previously include increased risk associated with change of field in the previous 2 weeks (Wood *et al.* 1998), non-feeding of hay or haylage and change of feed type or quantity 14 days prior to disease (McCarthy *et al.* 2004b). The seasonal pattern of EGS identified in the present study coincides with months of the year that may be associated with change in grazing practices and feed types in the UK.

Use of this model also confirmed our hypothesis that EFE would exhibit seasonality. Using data arising over a 10 year period at the same hospital (1991-2001), multivariable modelling confirmed that EFE was consistently more prevalent in the months of December, January and February (Archer *et al.* 2004b). There was a suggestion of a seasonal pattern of distribution for each year studied but, using traditional methods of analysis, we were unable to confirm this statistically. The results from the present study revealed 6- and 12- month cyclical components to cases of EFE presented at this hospital; the main peak occurred in the months of November, December and January with a secondary, less pronounced peak in the months of April, May and June. In Germany, Scheideman (1989) reported that although EFE cases were seen throughout the year, a marked increase in cases was evident during the period between December and April. The seasonality of EFE may reflect changes in stabling, turnout, exercise and feeding practices common to these times of the year; these are currently under investigation in a prospective study.

The large colon impaction colic group exhibited 12 month cyclicity, with an increasing number of cases identified in the autumn and winter months (peak December / January) decreasing over the spring months with the lowest incidence over the months of July and August. A slightly different cyclical pattern was identified in the large colon displacement / torsion colic group with peak incidence in the months of Spring and Autumn, similar to that seen in the all colic and all medically or surgically treated colic groups. Hillyer *et al.* (2002) identified a number of factors associated with increased risk of simple colonic obstruction and distension colic (defined as primary large colon impactions and simple large colon displacements). These included an increasing number of hours spent in a stable, recent change in a regular exercise programme and stabling for 24 hours per day. These factors may explain the reduced incidence of colic of either type evident in the months of June, July and August when horses, in general, are less likely to be stabled for prolonged periods in the UK. Many factors have been associated with large colon impactions including acute decrease in exercise or cessation of daily turnout (Dabareiner and White 1995) and feeding of coarse roughage (White 1997). These factors may, in part, account for the increased incidence of this colic type coinciding with months of the year when cold, wet weather is more likely to occur in the UK. Under these conditions horses are more likely to be housed and to be given more supplementary roughage (i.e. hay / haylage in addition to grass). Large colon torsion has been associated with mares in the periparturient period (White 1997) which might explain the increased prevalence of this colic type between the months of January and May; however brood mares comprise a relatively small component of this hospital's caseload.

Obstruction of intestine by pedunculated lipomas in theory should be a random event, and this model confirmed our *a priori* hypothesis that no seasonal component to this condition would be identified.

We have alluded to the difficulties in detecting serial dependence in the presence of trend when samples are small. With larger samples it might be possible to separate more conclusively trend and latent serial dependence and further research using larger samples sizes is warranted.

Considering first the possible interpretation of latent serial correlation in the context of colic, we take EGS as an example. The role of *Clostridium botulinum* in EGS has received renewed interest (McCarthy *et al.* 2004a). Taking the assumption that *C. botulinum* does play a role in the aetiology of this specific cause of colic as a working hypothesis, it would seem plausible that the levels of the pathogen in the environment will be temporally structured so that they are similar in proximate months and less similar in months which are far apart, irrespective of the seasonal effect. Using space-time K-function analysis, French *et al.* (2005) demonstrated strong evidence of space-time clustering of this disease, particularly within the first 10km and 20 days of a case, which would support the latter idea. Similarly, feed types and amounts, periods of stabling and turnout are more likely to be similar in proximate months.

Considering now the interpretation of a positive linear trend which was evident in all models excepting that for EFE not including latent correlation, knowledge of continued improvements in the medical and surgical management of colic and resultant increased success rates following treatment (Moore 2005) may have positively influenced referring vets and owners making them more willing to undertake referral. This trend may also reflect increased levels of insurance in the hospital referral population, making surgical correction or intensive medical treatment an option when previously it may not have been affordable. In the case of colic due to intestinal obstruction by a peduncluated lipoma, which most frequently occurs in older ponies and horses (Blickslager *et al.* 1992; Edwards and Proudman 1994; Freeman and Schaeffer 2001), a combination of affordability and knowledge that surgical success rates following treatment of this condition are comparable to, or in some cases better than, other surgical lesions in younger horses (Proudman *et al.* 2002a) may account for this annual trend. Alternatively, there may simply be a greater number of older ponies or horses in the general equine population (Mellor *et al.* 1999). It was also interesting to note that an annual trend was not evident in cases of EFE admitted to the hospital. This finding may be due to insufficient power to detect a marked effect based on the relatively small numbers of EFE in this series.

Weather-related factors have not been shown to be statistically significant in relation to colic using traditional methods of analysis, despite many anecdotal reports to the contrary (Proudman 1992; Cohen 1997; McCarthy *et al.* 2001; Gonclaves *et al.* 2002). It is important to consider that climatic conditions may be confounded by other factors. For example, extreme weather conditions may result in altered management practices such as reduced level of horse activity (White 1998). Nevertheless, identification of any weather-related patterns associated with colic may assist identification of causal factors. Time-series analysis provides a more elegant and valid means of studying seasonal patterns to colic and may also provide a more appropriate means of investigating associations between weather patterns and disease (Ward 2002).

A number of approaches may be used to investigate temporal patterns in data and, when choosing the most suitable method, it is important to recognise that different types of dependence which are context-specific may occur. First, the number of events in month t might explicitly depend upon the number of events in month t-1 e.g. if one is considering the evolution of an infectious disease which propagates by direct contact between infected individuals. This type of dependence is described as "observation driven" (Cox 1981; Zeger and Qaqish 1988). Secondly, the counts in month t and month t-1 might be independent, conditional upon some latent process which is temporally structured and contains serial correlation. For example, the number of individuals suffering from hypothermia might be influenced by climatic conditions, which themselves vary with time, and are likely to be autocorrelated i.e. the weather in month t is likely to be in some way similar to the weather in month t-1. Here, dependence (and subsequent models) is described as "parameter driven" (Cox 1981; Zeger 1988). The two dependence assumptions are qualitatively different and require different modelling approaches. There is little reason to suppose that the number of colic cases admitted to a hospital facility in month t is directly influenced by the number in the previous month (t-1). Instead, it seems more plausible that there may be some underlying, unmeasured (or indeed immeasurable) process which has a direct influence on the monthly counts. It is our belief that the parameter driven approach is likely to be most relevant to data pertaining to colic in the horse and is the basis upon which the model was chosen.

An important issue in Markov Chain Monte Carlo (MCMC) based analysis is that of convergence of the Markov Chains and whether the samples being generated are from the true posterior distribution under the model framework. In order to test this, we ran two chains simultaneously using differing starting values, and found that in each case the posterior summaries obtained were analogous. In addition, we examined the $\hat{R}$ statistic (the "potential scale reduction factor") provided by WinBUGS and found that in all cases barring the models which attempted to incorporate both trend and latent correlation this was very close to 1.

A further issue in Bayesian analysis concerns the sensitivity of the resultant posterior distribution to the choice of prior distribution. Given that, for all parameters, we have selected vague priors we do not believe this to be an issue here; in addition, although the counts at each time point were relatively small, the length of each series was large ($n = 120$ in all but one case where $n = 119$) so we would expect the data to dominate.

The issue of determining a suitable autocorrelation structure for the error term in these models is also important. There exists only a single series of data, in contrast with a longitudinal data set for which we can gain knowledge about the autocorrelation structure by exploiting the replication in the data (Diggle *et al.* 2002). Our selection of a latent variable including only first-order correlation (correlation with the previous time point) is rather arbitrary, but seems reasonable on scientific grounds in that there may be environmental factors which are very similar in proximate months. It would be possible within this modelling framework to incorporate more complex error structures, for example, allowing dependence on even earlier time points. It is likely, however, that with the small counts available longer-term effects of this nature could not be detected.

The exact gastrointestinal dysfunction or lesion is unknown in many cases of colic that occur within the general equine population (Proudman 1992; Hudson *et al.* 2001; Mair 2004). It is important to recognise that data based on colic cases presented to a referral hospital represent only a small proportion of all colic cases occurring within a geographical location: such a population is biased towards horses with lesions requiring surgical correction or more intensive medical treatment, and whose owners are willing to undertake referral. In addition, studies investigating specifically diagnosed cases of colic would include only a minority of cases seen in the general population (Tinker *et al.*1997b). However such studies are necessary due to the fact that risk factors and patterns of disease may be different for various types of colic, and investigation of colic of any cause may miss some of these (Reeves *et al.* 1996). The colic types investigated in the present study also represent the more severe forms of the disease i.e. those which do not resolve spontaneously or following simple medical treatment, making the investigation of causality and potential prevention of relatively greater importance. It is unlikely that there would be any effect of season on the referral of colic cases to the clinic.

The models produced in this paper are biologically plausible and provide useful information on the temporal patterns of different colic types. This work demonstrates in principle how standard and non-standard Poisson regression-based approaches can be used in other veterinary applications where disease incidence is relatively rare. These results also provide an insight into the aetiology of different colic types admitted to a UK referral hospital. There is a suggestion of increased admissions of certain colic types at times of managemental change (surgically and / or medically treated colics, large colon displacements / torsions and EGS) and during periods of intensive management (months of the year when horses are more likely to be stabled or stabled for longer periods of time) e.g. EFE and large colon impaction. These results are based on the findings from a single UK referral equine hospital; further studies are required to determine the relationship between season and colic incidence in other geographical locations using hospital and non-hospital based populations.

We have used a regression model which has the flexibility to incorporate latent serial correlation to explore the seasonal prevalence of different colic types presented at a UK equine referral hospital. This is a novel statistical approach in the field of equine colic research and it has enabled us to confirm a seasonal pattern for equine grass sickness, as demonstrated by other workers using different methods of analysis, and to formally establish the existence of a marked seasonal effect in cases of epiploic foramen entrapment. In addition, a seasonal pattern was evident to admissions of all colic types, all surgical and medical colics and in cases of large colon impaction and large colon displacement / volvulus. Use of this model confirmed that intestinal obstruction by pedunculated lipomas showed no seasonal effect. Knowledge of the seasonal associations with certain types of colic is consistent with an aetiological role for managemental change and periods of intense management such as prolonged stabling. Further studies are required to identify the determinants of the observed seasonality. This type of regression model has applications beyond the study of equine colic and it may be useful in the investigation of seasonal patterns in other, relatively rare, conditions in all species.

CHAPTER 3

A matched case-control study to investigate risk factors for epiploic foramen entrapment

Abstract

Epiploic foramen entrapment (EFE) is one of the most common causes of small intestinal strangulation in the horse. Crib-biting / windsucking behaviour, breed and season have been identified as risk factors for EFE using other horses with colic as a comparison but other horse- and management-level risk factors have not been investigated. The aim of this study was to investigate the epidemiology of EFE using a population of healthy horses as controls.

A case-control study was conducted between January 2004 – February 2006 in the UK, Ireland and USA. Controls were matched to cases on clinic and time to control for differences between geographic regions. Data on 109 cases and 310 control horses were obtained and conditional logistic regression was used to identify associations between a number of horse- and management-level variables and the risk of EFE.

In the final, multivariable model crib-biting / windsucking behaviour was associated with the largest increase in risk of EFE (OR 67.3, 95%CI 15.3 – 296.4). A history of colic in the previous 12 months and horses of greater height were also associated with increased risk of EFE. In addition the person(s) responsible for horses' daily care and a number of behavioural features relating to individual horses' responses to a stimulus causing fright or excitement, reaction to their surroundings and their feeding behaviour when stressed were associated with altered risk of EFE.

Introduction

The epiploic foramen (foramen of Winslow / foramen epiploicum) is a 4cm-wide slit-like opening from the peritoneal cavity into the omental bursa. It is located in the right dorsal abdomen of the horse and is bordered by the caudate process of the liver, the portal vein and gastropancreatic fold (Schmid 1998). Entrapment of intestine in the epiploic foramen (EFE) most frequently involves the small intestine, resulting in strangulating obstruction of a variable length of intestine. EFE is one of the most common causes of small intestinal strangulation in the horse, accounting for 5-23% of all strangulating lesions of the small intestine and representing 2–8% of horses with colic that undergo surgery (Freeman 2005).

To date, few studies have investigated the epidemiology of EFE. Previous suggestions that increasing age was a risk factor for EFE have recently been refuted (Freeman and Schaeffer 2001). Crib-biting or windsucking behaviour was identified as a risk factor for EFE in two hospital populations (Archer *et al.* 2004a). In one of these populations, breed and season were also found to be significantly associated with increased risk of EFE (Archer *et al.* 2004b). However, the latter studies used other horses with colic as controls and this may introduce bias i.e. these horses may have been exposed to risk factors that predispose to other forms of colic. To date, no studies have investigated risk factors for EFE using a population of healthy horses as controls. In addition, no studies have investigated other horse- or management-level risk factors for EFE.

In a case-control study, individuals with a particular condition or disease (cases) are selected for comparison with individuals in whom the condition or disease is absent (controls). Case-control studies enable comparison of existing or past exposures considered to be relevant to the disease being studied and are especially useful for the study of rare diseases within the general population (Schlesselman 1982). Matching refers to the pairing of one of more controls to each case on the basis of their similarity with respect to selected variables and is used to prevent confounding and, to a lesser extent, to increase the efficiency (or power) of the study (Dohoo *et al.* 2003).

The aim of this study was to identify horse- and management-level risk factors for EFE. Knowledge of risk factors for this condition could aid our understanding of disease causality, enable identification of high-risk horses and potentially this information could be used to devise disease prevention strategies. The *a priori* hypotheses were that individuals exhibiting certain behavioural patterns and those exposed to particular management practices such as long periods of stabling and those receiving certain feed types e.g. large amounts of concentrate feed would be at increased risk of EFE. A matched case-control study design was used to control for differences in horse- and management-level factors between different geographical regions.

Materials and methods

Study Design

An international, multi-centre, matched, case-control study was conducted between 2004 – 2006 to identify associations between various horse- and management-level risk variables and EFE (outcome variable).

Sample size estimation was performed using Win Episcope 2.0 (www.clive.ed.ac.uk/winepiscope). For crib-biting / windsucking as the exposure of interest (OR for association with EFE = 8, Archer *et al.* 2004b) a study with 62 cases and 3 controls per case, assuming 2% exposure in controls (e.g. crib-biting / windsucking behaviour), has greater than 90% power to detect odds ratios of 8 or higher with 95% confidence. If an exposure of interest has 10% exposure in controls, a study with 61 cases and 3 controls per case would have 80% power to detect odds ratios of 3.0 or greater with 95% confidence. This study was matched on clinic to control for differences between individual clinic populations e.g. breeds and management practices common to certain geographical locations. A ratio of 3:1 controls: cases was used.

Recruitment of collaborating clinics

All university and private clinics based in the UK, USA and Ireland that performed colic surgery on a regular basis and where surgeons were experienced in the diagnosis and treatment of surgical colic (Diplomates of the American College of Veterinary Surgeons / European College of Veterinary Surgeons / Royal College of Veterinary Surgeons or those with equivalent surgical experience) were identified. Twenty-three clinics were selected based on geographical location (in order to ensure all geographical regions were incorporated where possible) and likely willingness to participate in the study.

A contact person was identified in each clinic; this was an equine surgeon who had a known interest in colic surgery or research. These surgeons were contacted individually by the principal investigator either by telephone, email or were approached in person during attendance at surgical conferences. A brief description of the study was given to each of these surgeons and, if they confirmed that they might be willing to collaborate in the study, further information about the study was then provided. In some instances, the initial contact person suggested the name of a colleague who should be approached about the study and this was duly performed.

In two of the clinics based in the USA, research project applications had to be completed by the principal investigator and approved by the relevant research ethics committees before they could confirm their collaboration.

Twenty-one clinics in total participated in the study; they were located in the UK (n=10), Ireland (n=2) and USA (n=9). One clinic in the USA did not wish to participate in the study due to concerns that owners of case and control horses might be unhappy if they were contacted about a research project. One clinic in the UK initially agreed to help and were able to recruit cases but they were unwilling to provide lists of potential control owners. This clinic was therefore dropped from the study.

All the collaborating clinics in the UK were visited by the principal investigator in order to confirm the samples and data that were required, and to distribute the study kits. This information was given to the collaborating clinics in Ireland and the USA by email and telephone contact and the study kits were sent by post. A project website was developed that contained all this information together with study forms in a PDF format that could be downloaded from this site and printed by the clinics. Study kits were given to each of the collaborating clinics (these were suitably sized, labelled and sealed plastic containers) and these contained:

- a booklet detailing the study aims, case definition (including photographs), samples required and procedure for notifying the principal investigator about a case
- study leaflets to be given to the owner / carers of case horses

- posters to be put up in the scrub areas / operating theatres
- notification forms
- submission forms
- sample pots and blood tubes
- pre-paid envelopes
- relevant stickers and packaging material

On request, consent forms were designed and sent to one clinic for the owner / carer of case horses to complete to confirm their willingness to participate in the study.

The key contact person who would be responsible for notification of cases and who could be contacted by the principal investigator to collect further details was confirmed, together with the most convenient means of contact for them (e.g. e mail, telephone or fax). In order to collect study controls, one person in each clinic (surgeon, technician, nurse or office staff) was nominated to this task. This person was contacted directly by the principal investigator as necessary to obtain lists of clients (names, addresses and contact telephone numbers) that had been seen at the clinic in the previous calendar year using random number and date selections. Inducement in the form of chocolates / biscuits were sent with study paperwork in order to assist compliance with the study; if this was unsuccessful and these lists could not be obtained within a defined period of time, data were obtained by the principal investigator visiting the clinic. This was only necessary in order to obtain client contact details in one clinic.

Case definition and recruitment

Cases of EFE diagnosed at laparotomy or post-mortem examination at any of the collaborating clinics during the 25 months under investigation were recruited onto the study. By recruiting clinicians experienced in the diagnosis and treatment of surgical colic, we attempted to ensure that potential case misclassification would be avoided. Regular contact was maintained with these clinics to ensure that as few cases as possible were missed.

The owner or carer of each case horse was informed about the study by the collaborating clinic and were asked if they would be willing to participate. Client information leaflets were also requested to be given to these owners or carers by the clinics at this time. Once owner /

carer consent had been obtained, telephone (or in some cases e mail) contact was made by the principal investigator with the client to confirm their willingness to participate in the study and to arrange a convenient time to conduct the questionnaire (as soon as possible after surgery, depending on individual clinic requests and client wishes). If this person did not know the day-to-day care of the case horse, they were asked if the relevant person might be willing to complete the questionnaire and if so, they were duly contacted.

After initial contact with the owner / carer of case horses, a letter was sent confirming the date and time that the questionnaire had been scheduled for together with a leaflet describing the study aims (if they had not already been given this by the collaborating clinic). In some instances, if requested by the owner / carer, the questionnaire was administered at the time of initial contact. Owners / carers were also asked to provide accurate weights of the feed that the horse was receiving in the days prior to surgery, details of the last and penultimate anthelmintic administered (date and product used) and the last vaccination administered (date and product) prior to surgery. They were asked to have this information ready at the time of questionnaire administration or to send this information on the answer sheet provided after the questionnaire had been completed.

Control definition and recruitment

Three potential owners / carers of control horses were selected at random from the list of clients that had been seen at the same collaborating clinic in the previous calendar year for each case of EFE. Control selection took place within 2 - 4 weeks of notification of a case. The majority of these clients were contacted initially by post followed by a telephone call to ask if they would be willing to participate in the study. Some clinics preferred to contact these clients directly to obtain consent prior to telephone contact by the principal investigator.

At initial contact, the selected client was asked how many 'horses' (defined as a horse or pony) that they owned / looked after and knew the day-to-day care of. Random numbers were used to select a horse or the horse whose name (or whose dam's name in the case of foals / yearlings) came first alphabetically was selected. The horse had to fulfil the following inclusion criteria: i) it must not have suffered from colic in the previous 4 weeks and ii) surgery for colic would be undertaken on this horse if deemed necessary. The latter criteria was taken to avoid selection bias i.e. the controls would potentially have been eligible to become cases. If the selected horse did not fulfil these criteria, another horse was selected using the same random selection procedure or, if none fulfilled the criteria, a new control client was selected and the process was repeated (Hillyer *et al.* 2002). The process of organising a convenient time to administer the questionnaire and the data that would be required was the same as detailed for the case horses.

Questionnaire design

The questionnaire was constructed using information from previous epidemiological studies investigating colic and other hypotheses considered to be biologically plausible as risk factors for EFE. These included information on breed, carer, anthelmintic administration, feed types and quantities, all of which have been shown to be risk factors for colic in general (Archer and Proudman 2006). More specifically, we wished to obtain information about feed types, stabling and turnout routines, changes in feeding and stabling, horses' behaviour in response to specific stimuli and whether stereotypic behaviour was exhibited in these horses as possible risk factors for EFE. Questions were grouped into the following categories: signalment and use, medical history, general premises details, stabling and turnout, nutrition, exercise and transport, behaviour and preventive healthcare (General Appendix: Study Questionnaire).

Questionnaire administration

The questionnaire was administered over the telephone by the principal investigator. To maximise client compliance, owners of case and control horses were informed that this study was investigating colic in the horse and that we wished to collect general information about horses and their daily care. Owners / carers were unaware of the hypotheses being tested and they were informed that there were no correct answers to the questions posed. Care was taken not to influence their answers in order to obtain the most unbiased and correct information possible.

Data collection

Data were entered onto a data-capture form based on the responses given to the principal investigator by the owner / carer of case and control horses over the telephone. An Access database was created using a data entry scanner (Fujitsu fi-4120C2) and software (TeleForm v9, Verity Inc.). Scanned data were verified using the software programme to identify values out-with pre-defined ranges and multiple instead of single data entries in tick boxes before committing the scanned data into the database. Five percent of the questionnaires were randomly selected for double checking of data entry and the error rate was 0.32%.

Sample collection and analysis

Faecal samples were collected from the cases during hospitalisation. The owners / carers of control horses were asked to collect a faecal sample from the selected control horses within 4 weeks following completion of the questionnaire and prior to the next administration of an anthelmintic. For logistical reasons, faecal samples were only collected from control horses in the UK and Ireland. To maximise compliance, owners were offered the results of the faecal worm egg count free of charge and were provided with sample pots and pre-paid envelopes for sample return. A faecal egg count test was performed using the McMaster method.

Statistical Analysis

Screening of all variables was performed using a univariable conditional logistic regression model, to account for matching of cases and controls, with EFE as the dependent variable. The statistical package Stata (Stata Corp. LP) was used for data analysis. Categorical variables with small numbers of observations in one or more categories, or where the reference category contained relatively few individuals, were re-coded to create fewer categories or to create a different reference category. Continuous variables were examined in their continuous state and were categorised into quintiles, quartiles or other biologically plausible categories. If the relationship between the continuous variables and outcome was considered to be significantly non-linear, other polynomial relationships were explored to see if they significantly improved the fit of the model. To reduce the effects of collinearity, continuous variables were centred by subtracting the mean of the variable from all recorded observations (Kleinbaum *et al.* 1988) prior to producing higher order terms.

Variables with a univariable P-value <0.2 were considered for subsequent inclusion in a multivariable model. Variables with >20% of missing values were excluded from the initial model-building procedure. To avoid problems associated with collinearity, where variables were considered to be measuring the same exposure or were shown to be highly correlated (Pearson correlation coefficient >0.9), the most statistically significant or biologically plausible variable was selected.

The model was built using a backwards stepwise approach where variables were retained in the model if their manual exclusion resulted in a likelihood ratio test statistic (LRTS) of $P<0.05$. A change in the coefficient of >25% was considered to be indicative of confounding. Four submodels were initially created: behaviour, signalment and medical history, nutrition and other management factors. The variables identified in each of these models were pooled and used to develop the final effects model (Reeves *et al.* 1996). All the remaining variables considered for inclusion were then forced back into the model to ensure that no significant or confounding variables had been excluded. Variables with >20% missing values were also re-tested in the model at this stage. The effect of biologically plausible interaction terms was tested in the model. Model stability was assessed by examination of the standardised delta-betas for all of the variables in the final model using the computer programme Egret (Cytel Software Corp.). The delta-beta statistic reflects the number of standard errors by which the regression coefficient for an exposure variable of interest changes when a specific observation is deleted (Dohoo *et al.* 2003). Thus, the delta-betas provide a means of determining the influence of each individual observation on the fit of the model (Hillyer *et al.* 2002). The model was considered to be stable if removal of individual cases or controls altered the odds ratio by <25% and did not affect the significance of individual variables in relation to the critical P-value of 0.05.

Results

Descriptive analysis

Notification of a total of 119 cases of EFE occurred between 26th January 2004 – 28th February 2006. Of these cases, 109 were recruited from 16 of the collaborating clinics onto the study (Figures 1 & 2). Reasons for not being recruited onto the study included: clinic requested that the client was not contacted (n=5), lists of clients to select as controls could not be obtained within the set time period (n=2), notification occurred too late for collected data to be considered valid (n=1), inability to contact the owner (n=1) and owner did not wish to participate in the study (n=1). Cases were identified all year round with the greatest number identified in the month of January (Figure 3). A total of 310 control owners were recruited onto the study. The questionnaires for cases and controls took a mean of 23 minutes to complete (range 12 - 67 minutes).

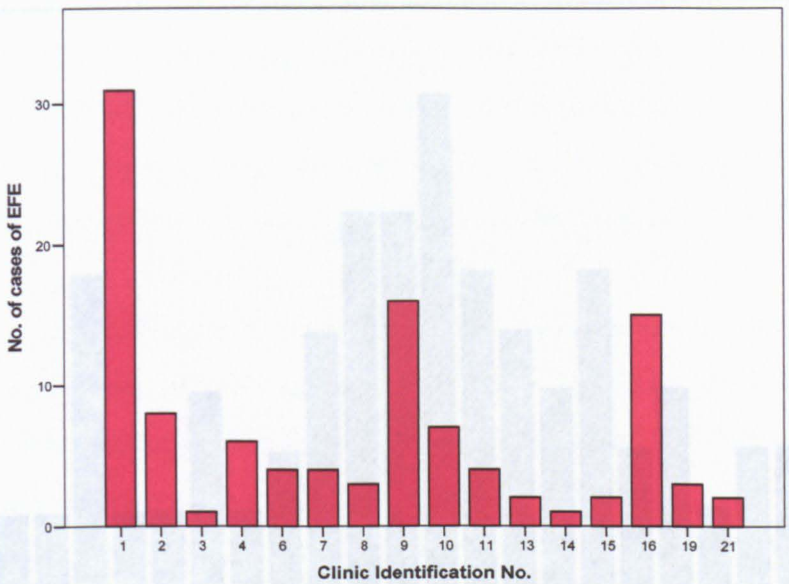


Figure 1. Distribution of 109 cases of epiploic foramen entrapment (EFE) recruited onto the study from 16 of the collaborating clinics.

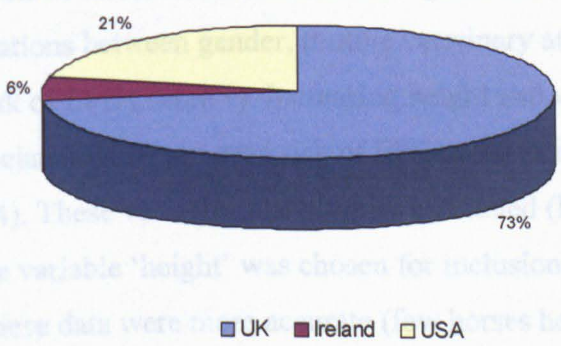


Figure 2. Pie chart detailing the distribution of 109 cases of epiploic foramen entrapment (EFE) recruited onto the study from the UK, Ireland and USA.

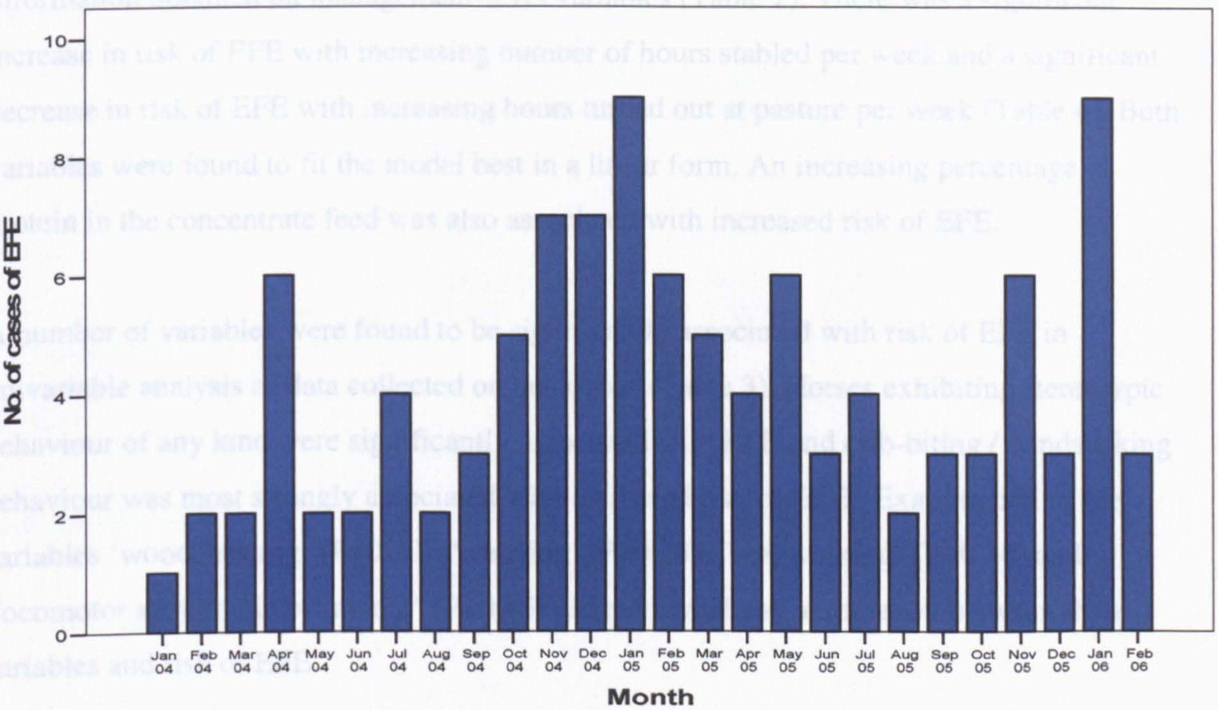


Figure 3. Seasonal distribution of 109 cases of epiploic foramen entrapment (EFE) occurring between 26th January 2004 – 28th February 2006.

Univariable analysis

Univariable analysis of information obtained on signalment and medical history revealed significant associations between gender, routine veterinary attention and colic in the previous 12 months and risk of EFE (Table 1). Increasing height and weight were shown to be significantly associated with increased risk of EFE in univariable analysis of continuous variables (Table 4). These variables were highly correlated (Pearson correlation coefficient > 0.9); therefore the variable 'height' was chosen for inclusion into the model as it was considered that these data were more accurate (few horses had been weighed nor had many owners used a specifically designed measuring tape to obtain an estimate of their horses weight). A squared term for height was found to fit the model best (Table 4). Increasing age was not significant in its linear form (P= 0.266) but a squared term for age was significantly associated with increased risk of EFE (Table 4).

The variables 'principal carer', 'current management', 'current stabling' and 'currently fed haylage' were significantly associated with risk of EFE in the univariable analysis of information obtained on management-level variables (Table 2). There was a significant increase in risk of EFE with increasing number of hours stabled per week and a significant decrease in risk of EFE with increasing hours turned out at pasture per week (Table 4). Both variables were found to fit the model best in a linear form. An increasing percentage of protein in the concentrate feed was also associated with increased risk of EFE.

A number of variables were found to be significantly associated with risk of EFE in univariable analysis of data collected on behaviour (Table 3). Horses exhibiting stereotypic behaviour of any kind were significantly associated with EFE and crib-biting / windsucking behaviour was most strongly associated with increased risk of EFE. Examination of the variables 'woodchewing' (P=0.70), 'weaving' (P=0.24), 'box-walking' (P=0.36) and 'locomotor stereotypic behaviour' (P=0.45) did not reveal any association between these variables and risk of EFE.

Table 1. Results of univariable conditional logistic regression analysis of categorical variables with a P-value <0.2 obtained from information on signalment and medical history.

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95%CI*	*P-value*
Breed						
	TB	33 (36)	24 (74)	Ref.		
	TBx	17 (19)	20 (63)	0.58	0.29 – 1.17	
	WB / WBx	16 (17)	9 (29)	1.39	0.65 – 2.98	
	Pony / miniature horse	10 (11)	16 (48)	0.46	0.21 – 1.04	0.086
	Cob / Cob x	3 (3)	6 (18)	0.33	0.09 – 1.23	
	Other horse	21 (23)	25 (76)	0.65	0.35 – 1.21	
Gender						
	Male	75 (82)	63 (194)	Ref.		
	Female	25 (27)	37 (116)	0.58	0.36 – 0.94	0.023
Veterinary attention in previous 12 months (non-routine)						
	No	53 (54)	41 (123)	Ref.		
	Yes	47 (48)	59 (175)	0.62	0.38 – 0.99	0.044
Orthopaedic problem						
	No	78 (79)	68 (203)	Ref.		
	Yes	22 (22)	32 (94)	0.61	0.36 – 1.05	0.070
Dental / Gastrointestinal						
	No	82 (83)	89 (263)	Ref.		
	Yes	18 (18)	11 (33)	1.66	0.88 – 3.17	0.122
Episode of colic in the previous 12 months						
	No	76 (75)	91 (273)	Ref.		
	Yes	24 (24)	9 (26)	2.90	1.59 – 5.31	<0.001
No. of colic episodes in previous 12 months						
	0	76 (75)	91 (273)	Ref.		
	1	15 (15)	5 (15)	3.23	1.51 – 6.85	0.002
	≥ 2	9 (9)	4 (11)	2.46	0.98 – 6.20	

Table 2. Results of univariable conditional logistic regression analysis of categorical variables with a P-value <0.2 obtained from information on management-level variables.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95%CI*	*P-value*
Principal carer					
Owners(s) / relative / spouse involved in daily care	48 (52)	72 (222)	Ref.		
Owner(s) / relative / spouse not involved in daily care	52 (57)	28 (87)	2.85	1.76 – 4.61	<0.001
Premises type					
Private yard	49 (53)	52 (162)	Ref.		
Working / competition yard	23 (25)	13 (40)	2.10	1.11 – 3.98	
Livery yard	24 (26)	29 (91)	0.88	0.50– 1.54	
Stud farm	4 (4)	5 (16)	0.56	0.14 – 2.20	0.050
Premises change in previous 28 days					
No	89 (93)	93 (276)	Ref.		
Yes	11 (12)	7 (21)	1.75	0.78 – 3.92	0.179
Current management					
Stabled with 2 / >2hrs turnout every day	59 (61)	54 (163)	Ref.		
Stabled all the time / stabled apart from when exercised	15 (16)	10 (31)	1.59	0.75 – 3.36	0.040
Stabled with <2h turnout daily / irregular turnout	13 (14)	11 (35)	1.14	0.57 – 2.27	
Not stabled – turned out all the time	13 (13)	25 (75)	0.49	0.25 – 0.94	
Current stabling					
No	12 (13)	25 (75)	Ref.		
Yes	88 (91)	75 (229)	2.21	1.17 – 4.20	0.009
Increased stabling in the previous 14 days					
No	78 (75)	84 (231)	Ref.		
Yes	22 (21)	16 (44)	1.65	0.88 – 3.11	0.122
Change in type / batch of bedding in previous 28 days					
No	88 (86)	94 (234)	Ref.		
Yes	12 (12)	6 (16)	1.92	0.86 – 4.32	0.118
Water source when turned out					
Manually filled source only	46 (43)	40 (109)	Ref.		
Automatic water source only	45 (42)	42 (115)	0.86	0.51 – 1.45	0.102
Pond / stream or more than one water source	9 (8)	18 (48)	0.41	0.18 – 0.97	
Roughage type					
Grass only	5.5 (6)	10 (30)	Ref.		
Hay	52 (57)	57 (177)	1.52	0.59 – 3.93	
Haylage	37 (40)	30 (92)	2.46	0.90 – 6.69	0.102
Hay & Haylage	5.5 (6)	3 (9)	3.57	0.92 – 13.88	
Currently fed hay / haylage					
Yes	94(103)	90 (278)	Ref.		
No	6 (6)	10 (30)	0.54	0.21 – 1.38	0.180
Currently fed haylage					
No	58 (63)	67 (207)	Ref.		

Yes	42 (46)	33 (101)	1.77	1.07 – 2.95	0.026
Concentrate feeding					
Once daily	10 (10)	17 (47)	Ref.		
Twice daily	73 (75)	70 (198)	2.07	0.92 – 4.66	0.105
Three times daily or more	17 (18)	13 (37)	2.69	1.01 – 7.14	

Table 3. Results of univariable conditional logistic regression of categorical variables with P<0.2 obtained from information on behaviour

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95%CI*	*P-value*
Easily frightened					
No	82 (89)	66 (205)	Ref.		
Yes	18 (20)	34 (104)	0.43	0.25 – 0.74	0.001
Settle after fright					
Instantly	69 (75)	59 (182)	Ref.		
Few minutes / longer than few minutes	31 (33)	41 (128)	0.62	0.39 – 0.99	0.045
Response to unknown object					
Interested / Excited	71 (77)	84 (261)	Ref.		
Not bothered	29 (31)	16 (48)	2.11	1.27 – 3.51	0.005
Sweat up when excited					
Never	80 (86)	66 (202)	Ref.		
Easily, every time / occasionally	20 (22)	34 (105)	0.48	0.28 – 0.83	0.006
Reaction to surroundings					
Will watch / Not interested	57 (62)	42 (130)	Ref.		
Very inquisitive	43 (46)	58 (179)	0.52	0.33 – 0.83	0.005
Reaction to other horses					
Excited / interested	47 (51)	63 (195)	Ref.		
Not bothered	53 (57)	37 (115)	2.08	1.31 – 3.30	0.002
Feeding behaviour when stressed					
Eats normally	92 (96)	83 (249)	Ref.		
Goes off food in full / part	8 (8)	17 (51)	0.46	0.21 – 1.00	0.035
Stereotypic behaviour of any kind					
No	45 (49)	83 (256)	Ref.		
Yes	55 (59)	17 (52)	5.24	3.21 – 8.52	<0.001
Crib-biting / windsucking behaviour					
No	53 (57)	95 (294)	Ref.		
Yes	47 (51)	5 (14)	16.67	7.88 – 35.26	<0.001
Other oral stereotypic behaviour (not woodchewing / crib-biting / windsucking)					
No	97 (105)	99.7 (307)	Ref.		
Yes	3 (3)	0.3 (1)	5.60	0.55 – 57.28	0.114
Oral stereotypic behaviour of any type					
No	50 (54)	92 (283)	Ref.		
Yes	50 (54)	8 (25)	10.5	5.60 – 19.87	<0.001

Table 4. Continuous variables with a P<0.2 in the univariate conditional logistic regression analysis of potential horse- and management-level risk factors for epiploic foramen entrapment.

Variable	*Unit of measurement*	*Mean / median*	*Coefficient*	*Standard error*	*P-value*
Horse					
Age	years	9	0.025	0.023	0.266
Age (centred)^2	years^2		-0.017	0.004	0.034
Height	cm	160	0.021	0.009	0.017
Height (centred)^2	cm^2		0.001	0.001	0.010
Weight	kg	514	0.003	0.001	0.011
Premises					
No. horses on premises		13	-0.004	0.004	0.101
Housing and grazing					
No. of hours stabled per week	hours	113	0.007	0.003	0.001
No. of hours grazing per week	hours	52	-0.006	0.002	0.003
Duration on current pasture	months	3.5	0.006	0.004	0.129
Nutrition					
Supplementary forage weight	kg	7.5	0.039	0.030	0.191
Concentrate protein	%	11.4	0.265	0.118	0.017

Crib-biting / windsucking behaviour

The prevalence of crib-biting or windsucking behaviour was 47% in the case population (n=51) and 5% in the control population (n=14). A chi-squared test revealed a significant association between crib-biting / windsucking behaviour and an episode of colic in the previous 12 months (P<0.0001). There was a significant difference between the number of hours stabled per week (two-sample t-test, P=0.004) in horses exhibiting crib-biting / windsucking behaviour (mean 127.87 hours, standard deviation [s.d.] 42.57) compared to horses not exhibiting this behaviour (mean 107.09, s.d.54.78) and in the number of hours at pasture per week (P=0.001) between the two groups (crib-biting / windsucking group mean 46.29 hours, s.d. 53.36, non crib-biting / windsucking group mean 72.40 hours, s.d. 60.99).

Multivariable analysis

The final multivariable logistic regression model is shown in Table 5. Crib-biting / windsucking behaviour was associated with the largest risk of EFE. Increasing height and a history of colic in the previous 12 months were also associated with increased risk of EFE. Horses that were considered to be easily frightened, those who actively investigated their surroundings, those who did not sweat up when excited and those who went off their feed when perceived to be stressed were at reduced risk of EFE. The variable 'feeding when stressed' significantly improved the fit of the model. However, the change in risk associated with this variable should be interpreted with caution due to the wide 95% CI that cross 1. The principal carer of the horse was associated with altered risk of EFE and there was a statistically significant multiplicative interaction (p=0.02) between this variable and the variable 'crib-biting / windsucking' (Table 5).

Individual cases and controls with delta betas greater than 0.4 or less than -0.4 were removed from the dataset and the model was re-run. Removal of a single case and two controls with large delta-betas for height (Appendix to Chapter 3: Figure 1) changed the significance of the $height^2$ term in relation to the critical P-value of 0.05 but the linear height term remained significant in the model (p=0.007, OR 1.05, 95%CI 1.01 – 1.09). These data were correct and so these individuals were retained in the final model. The other variables in the model remained statistically significant when cases and controls with large delta betas were removed from the model. The odds ratios for the variables 'easily frightened', 'sweats up when excited', 'feeding behaviour when stressed' and 'crib-biting / windsucking behaviour' increased in magnitude when these cases and controls were removed.

Table 5. Multivariable conditional logistic regression model of horse- and management-level risk factors for epiploic foramen entrapment. The table shows the coefficients, standard errors, P-values (LRS = likelihood ratio test statistic), odds ratios and 95% confidence intervals (CI)

Variable	*Coefficient*	*Standard Error*	*LRS P-value*	*Adjusted Odds ratio*	*95% CI*
Crib-biting /windsucking behaviour exhibited					
No	Ref.			1.00	
Yes	4.21	0.76	<0.01	67.27	15.26 – 296.54
Colic in previous 12 months					
No	Ref.			1.00	
Yes	1.48	0.54	<0.01	4.38	1.51 – 12.68
Principal carer					
Owners(s) / relative or spouse involved in daily care	Ref.			1.00	
Owner / relative / spouse not involved in daily care	1.71	0.45	<0.01	5.50	2.27 – 13.33
Easily frightened					
No	Ref.			1.00	
Yes	-0.94	0.48	0.04	0.39	0.15 – 1.00
Sweats up when excited					
No	Ref.			1.00	
Yes	-1.13	0.44	0.01	0.32	0.13 – 0.77
Reaction to surroundings					
Some / little interest	Ref.			1.00	
Inquisitive	-0.90	0.36	0.01	0.41	0.20 – 0.83
Feeding when stressed					
Eats normally	Ref.			1.00	
Goes off food in full / part	-1.23	0.65	0.03	0.29	0.08 – 1.04
Height (per cm increase)					
Height (centred)	0.05	0.02	<0.01	1.05	1.01 – 1.08
Height (centred)^2	<0.01	<0.01	0.04	1.001	1.00 – 1.001
Interaction term*					
Crib-biting / windsucking behaviour x carer	-2.39	1.01	0.02	0.091	0.01 – 0.66

*Explanation of interaction term:

- Owner / carer / spouse involved in daily care and horse not exhibiting crib-biting / windsucking behaviour, OR = 1
- Owner / carer / spouse involved in daily care and horse that does exhibit crib-biting / windsucking behaviour, OR = 67
- Owner / carer / spouse not involved in daily care and horse that does not exhibit crib-biting / windsucking behaviour, OR = 5.5
- Owner / carer / spouse not involved in daily care and horse exhibits crib-biting / windsucking behaviour, OR= 34 (67.27x5.50x0.09)

DISCUSSION

Few studies have investigated the epidemiology of specific types of colic using a population of non-colic controls. This is the first epidemiological study to investigate horse- and management-level risk factors for epiploic foramen entrapment (EFE) using a representative population of at risk horses as controls. To the author's knowledge, this is also the first international study to investigate risk factors for colic in more than one country.

In the present study, crib-biting / windsucking behaviour was associated with the greatest risk of EFE. This is consistent with previous findings (Archer *et al.* 2004a; Archer *et al.* 2004b) where this behaviour was found to be a risk factor for EFE using other horses with colic as controls. The prevalence of crib-biting / windsucking behaviour in the control population in the present study was comparable to the findings of studies investigating the prevalence of this behaviour in normal horse populations (McGreevy and Nicol 1998). In contrast the prevalence of crib-biting / windsucking behaviour in the case population was far higher than reported in any other horse populations and was similar to the prevalence of this behaviour in the EFE cases reported by Archer *et al.* (2004a; 2004b).

Anecdotally, crib-biting and windsucking behaviour has been associated with colic (Frauenfelder 1981) but this association had not been proven (McGreevy and Nicol 1998). In the present study, case and control horses exhibiting this behaviour were significantly more likely to have suffered from colic in the previous 12 months compared to case and control horses who did not exhibit this behaviour. Crib-biting / windsucking behaviour has also been associated with a large increase in risk of simple colonic obstruction / distension (SCOD) colic (Hillyer *et al.* 2002).Therefore the evidence from the present study and the studies by Hillyer *et al.* (2002) and Archer *et al.* (2004a; 2004b) may suggest that crib-biting / windsucking behaviour is associated with some specific forms of colic and with colic in general. This finding would support the theory that this behaviour is associated with some underlying gastrointestinal dysfunction (McGreevy *et al.* 2001) and requires further investigation.

Horses with a history of colic in the previous 12 months were identified to be 4.4 times more likely to develop EFE compared to horses who had not suffered colic in the previous 12 months. A history of a previous episode of colic has also been identified as a risk factor for colic in general (Cohen *et al.* 1995; Reeves *et al.* 1996; Tinker *et al.* 1997a; Cohen *et al.* 1999) and for SCOD colic (Hillyer *et al.* 2002). There was no interaction between the variables 'crib-biting / windsucking' and 'colic in the previous 12 months' in the model i.e. a history of colic in a horse exhibiting this behaviour does not increase the risk of EFE further. Again, the finding that a previous episode of colic is a risk factor for EFE may suggest these horses have some underlying gastrointestinal dysfunction.

The person(s) looking after the horse on a daily basis was found to be associated with altered risk of EFE in the present study. This is similar to the findings of Reeves *et al.* (1996) and Hillyer *et al.* (2001) who found that horses whose owners provided their care were at decreased risk of colic or recurrence of colic compared to horses cared for by a non-owner. In this study we used a slightly different definition and considered this variable to be a marker for a number of management-level variables that in themselves are insignificant but when grouped together become significant e.g. feeding practices, stabling and turnout routines. There was a significant multiplicative interaction between the variables 'carer' and 'crib-biting / windsucking' in the final model. A chi-squared test revealed no significant difference between the variables 'carer' and 'crib-biting / windsucking' i.e. horses exhibiting this behaviour were no more likely to have their owner / owner's relative or spouse involved in their daily care than those not exhibiting this behaviour. For horses not exhibiting this behaviour, horses whose principal care did not involve the owner, owner's spouse or relative were at increased risk of EFE (OR 5.5) compared to horses whose principal care did involve the owner, owner's spouse or relative (OR 1.0). Interestingly, horses who exhibited crib-biting / windsucking behaviour were at less risk of EFE if an owner, owner's spouse or relative was not involved in their daily care (OR 33.8) compared to horses whose owner, owner's spouse or relative was involved in their daily care (OR 67.3). This may be a spurious finding but was considered to be biologically plausible if the type of carer influences how horses that exhibit crib-biting / windsucking behaviour are managed. This finding merits further investigation.

Few studies have investigated the relationship between equine behaviour and colic. In the study by Hillyer *et al.* (2002), horses whose carers described their temperament as 'nervous' were significantly more likely to suffer SCOD colic compared to those who were not perceived to be nervous. Although this variable was significant in the univariable analysis of risk-factors for SCOD colic, it did not remain in the final model of the latter study. In the present study a number of behavioural features were identified to place horses at increased risk of EFE and several of these remained in the final, multivariable model. Horses who were considered by their carers' not to be easily frightened, those who never sweated up when excited and those who did not actively investigate their surroundings were at increased risk of EFE compared to horses considered to be easily frightened, those who always or occasionally sweated up when excited or those who actively investigated their surroundings. Work in other species has demonstrated that in the later stages of stereotypic behaviour, where the behaviour has become established, animals may begin to withdraw from their environment (Cooper and Nicol 1991). The behavioural risk-factors identified in the present study seem to suggest that these horses do not exhibit the behavioural response that might be expected in the wild to a stimulus that causes a fright response, excitement or interest. These behavioural features may represent a means by which these individuals try to cope with an environment that induces stress.

It was interesting to find that horses who did not eat all / part of their feed when exposed to a stressful situation e.g. competition or change of premises were at reduced risk of EFE compared to horses who ate normally. If EFE is associated with some underlying gastrointestinal dysfunction, this finding may reflect a need to maintain normal feed patterns to compensate for this.

The variables used to measure behaviour in the present study were subjective and based on the owner's or carer's assessment of the horse. Other, more objective measurements of equine behaviour using specific stimuli have been described (Momozawa *et al.* 2003). However, in the present study the questionnaire was administered over the telephone by the same investigator who was able to provide more detailed explanation of the question if required. Therefore this method should produce a relatively consistent and accurate assessment of individual horses' behaviour. In addition, a horse's response to feed or a stimulus that causes fright / interest / excitement or feed anticipation are evoked responses and are more reliable than measurement of perceived personality traits (Mills 1998).

Increasing height was associated with an increased risk of EFE and this remained significant in the final model even when other potentially confounding factors such as stabling, turnout, nutrition and exercise were taken into account. This may reflect anatomical differences in the relative dimensions of the epiploic foramen making entrapment more likely to occur in larger horses. It is interesting to note that in the cases of EFE recently reported in cattle (Deprez *et al.* 2006), out of 900 other cattle with clinical signs of intestinal obstruction, the 3 with EFE were all Belgian Blue breed calves aged between 1.5 – 3 months. Whilst being careful not to over-interpret this finding in view of the small numbers of cases reported, this finding could reflect a change in the relative dimensions of the epiploic foramen in this age group and particular breed of cattle. In a study of the anatomy of the epiploic foramen in horses (Schmid 1998) the dimensions of the foramen were measured in 15 horses euthanased for reasons unrelated to the gastrointestinal tract. There was no relationship between the width of the foramen and age of horses but a slight correlation between the width of the foramen and weight of the horse. The latter finding was not statistically significant but this may have been due to insufficient study power. Further work is required to investigate the relative dimensions of the epiploic foramen in a larger number of horses of different breeds and sizes.

The findings of the present study are consistent with other studies investigating EFE. Age in its linear form was not significantly associated with risk of EFE in univariable analysis but addition of squared term for age did improve the fit of the model. However the age squared term was not retained in final model supporting the findings of Freeman and Schaeffer (2001) that increasing age is not associated with increased risk of EFE. Thoroughbred (TB) and TB-cross horses have been associated with increased risk of EFE (Archer *et al.* 2004b) but breed was not statistically significant in univariable analysis nor did it remain in the final model. However, height did remain in the final model and may explain why these breeds have been associated with increased risk of EFE compared to other, smaller breeds.

In the present study, the majority of owners / carers were able to provide precise information about the dates on which anthelmintics and vaccinations had been administered, and the products that had been given, using diaries / calendars and vaccination certificates. However, whilst they could provide precise details about feed brands and dietary supplements, a large number of owners / carers did not know the precise weights of feed that the horses were receiving nor were they able or willing to provide this information. Therefore in the present study, feed weights were estimated based on scoop sizes / quarts and haynet sizes. This method was considered to provide the most accurate information given the telephone based nature of the study. This information was validated by the principal investigator by weighing various feeds in different scoops / measures and by checking the estimated feed weights with the precise feed weights provided by some of the owners / carers. White (1997) stated the need to investigate the relationship between specific types of feed and colic. The difficulties encountered when tying to obtain accurate feed weights in the present study should be considered when designing future studies to investigate nutritional variables associated with risk of colic. More accurate data may need to be obtained in different ways e.g. face-to-face interviews, feed diaries and weighing of feed at stable yards by study investigators.

The results of the present study suggest that some horses may be inherently predisposed to EFE. This knowledge can assist identification of horses at high-risk of EFE and has identified areas that require further research. Relatively few modifiable risk-factors were identified in the present study limiting advice that can be given to reduce the risk of EFE occurring in high-risk individuals. In horses that do not exhibit crib-biting / windsucking behaviour, daily care involving the owner, a relative or spouse should reduce the risk of EFE. However, in horses exhibiting crib-biting / windsucking behaviour, daily care not involving the owner, owners relative or spouse should decrease the risk of EFE. Further work is required to determine the factors that may explain these findings e.g. feed and turnout routines may vary depending on the person looking after the horse and whether the horse exhibits crib-biting / windsucking behaviour.

The findings from the present study demonstrate that crib-biting / windsucking behaviour is strongly associated with increased risk of EFE using a population of normal horses as controls. In addition, an episode of colic in the previous 12 months and increasing height are also associated with increased risk of EFE. A number of behavioural features relating to individual horses' responses to frightening or exciting stimuli or to their environment also increased the risk of EFE. The interaction between crib-biting / windsucking behaviour and carer merits further investigation and may represent a number of management-level variables that, on their own are insignificant, but when grouped together become highly significant. This was a study based in several countries and the findings of the present study have widespread applicability to horses based in the UK, Ireland and USA.

APPENDIX TO CHAPTER 3

Table 1. Univariable conditional logistic regression analyses of binary and categorical horse- and management-level variables and their relationship with the risk of developing epiploic foramen entrapment (EFE).

Variable		Case % (n)	Control % (n)	Odds Ratio	95% CI	P-value
General horse and management details						
Breed	TB	33 (36)	24 (74)	Ref.		
	TBx	17 (19)	20 (63)	0.58	0.29 – 1.17	
	WB / WBx	16 (17)	9 (29)	1.39	0.65 – 2.98	
	Pony / miniature horse	10 (11)	16 (48)	0.46	0.21 – 1.04	0.086
	Cob / Cob x	3 (3)	6 (18)	0.33	0.09 – 1.23	
	Other horse	21 (23)	25 (76)	0.65	0.35 – 1.21	
Gender	Male	75 (82)	63 (194)	Ref.		
	Female	25 (27)	37 (116)	0.58	0.36 – 0.94	0.023
Principal use	Pleasure	38 (41)	35 (110)	Ref.		
	Competition (local / regional)	17 (19)	14 (42)	1.25	0.64 – 2.44	
	Competition (national / international)	10 (11)	4 (13)	0.58	0.28 – 1.21	
	Working horse	5.5 (6)	17 (52)	1.33	0.46 – 3.84	
	Pet / retired	5.5 (6)	8 (25)	0.64	0.24 – 1.65	
	Injured	5 (5)	5 (15)	0.83	0.28 – 2.44	0.327
	Broodmare	11 (12)	6 (18)	1.55	0.67 – 3.56	
	Breeding stallion	4 (4)	2 (7)	1.25	0.34 – 4.57	
	Unbroken / recently broken	5 (5)	9 (28)	0.48	0.17 – 1.38	
Currently competing	No	75 (82)	72 (223)	Ref.		
	Yes	25 (27)	28 (87)	0.87	0.53 – 1.43	0.600
Competition type	Flat racing	12.5 (5)	11 (12)	Ref.		
	Jump racing / PTP	5 (2)	6 (7)	0.51	0.05 – 4.79	
	Dressage	25 (10)	21 (23)	1.27	0.15 – 10.67	

	Show-jumping	22.5 (9)	9 (11)	2.81	0.31 – 25.72	
	Eventing	12.5 (5)	8 (9)	1.50	0.14 – 15.45	0.462
	Showing	10 (4)	18 (20)	0.37	0.05 – 2.74	
	Driving / endurance / polo / western	5 (2)	9 (10)	0.64	0.04 – 11.62	
	Combination competition types	7.5 (3)	18 (20)	0.71	0.07 – 7.53	
Medical details						
Veterinary attention in last 12 months (non-routine)	No	53 (54)	41 (123)	Ref.		
	Yes	47 (48)	59 (175)	0.62	0.38 – 0.99	0.044
Type of problem						
Orthopaedic	No	78 (79)	68 (203)	Ref.		
	Yes	22 (22)	32 (94)	0.61	0.36 – 1.05	0.070
Respiratory	No	93 (94)	95 (281)	Ref.		
	Yes	7 (7)	5 (15)	1.55	0.59 – 4.10	0.390
Dental / Gastrointestinal	No	82 (83)	89 (263)	Ref.		
	Yes	18 (18)	11 (33)	1.66	0.88 – 3.17	0.122
Weight loss	No	97 (98)	98 (292)	Ref.		
	Yes	3 (3)	2 (5)	1.71	0.41 – 7.17	0.477
Reproductive / urinary	No	97 (98)	98 (289)	Ref.		
	Yes	3 (3)	2 (7)	1.19	0.29 – 4.88	0.807
Eyes / ears	No	98 (99)	97 (288)	Ref.		
	Yes	2 (2)	3 (8)	0.85	0.17 – 4.31	0.840
Skin / hair	No	92 (99)	89 (264)	Ref.		
	Yes	2 (2)	11 (32)	0.71	0.32 – 1.60	0.398
Neurological	No	99 (100)	99 (293)	Ref.		
	Yes	1 (1)	1 (3)	1.30	0.12 – 14.51	0.832
Lethargy / fever	No	97 (98)	98 (289)	Ref.		
	Yes	3 (3)	2 (7)	1.25	0.31 – 5.11	0.759
Other	No	95 (96)	93 (274)	Ref.		
	Yes	5 (5)	7 (22)	0.60	0.22 – 1.60	0.285

Medication (other than anthelmintic or vaccination) administered in previous 12 months	no	57 (58)	47 (136)	Ref.		
	yes	43 (43)	53 (156)	0.64	0.40 – 1.02	0.061
Currently receiving medication	No	93 (100)	91 (277)	Ref.		
	Yes	7 (7)	9 (29)	0.65	0.27 – 1.53	0.305
NSAIDs in previous 12 months	No	57 (58)	47 (136)	Ref.		
	Yes	43 (43)	53 (156)	0.73	0.44 – 1.20	0.211
NSAIDs in previous 28 days	No	93 (79)	88 (232)	Ref.		
	Yes	7 (6)	12 (30)	0.67	0.26 – 1.71	0.385
Episode of colic in previous 12 months	No	76 (75)	91 (273)	Ref.		
	Yes	24 (24)	9 (26)	2.90	1.59 – 5.31	<0.001
Number of colic episodes in previous 12 months	None	76 (75)	91 (273)	Ref.		
	1	15 (15)	5 (15)	3.23	1.51 – 6.85	0.002
	2 or more	9 (9)	4 (11)	2.46	0.98 – 6.20	
Previous abdominal surgery	No	96 (103)	94 (291)	Ref.		
	Yes	4 (4)	6 (19)	0.50	0.15 – 1.63	0.229
Premises						
Premises type	Private yard	49 (53)	52 (162)	Ref.		
	Working / competition yard	23 (25)	13 (40)	2.10	1.11 – 3.98	
	Livery yard	24 (26)	29 (91)	0.88	0.50– 1.54	
	Stud farm	4 (4)	5 (16)	0.56	0.14 – 2.20	0.050
Carer	Owners(s) / relative or spouse involved in	48 (52)	72 (222)	Ref.		

	daily care					
	Owner(s) / relative / spouse not involved in daily care	52 (57)	28 (87)	2.85	1.76 – 4.61	<0.001
Owner involved in daily care	Yes	46 (50)	69 (214)	Ref.		
	No	54 (59)	31 (95)	2.61	1.64 – 4.16	<0.001
Premises change in previous 12 months	No	52 (55)	54 (161)	Ref.		
	Yes	48 (50)	46 (136)	1.13	0.73 – 1.76	0.583
Premises change in previous 28 days	No	89 (93)	93 (276)	Ref.		
	Yes	11 (12)	7 (21)	1.75	0.78 – 3.92	0.179
Premises change in previous 14 days	No	94 (99)	97 (288)	Ref.		
	Yes	6 (6)	3 (9)	1.93	0.59 – 6.28	0.280
Premises change in previous 7 days	No	96 (101)	98 (292)	Ref.		
	Yes	4 (4)	2 (5)	2.07	0.50 – 8.57	0.320
No. of premises in last 12 months	1	51 (55)	53 (161)	Ref.		
	2 - 3	45 (48)	40 (121)	1.13	0.73 – 1.78	0.347
	>3	4 (4)	7 (23)	0.52	0.17 – 1.62	
No. of premises changes in last 12 months	0	51 (55)	53 (161)	Ref.		
	1	35 (37)	31 (95)	1.33	0.76 – 2.34	0.317
	2-4	11 (12)	12 (37)	1.01	0.58 – 1.75	
	>4	3 (3)	4 912)	0.35	0.07 – 1.69	
Housing and grazing						

Current management	Stabled with 2 / >2hrs turnout every day	59 (61)	54 (163)	Ref.		
	Stabled all the time / stabled apart from when exercised	15 (16)	10 (31)	1.59	0.75 – 3.36	0.040
	Stabled with <2h turnout daily / irregular turnout	13 (14)	11 (35)	1.14	0.57 – 2.27	
	Not stabled – turned out all the time	13 (13)	25 (75)	0.49	0.25 – 0.94	
Current stabling	No	12 (13)	25 (75)	Ref.		
	Yes	88 (91)	75 (229)	2.21	1.17 – 4.20	0.009
Change in stabling / turnout routine in previous 28 days	No	62 (65)	59 (175)	Ref.		
	Yes	38 (40)	41 (122)	0.94	0.59 – 1.49	0.781
Change in stabling / turnout routine in previous 14 days	No	73 (72)	75 (199)	Ref.		
	Yes	27 (26)	25 (68)	1.01	0.59 – 1.72	0.982
Change in stabling / turnout routine in previous 7 days	No	81 (79)	84 (224)	Ref.		
	Yes	19 (19)	16 (43)	1.22	0.67 – 2.23	0.517
Increased stabling in previous 28 days	No	67 (69)	73 (217)	Ref.		
	Yes	33 (34)	27 (80)	1.38	0.84 – 2.26	0.204
Increased stabling in previous 14 days	No	78 (75)	84 (231)	Ref.		
	Yes	22 (21)	16 (44)	1.65	0.88 – 3.11	0.122
Increased stabling in previous 7 days	No	85 (82)	88 (243)	Ref.		

	Yes	15 (14)	12 (32)	1.50	0.70 – 3.22	0.304
Increased turnout in previous 28 days	No	93 (96)	93 (275)	Ref.		
	Yes	7 (7)	7 (22)	0.80	0.32 – 2.01	0.637
Increased turnout in previous 14 days	No	96 (98)	96 (280)	Ref.		
	Yes	4 (4)	4 (13)	0.76	0.22 – 2.57	0.652
Increased turnout in previous 7 days	No	96 (98)	98 (286)	Ref.		
	Yes	4 (4)	2 (7)	1.71	0.45 – 6.57	0.441
Stable type	Indoor American barn	37 (37)	33 (85)	Ref.		
	Outside stable block	48 (48)	52 (133)	0.84	0.47 – 1.49	0.394
	Single stable	1 (1)	3 (8)	0.22	0.03 – 1.85	
	Other	13 (13)	12 (30)	1.02	0.48 – 2.19	
Bedding type	Straw	35 (35)	32 (81)	Ref.		
	Woodshavings	53 (53)	58 (148)	0.88	0.52 – 1.48	
	Other	12 (12)	10 (27)	1.24	0.55 – 2.81	0.671
Bedding change (type / batch) in last 28 days	No	88 (86)	94 (234)	Ref.		
	Yes	12 (12)	6 (16)	1.92	0.86 – 4.32	0.118
Manually filled water supply in stable	No	25 (25)	20 (52)	Ref.		
	Yes	75 975)	80 (204)	0.79	0.44 – 1.43	0.444
Automatic water supply in stable	No	75 (75)	77 (197)	Ref.		
	Yes	25 (25)	23 (59)	1.09	0.61 – 1.98	0.762
Turnout type	Grass field only	83 (91)	85 (263)	Ref.		
	Field and yard / arena	1 (1)	3 (9)	0.25	0.03 – 2.09	
	Yard / arena only	6 (5)	4 (12)	1.08	0.36 – 3.26	0.276

	No turnout	11 (12)	8 (24)	1.66	0.73 – 3.77	
Current access to pasture	No	16 (17)	12 (36)	Ref.		
	Yes	84 (92)	88 (272)	0.67	0.34 – 1.30	0.241
Pasture type	Mature	91 (81)	88 (236)	Ref.		
	Part / all reseeded	9 (8)	12 (31)	0.70	0.31 – 1.60	0.386
Change in pasture in previous 28 days	No	82 (74)	83 (225)	Ref.		
	Yes	18 (16)	17 (45)	0.92	0.47 – 1.78	0.801
Turned out on own	No	76 (71)	73 (203)	Ref.		
	Yes	24 (22)	27 (75)	0.72	0.40 – 1.31	0.278
Other species on pasture within previous 12 months	No	73 (65)	72 (200)	Ref.		
	Yes	27 (24)	28 (76)	0.98	0.55 – 1.73	0.942
Pasture treatment within previous 28 days	No	94 (81)	96 (248)	Ref.		
	Yes	6 (5)	4 (11)	1.21	0.36 – 4.11	0.753
Water source when turned out	Manually filled source only	46 (43)	40 (109)	Ref.		
	Automatic water source only	45 (42)	42 (115)	0.86	0.51 – 1.45	0.102
	Pond / stream or more than one water source	9 (8)	18 (48)	0.41	0.18 – 0.97	
Nutrition						
Do the same people feed every day / most days	No	9 (9)	7 (22)	Ref.		
	Yes	91 (92)	93 (273)	0.84	0.37 – 1.88	0.670

No. of people feeding daily	1	45 (47)	50 (139)	Ref.		
	2	35 (37)	36 (106)	1.11	0.68 – 1.83	0.352
	>2	20 (21)	14 (42)	1.59	0.85 – 2.97	
Roughage type	Grass only	5.5 (6)	10 (30)	Ref.		
	Hay	52 (57)	57 (177)	1.52	0.59 – 3.93	
	Haylage	37 (40)	30 (92)	2.46	0.90 – 6.69	0.102
	Hay & Haylage	5.5 (6)	3 (9)	3.57	0.92 – 13.88	
Feeding of hay / haylage	Yes	94(103)	90 (278)	Ref.		
	No	6 (6)	10 (30)	0.54	0.21 – 1.38	0.180
Currently fed hay	No	42 (46)	40 (122)	Ref.		
	Yes	58 (63)	60 (186)	0.82	0.51 – 1.32	0.416
Currently fed haylage	No	58 (63)	67 (207)	Ref.		
	Yes	42 (46)	33 (101)	1.77	1.07 – 2.95	0.026
Supplementary forage feeding	Once daily	20 (21)	27 (73)	Ref.		
	Twice daily	50 (51)	44 (120)	1.43	0.79 – 2.59	
	Three - four times daily	19 (20)	17 (47)	1.39	0.67 – 1.88	0.637
	Ad libitum	11 (11)	12 (33)	1.10	0.47 – 2.62	
Concentrate fed	No	5 (5)	7 (23)	Ref.		
	Yes	95 (103)	93 (287)	1.60	0.60 – 4.34	0.330
Concentrate feeding	Once daily	10 (10)	17 (47)	Ref.		
	Twice daily	73 (75)	70 (198)	2.07	0.92 – 4.66	0.105
	Three times daily or more	17 (18)	13 (37)	2.69	1.01 – 7.14	
Fed at same time and frequency as horses in group / yard	Yes	90 (96)	75 (228)	Ref.		
	No	10 (11)	25 (76)	0.35	0.17 – 0.70	0.010
Fed at the same time (to within an	Never / occasionally	82 (84)	72 (207)	Ref.		

hour) every day of the week	varies					
	Varies on a regular basis	19 (19)	28 (80)	0.59	0.33– 1.04	0.062
Frequency of feed (non forage) delivery	Weekly or less	33 (12)	39 (40)	Ref.		
	More than weekly	67 (24)	61 (62)	1.83	0.67 – 4.97	0.223
Days since new bag of feed opened	Within 7 days	65 (22)	67 (65(	Ref.		
	Greater than 7 days	35 (12)	33 (32)	1.71	0.60 – 4.9	0.312
Change in frequency forage feeding:						
Last 28 days	No	89 (87)	86 (245)	Ref.		
	Yes	11 (11)	14 (41)	0.82	0.41 – 1.64	0.565
Last 14 days	No	93 (87)	92 (254)	Ref.		
	Yes	7 (7)	8 (23)	1.00	0.41 – 2.42	1.000
Last 7 days	No	96 (90)	96 (265)	Ref.		
	Yes	4 (4)	4 (12)	0.43	0.09 – 2.09	1.000
Change in quantity forage feeding:						
last 28 days	No	83 (85)	85 (255)	Ref.		
	Yes	17 (18)	15 (45)	1.20	0.64 – 2.27	0.565
Last 14 days	No	92 (88)	90 (240)	Ref.		
	Yes	8 (8)	10 (28)	0.98	0.41 – 2.36	0.970
Last 7 days	No	96 (92)	96 (256)	Ref.		
	Yes	4 (4)	4 (12)	1.22	0.36 – 4.12	0.751
Change in type of roughage fed in :						
last 28 days	No	95 (93)	92 (258)	Ref.		
	Yes	5 (5)	8 (22)	0.71	0.25 – 2.05	0.518
Last 14 days	No	97 (94)	95 (264)	Ref.		
	Yes	3 (3)	5 (13)	0.83	0.21 – 3.20	0.779
Last 7 days	No	98 (95)	98 (272)			
	Yes	2 (2)	2 (5)	2.00	0.33 – 11.97	0.462
Change in batch roughage in:						

Last 28 days	No	80 (57)	74 (172)	Ref.		
	Yes	20 (14)	26 (60)	0.63	0.31 – 1.30	0.203
Last 14 days	No	88 (59)	86 (187)	Ref.		
	Yes	12 (8)	14 (30)	0.66	0.25 – 1.72	0.385
Last 7 days	No	93 (62)	92 (200)	Ref.		
	Yes	7 (5)	8 (17)	1.57	0.21 – 2.19	0.511
Overall change in forage feeding in:						
Last 28 days	No	66 (46)	55 (120)	Ref.		
	Yes	34 (24)	45 (98)	0.56	0.30 – 1.04	0.062
Last 14 days	No	73 (48)	76 (143)	Ref.		
	Yes	27 (18)	24 (45)	1.19	0.57 – 2.45	0.643
Last 7 days	No	85 (56)	86 (163)	Ref.		
	Yes	15 (10)	26 (26)	1.56	0.61 – 4.00	0.353
Proprietary concentrate diet fed	No	36 (35)	34 (97)	Ref.		
	Yes	64 (62)	66 (192)	0.85	0.52 – 1.38	0.506
Local feed mill concentrate fed	No	78 (70)	81 (226)	Ref.		
	Yes	22 (20)	19 (53)	1.40	0.76 – 2.54	0.283
Grain fed	No	90 (94)	87 (265)	Ref.		
	Yes	10 (11)	13 (38)	0.76	0.37 – 1.56	0.446
Sugar beet pulp fed	No	79 (83)	75 (226)	Ref.		
	Yes	21 (22)	25 (77)	0.79	0.46 – 1.36	0.382
Fibre source fed	No	45 (46)	37 (114)	Ref.		
	Yes	55 (57)	63 (191)	0.76	0.48 – 1.19	0.227
Change in frequency of concentrate feeding in:						
Last 28 days	No	94 (95)	95 (270)	Ref.		
	Yes	6 (6)	5 (15)	1.06	0.39 – 2.86	0.899
Last 14 days	No	97 (96)	98 (276)	Ref.		
	Yes	3 (3)	2 (7)	1.18	0.29– 4.78	0.809

Last 7 days	No	99 (98)	99 (279)	Ref.		
	Yes	1 (1)	1 (4)	0.81	0.08 – 7.84	0.852
Change in quantity of concentrate in:						
Last 28 days	No	81 (77)	85 (226)	Ref.		
	Yes	19 (18)	15 (40)	1.11	0.61 – 2.02	0.738
Last 14 days	No	92 (79)	93 (239)	Ref.		
	Yes	8 (7)	7 (18)	1.08	0.42 – 2.74	0.873
Last 7 days	No	95 (82)	96 (247)	Ref.		
	Yes	5 (4)	4 (10)	1.30	0.36 – 4.70	0.696
Change in concentrate type / brand in:						
Last 28 days	No	92 (96	93 (280)	Ref.		
	Yes	8 (8)	7 (20)	1.18	0.50 – 2.77	0.711
Change in concentrate feeding in:						
Last 28 days	No	80 (70)	80 (213)	Ref.		
	Yes	20(17)	20 (52)	0.89	0.48 – 1.63	0.801
Last 14 days	No	92 (76)	93 (241)	Ref.		
	Yes	8 (7)	7 (18)	1.25	0.48 – 3.22	0.650
Last 7 days	No	95 (79)	96 (249)	Ref.		
	Yes	5 (4)	4 (10)	1.39	0.39 – 4.96	0.615
Overall diet change in:						
Last 28 days	No	63 (46)	56 (120)	Ref.		
	Yes	37 (27)	44 (95)	0.69	0.38 – 1.26	0.225
Last 14 days	No	77 (50)	75 (141)	Ref.		
	Yes	23 (15)	25 (48)	0.79	0.38 – 1.63	0.522
Last 7 days	No	86 (56)	86 (163)	Ref.		
	Yes	14 (9)	14 (27)	0.94	0.40 – 2.22	0.884
Supplements fed	No	17 (18)	14 (43)	Ref.		
	Yes	83 (90)	86 (265)	0.80	0.43 – 1.49	0.490
Vegetables / fruit	No	49 (53)	55 (171)	Ref.		

	Yes	51 (55)	45 (138)	1.26	0.82 – 1.95	0.294
Garlic / herbal	No	78 (84)	77 (239)	Ref.		
	Yes	22 (24)	23 (70)	0.93	0.55 – 1.58	0.791
Chondroitin / glucosamine	No	87 (94)	84 (259)	Ref.		
	Yes	13 (14)	16 (50)	0.74	0.39 – 1.40	0.343
Probiotics	No	94 (101)	96 (297)	Ref.		
	Yes	6 (6)	6 (11)	1.63	0.59 – 4.53	0.360
Salt / mineral lick or supplement	No	67 (72)	63 (194)	Ref.		
	Yes	33 (36)	37 (115)	0.84	0.53 – 1.33	0.454
Oil	No	72 (78)	73 (226)	Ref.		
	Yes	28 (30)	27 (83)	1.02	0.63 – 1.63	0.936
Other supplement	No	67 (72)	61 (188)	Ref.		
	Yes	33 (36)	39 (120)	0.80	0.51 – 1.27	0.348
Supplement added within last 28 days	No	90 (81)	93 (248)	Ref.		
	Yes	10 (9)	20 (7)	1.44	0.61 – 3.38	0.408
Exercise and transport						
Change in exercise routine in previous 28 days	No	71 (77)	76 (232)	Ref.		
	Yes	29 (31)	24 (72)	1.27	0.78 – 2.07	0.345
Type of exercise	None	25 (27)	27 (83)	Ref.		
	Ridden only	40 (44)	37 (114)	1.22	0.70 – 2.13	
	Lunged / treadmill / horsewalker only	6 (6)	3 (10)	1.66	0.55 – 5.03	0.704
	Other	29 (32)	33 (103)	1.00	0.56 – 1.78	
Location of exercise	Not applicable	24 (26)	27 (83)	Ref.		
	Arena / school only	12 (13)	14 (42)	1.00	0.47 – 2.13	
	Other	64 (69)	59 (182)	1.30	0.76 – 2.21	0.533
Transport in previous 28 days	No	66 (71)	63(193)	Ref.		
	Yes	34 (37)	37 (111)	0.93	0.58 – 1.50	0.764

Transport in previous 14 days	No	76 (80)	74 (214)	Ref.		
	Yes	24 (25)	26 (74)	0.87	0.51 – 1.49	0.622
Transport in previous 7 days	No	85 (89)	84 (242)	Ref.		
	Yes	15 (16)	16 (46)	0.98	0.52 – 1.85	0.957
Behaviour						
General behaviour						
Easily frightened	No	82 (89)	66 (205)	Ref.		
	Yes	18 (20)	34 (104)	0.43	0.25 – 0.74	0.001
Settle after fright	Instantly	69 (75)	59 (182)	Ref.		
	Few minutes / longer than few minutes	31 (33)	41 (128)	0.62	0.39 – 0.99	0.045
Response to unknown object	Interested / Excited	71 (77)	84 (261)	Ref.		
	Not bothered	29 (31)	16 (48)	2.11	1.27 – 3.51	0.005
Sweat up when excited	Never	80 (86)	66 (202)	Ref.		
	Easily, every time / occasionally	20 (22)	34 (105)	0.48	0.28 – 0.83	0.006
Tremble / shake when frightened	No	91 (97)	81 (249)	Ref.		
	Yes	9 (10)	19 (59)	0.74	0.16 – 3.45	0.696
Reaction to surroundings	Some / little interest	57 (62)	42 (130)	Ref.		
	Very inquisitive	43 (46)	58 (179)	0.52	0.33 – 0.83	0.005
Reaction to other horses	Excited / interested	47 (51)	63 (195)	Ref.		
	Not bothered	53 (57)	37 (115)	2.08	1.31 – 3.30	0.002
Restlessness when stabled	No	84 (89)	81 (241)	Ref.		
	Yes	16 (17)	19 (56)	0.81	0.44 – 1.48	0.485
Distressed when stabled alone	No	69 (68)	66 (181)	Ref.		

	Yes	31 (31)	34 (95)	0.94	0.57 – 1.57	0.829
Behaviour at feed time	Interested / little interest	77 (84)	71 (218)	Ref.		
	Agitated	23 (25)	29 (87)	0.72	0.43 – 1.21	0.203
Concentrate feeding	Normal / fast	99 (107)	98 (292)	Ref.		
	Doesn't eat all feed, picky	1 (1)	2 (7)	0.43	0.05 – 3.58	0.389
Forage feeding	Normal / fast	89 (93)	91 (268)	Ref.		
	Doesn't eat all forage	11 (12)	9 (28)	1.26	0.60 – 2.65	0.540
Feeding when stressed	Eats normally	92 (96)	83 (249)	Ref.		
	Goes off food in full / part	8 (8)	17 (51)	0.46	0.21 – 1.00	0.035
Aggression towards humans when given food	No	90 (97)	89 (269)	Ref.		
	Yes	10 (11)	11 (32)	0.92	0.45 – 1.90	0.822
Vision other horses when in stable	No	5 (5)	8 (20)	Ref.		
	Yes	95 (90)	92 (219)	1.86	0.59 – 5.89	0.265
Touch other horses when in stable	No	19 (21)	19 (58)	Ref.		
	Yes	81 (88)	81 (251)	1.00	0.58 – 1.73	0.993
Irritated when handled	Yes – regularly / occasionally	63 (68)	58 (180)	Ref.		
	No	37 (40)	42 (129)	0.84	0.54 – 1.31	0.434
Direct physical contact with other horses	Regular / occasional	83 (90)	86 (266)	Ref.		
	None	17 (19)	14 (43)	1.24	0.68 – 2.26	0.476
Light source in stable	Daylight +/- lights	91 (85)	94 (223)	Ref.		
	Artificial lighting only	9 (8)	6 (15)	1.39	0.57 – 3.43	0.477

Stereotypic behaviour						
Stereotypic behaviour	No	45 (49)	83 (256)	Ref.		
	Yes	55 (59)	17 (52)	5.24	3.21 – 8.52	<0.001
Crib-biting / windsucking	No	53 (57)	95 (294)	Ref.		
	Yes	47 (51)	5 (14)	16.67	7.88 – 35.26	<0.001
Woodchewing	No	97 (105)	97 (298)	Ref.		
	Yes	3 (3)	3 (10)	0.76	0.20 – 2.99	0.695
Weaving	No	94 (101)	96 (296)	Ref.		
	Yes	6 (7)	4 (12)	1.79	0.69 – 4.65	0.244
Box walking	No	97 (105)	95 (292)	Ref.		
	Yes	3 (3)	5 (16)	0.56	0.15 – 2.04	0.358
Other locomotor stereotypic behaviour	No	99 (107)	99.7 (307)	Ref.		
	Yes	1 (1)	0.3 (1)	3.00	0.19 – 47.96	0.448
Other oral stereotypic behaviour	No	97 (105)	99.7 (307)	Ref.		
	Yes	3 (3)	0.3 (1)	5.60	0.55 – 57.28	0.114
Oral stereotypic behaviour of any type	No	50 (54)	92 (283)	Ref.		
	Yes	50 (54)	8 (25)	10.5	5.60 – 19.87	<0.001
Locomotor stereotypic behaviour of any type	No	91 (98)	91 (281)	Ref.		
	Yes	9 (10)	9 (27)	1.17	0.53 – 2.57	0.693
Preventative health care						
Frequency of dental care	Every 12 months	52 (51)	41 (124)	Ref.		
	More than 12 monthly	32 (31)	42 (128)	0.57	0.34 – 0.95	

	Less than 12 monthly	12 (11)	12 (37)	0.66	0.30 – 1.46	0.163
	Never done	6 (6)	5 (15)	1.01	0.36 – 2.87	
Duration since teeth last checked	Last 6-12 months	29 (26)	24 (71)	Ref.		
	> 12 months	8 (7)	15 (44)	0.47	0.18 – 1.19	0.400
	1 month or less	12 (11)	13 (38)	0.83	0.37 – 1.87	
	>1 - < 6 months	51 (45)	48 (144)	0.91	0.51 – 1.62	
Regular vaccination	Yes	83 (86)	92 (283)	Ref.		
	No	17 (17)	8 (24)	1.61	1.14 – 2.29	0.008
Duration since last vaccination	1 – 6 months	33 (27)	42 (115)	Ref.		
	7 – 12 months	41 (33)	27 (101)	1.56	0.84 – 2.90	
	>12 months	6 (5)	7 (18)	1.32	0.41 – 4.26	0.569
	< 1 month	18 (16)	15 (40)	1.28	0.62 – 2.62	
Vaccination in previous 14 days	No	95 (77)	96 (262)	Ref.		
	Yes	5 (4)	4 (12)	0.82	0.26 – 2.62	0.736
Vaccination in previous 28 days	No	80 (65)	85 (234)	Ref.		
	Yes	18 (16)	15 (40)	1.06	0.55 – 2.04	0.866
Last vaccination	Flu & tetanus	58 (38)	54 (123)	Ref.		
	Flu only	18 (18)	21 (48)	0.59	0.28 – 1.27	
	Tetanus only	5 (3)	7 (15)	0.76	0.19 – 3.02	0.571
	Other	20 (13)	18 (42)	1.07	0.21 – 5.28	
Anthelmintic administration	Every 6 – 13 weeks	64 (63)	70 (211)	Ref.		
	< 6 weekly	7 (7)	4 (13)	1.25	0.43 – 3.58	
	14 weeks – 6 monthly	19 (19)	18 (54)	1.18	0.64 – 2.17	0.928
	> 6 monthly	10 (10)	8 (25)	1.16	0.53 – 2.56	
Duration since last anthelmintic administered	> 12 weeks	18 (16)	14 (37)	Ref.		
	7 – 12 weeks	27 (24)	32 (85)	0.82	0.39 – 1.72	
	4 – 6 weeks	23 (20)	23 (61)	0.94	0.43 – 2.06	0.914

	1 - 3 weeks	23 (20)	23 (61)	0.71	0.33 – 1.52	
	< 1 week	9 (8)	9 (23)	0.82	0.28 – 2.41	
Anthelmintic administration in previous 7 days	No	90 (79)	86 (230)	Ref.		
	Yes	10 (9)	14 (37)	0.58	0.25 – 1.36	0.197
Anthelmintic administration in previous 14 days	No	78 (69)	78 (205)	Ref.		
	Yes	22 (19)	23 (62)	0.74	0.40 – 1.37	0.336
Anthelmintic administration in previous 28 days	No	61 (54)	61 (164)	Ref.		
	Yes	39 (34)	39 (103)	0.89	0.54 – 1.49	0.666
Last anthelmintic product administered	Benzimidazole	13 (10)	10 (25)	Ref.		
	Ivermectin	25 (20)	20 (50)	0.83	0.31 – 2.21	
	Moxidectin / doramectin	24 (18)	31 (76)	0.52	0.20 – 1.36	
	Pyrantel	16 (13)	21 (51)	0.59	0.22 – 1.58	0.503
	Praziquantel	2 (2)	4 (10)	0.59	0.11 – 3.25	
	Praziquantel + avermectin	19(15)	13 (33)	1.10	0.41 – 2.94	
Penultimate worming product	Benzimidazole	17 (10)	10 (21)	Ref.		
	Ivermectin	21 (12)	20 (52)	0.55	0.18 – 1.68	
	Moxidectin / doramectin	17 (10)	25 (55)	0.49	0.17 – 1.42	
	Pyrantel	26 (15)	26 (55)	0.72	0.26 – 1.99	0.816
	Praziquantel	3 (2)	4 (8)	0.78	0.12 – 4.96	
	Praziquantel + avermectin	16(9)	14 (29)	0.80	0.24 – 2.67	
Treated for tapeworms in previous 12 months	Yes	70(58)	79 (205)	Ref.		
	No	30 (25)	21 (55)	1.79	0.96 – 3.34	0.071

Other horses sharing pasture wormed	Yes	96 (77)	97(238)	Ref.		
	No	4 (3)	3(7)	2.80	0.56 – 13.96	0.217
Horses wormed at same time	Yes	88 (79)	86 (238)	Ref.		
	No	12 (11)	14 (39)	0.90	0.43 – 1.88	0.782
New horses on pasture	No	86 (81)	86 (229)	Ref.		
	Yes	14 (13)	14 (38)	0.88	0.44 – 1.78	0.725
Are specific measures taken to reduce the nos. of parasites on the pasture?	Yes	82 (80)	84 (243)	Ref.		
	No	18 (18)	16 (47)	1.21	0.64 – 2.29	0.548
Worm egg count or tapeworm ELISA performed within last 12 months	No	84 (89)	85 (248)	Ref.		
	Yes	16 (17)	15 (44)	1.12	0.59 – 2.12	0.729
Faecal worm egg count	0 – 24 eggs/gram	83 (45)	68 (83)	Ref.		
	25 – 200 eggs / gram	9 (5)	15 (18)	0.57	0.16 – 2.09	0.321
	>200 eggs / gram	7 (4)	17 (21)	0.44	0.13 – 1.48	

Table 2. Univariable conditional logistic regression analyses of categorised continuous horse- and management-level variables and their relationship with the risk of developing epiploic foramen entrapment (EFE).

Variable		Case % (n)	Control % (n)	Odds Ratio	95% CI	P-value
General horse & management details						
Age (years)	< 5	9 (10)	16 (51)	Ref.		
	5 – 7	22 (24)	22 (67)	1.91	0.84 – 4.32	
	8 – 10	23 (25)	22 (69)	1.87	0.79 – 4.42	0.389
	11 – 13	17 (18)	16 (50)	1.97	0.82 – 4.71	
	> 13	29 (31)	24 (73)	2.22	0.97 – 5.11	
Height (cm)	< 151	11 (12)	19 (59)	Ref.		
	152 – 159	7 (8)	19 (58)	0.71	0.27 – 1.86	
	160 – 162	17 (19)	17 (54)	1.67	0.76 – 3.66	0.003
	163 – 168	32 (35)	18 (57)	2.84	1.30 – 6.21	
	> 168	32 (35)	26 (82)	1.98	0.95 – 4.12	
Weight (kg)	< 300	2 (2)	3 (10)	Ref.		
	300 - 449	10 (11)	17 (54)	1.02	0.20 – 5.25	
	450 - 599	55 (60)	57 (177)	1.66	0.36 – 7.66	0.059
	>599	33 (36)	22 (69)	2.68	0.56 – 12.97	
Premises						
No. of horses on premises	1 - 5	25 (27)	28 (87)	Ref.		
	6 - 10	19 (21)	18 (56)	1.11	0.56 – 2.19	
	11 - 20	23 (25)	18 (56)	1.39	0.74 – 2.62	0.683
	>20	32 (35)	36 (111)	0.99	0.54 – 1.84	
Housing and grazing						
Hours stabled per week	0 – 76	12 (13)	22 (69)	Ref.		
	77 – 111	14 (15)	22 (67)	1.42	0.61 – 3.29	

	112 – 136	26 (27)	18 (56)	3.53	1.53 – 8.12	0.006
	137 – 160	23 (24)	19 (58)	2.86	1.26 – 6.47	
	161 - 168	24 (25)	19 (59)	3.25	1.40 – 7.54	
Hours grazing per week	0 – 9	25 (26)	18 (56)	Ref.		
	10 – 39	26 (27)	17 (52)	0.96	0.48 – 1.90	
	40 – 60	18 (19)	20 (62)	0.63	0.30 – 1.29	0.027
	61 – 165	16 (17)	22 (67)	0.41	0.19 – 0.89	
	166 - 168	14 (15)	23 (72)	0.38	0.17 – 0.81	
Stocking density	<0.5 acre / horse	20 (16)	24 (57)	Ref.		0.212
	0.5 – 0.9 acres / horse	35 (28)	25 (59)	1.51	0.71 – 3.21	
	1.0 – 1.9 acres / horse	21 (17)	31 (74)	0.70	0.30 – 1.65	
	2.0 acres per horse or greater	25 (20)	21 (51)	1.09	0.47 – 2.56	
Duration on current pasture	< 1 month	16 (14)	17 (42)	Ref.		
	1 – 6 months	48 (41)	49 (123)	1.23	0.58 – 2.62	
	7 – 12 months	5 (4)	13 (32)	0.50	0.14 – 1.72	0.143
	> 12 months	31 (27)	21 (52)	1.71	0.77 – 3.81	
Nutrition						
Total daily supplementary forage weight	<5kg	(11)	15 (45)	Ref.		
	5 – 7 kg	(15)	24 (41)	1.81	0.63 – 5.22	
	8 – 10 kg	(12)	24 (42)	2.25	0.70 – 7.24	0.359
	>10 kg	(20)	19 (48)	2.39	0.87 – 6.58	
Total concentrate / grain weight	0.1 – 0.5 kg	26 (14)	17 (30)	Ref.		
	0.6 – 1.0 kg	17 (9)	17 (29)	0.29	0.08 – 0.93	
	1.1 – 2.0 kg	15 (8)	28 (48)	0.27	0.07 – 0.10	0.070
	2.1 – 3.0 kg	15 (8)	18 (32)	0.39	0.08 – 1.17	
	> 3.0 kg	26 (14)	20 (34)	0.67	0.20 – 2.24	

Concentrate protein	8.0 – 10.0 %	29 (13)	52 (65)	Ref.		
	10.1 – 13.9 %	42 (19)	27 (34)	3.40	1.24 – 9.30	0.020
	14.0 % or greater	29 (13)	21 (26)	3.65	1.04 – 12.70	
Concentrate fat	2.5 – 3.9 %	21 (6)	23 (24)	Ref.		
	4.0 – 4.9 %	41 (12)	40 (42)	0.10	0.01 – 1.65	
	5.0 – 5.9 %	21 (6)	22 (23)	0.10	0.01 – 2.09	0.327
	6.0 % or greater	17 (5)	15 (16)	0.21	0.20 – 2.43	
Exercise and transport						
No. of days exercised per week	0	26 (28)	29 (90)	Ref.		
	1-2	13 (14)	12 (37)	1.15	0.55 – 2.40	
	3-4	16 (17)	21 (65)	0.87	0.44 – 1.73	0.635
	5-6	31 (34)	27 (83)	1.41	0.77 – 2.61	
	7	14 (15)	11 (35)	1.31	0.64 - 2.68	
No. of hours exercised per week	0	26 (28)	29 (90)	Ref.		
	1 – 2	18 (19)	17 (54)	1.12	0.57 – 2.19	
	3 – 4	25 (27)	21 (65)	1.31	0.71 – 2.39	0.944
	5 – 6	15 (16)	15 (47)	1.14	0.55 – 2.37	
	7	17 (18)	17 (53)	1.11	0.56 – 2.22	
No. of journeys in last 28 days	0	64 (66)	65 (198)	Ref.		
	1 – 2	13 (13)	13 (41)	1.08	0.55 – 2.13	
	3 – 6	16 (17)	13 (40)	1.40	0.74 – 2.65	0.704
	>6	7 (7)	8 (25)	0.81	0.33 – 1.99	
No. of hours being transported in previous 28 days	0	64 (66)	66 (198)	Ref.		
	1 – 2	17 (18)	16 (48)	1.16	0.63 – 2.12	0.536
	3 – 7	14 (14)	11 (33)	1.33	0.68 – 2.61	

	>7	5 (5)	8 (23)	0.58	0.19 – 1.76	

Table 3. Univariable conditional logistic regression analyses of continuous horse- and management-level variables and their relationship with the risk of developing epiploic foramen entrapment (EFE).

Variable	Unit of measurement	Mean / median	Coefficient	Standard error	P-value
Horse					
Age	years	9	0.025	0.023	0.266
Height	cm	160	0.021	0.009	0.017
Weight	kg	514	0.003	0.001	0.011
Premises					
No. horses on premises		13	-0.004	0.004	0.101
Housing and grazing					
No. of hours stabled per week	hours	113	0.007	0.003	0.001
No. of hours grazing per week	hours	52	-0.006	0.002	0.003
Stocking density	horses / acre	0.9	-0.061	0.068	0.251
Duration on current pasture	months	3.5	0.006	0.004	0.129
Nutrition					
Supplementary forage weight	kg	7.5	0.039	0.030	0.191
Total weight concentrate / grain	kg	1.3	-0.051	0.0666	0.436
Concentrate protein	%	11.4	0.265	0.118	0.017
Concentrate fat	%	4.6	-0.088	0.212	0.672
Exercise and transport					
No.of days exercised per week		3	0.054	0.043	0.208
Duration of exercise each week	hours	3.6	0.006	0.013	0.644
No. journeys in last 28 days		0	0.001	0.020	0.953
Duration of transport in last 28 days	hours	0	0.006	0.030	0.843

Standardised delta-betas were assessed for all the variables in the final multivariable model. Figure 1 shows an example of the standardised delta-beta for the variable height. Observation 170 had the largest delta-beta statistic. This was an EFE case which was a Shetland pony (height 67cm).

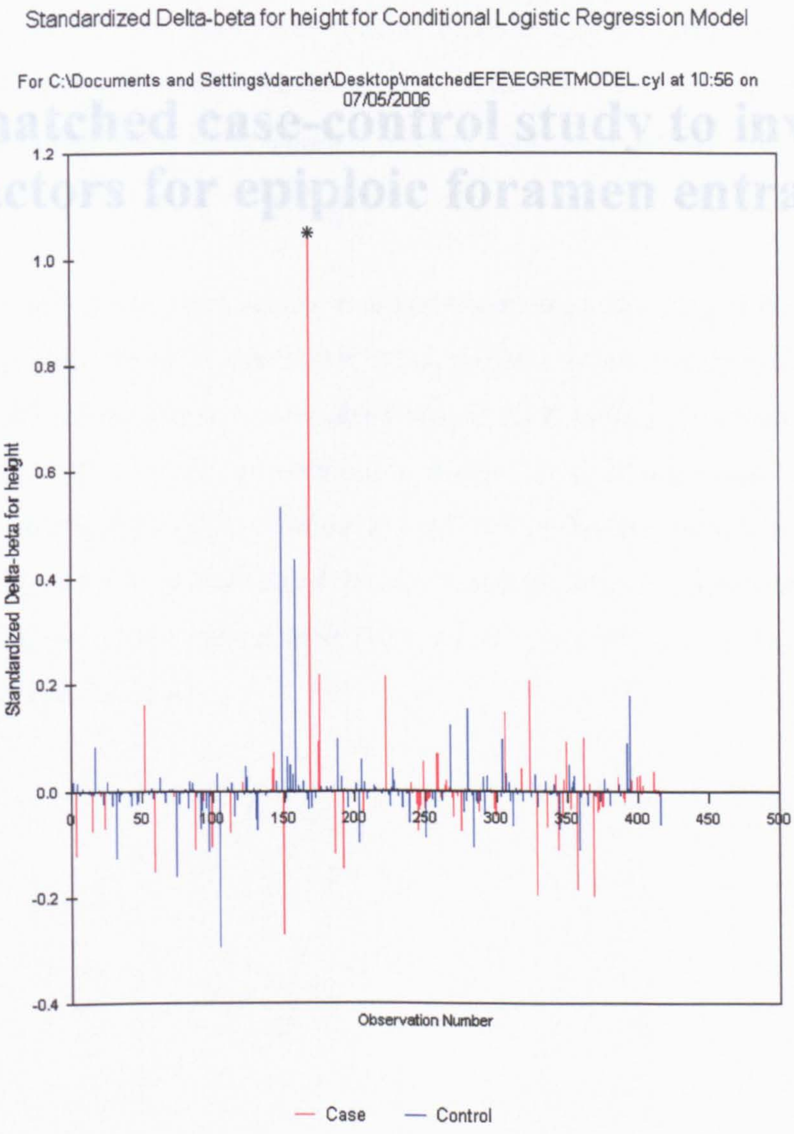


Figure 1. Standardised delta-beta for the variable height. * = Observation 170

CHAPTER 4

An unmatched case-control study to investigate risk factors for epiploic foramen entrapment

Abstract

Epiploic foramen entrapment (EFE) is one of the most common causes of small intestinal strangulation in the horse but little is currently known about the epidemiology of this condition. The aim of this study was to identify horse- and management-level risk factors for EFE using a population of healthy horses as controls.

An unmatched case-control study was conducted over a 24 month period in the UK. Data on 77 cases and 216 control horses were obtained and logistic regression was used to identify associations between a number of horse and management variables and the risk of EFE.

Crib-biting or windsucking behaviour was associated with the largest increase in risk of EFE in the final multivariable model (OR 71.6, 95%CI 14.3 – 359.2). Other factors that were significantly associated with increased risk of EFE included: a history of colic in the previous 12 months, increased stabling in the previous 28 days and horses of greater height. Horses that had access to a mineral / salt lick, those perceived to be easily frightened, horses who were not fed at the same time as others in the same group / part of the yard and those who went off their feed in full / part when perceived to be stressed were at reduced risk of EFE.

Introduction

Epiploic foramen entrapment (EFE) is one of the most common causes of small intestinal strangulation in the horse. Whilst EFE represents a relatively small proportion of colic cases occurring within the general population, it accounts for 5-23% of all strangulating lesions of the small intestine, is the second most prevalent type of small intestinal strangulating lesion in some hospital populations and represents 2–8% of horses with colic that undergo surgery (Freeman 2005).

Epidemiological studies investigating colic have identified a number of horse- and management-level factors that place horses at increased or decreased risk of colic. Knowledge of risk factors for EFE may assist early identification of these cases, which is reported to be important for improved post-operative survival (Proudman *et al.* 2005). Surgical correction carries risks of post-operative morbidity and mortality making identification of high-risk horses and prevention of this type of colic highly desirable.

To date, few studies have investigated the epidemiology of EFE. Previous suggestions that increasing age was a risk factor for EFE have recently been refuted (Freeman and Schaeffer 2001). Crib-biting or windsucking behaviour has been identified as a risk factor for EFE in two hospital populations (Archer *et al.* 2004a). In the Illinois (USA) population, horses exhibiting this behaviour were 35 times more likely to have EFE compared to other small intestinal strangulating lesions. In the Liverpool (UK) population, crib-biting / windsucking horses were 8 times more likely to have EFE compared to other types of surgical colic. In the latter population, breed and the months of December, January and February were also found to be significantly associated with increased risk of EFE (Archer *et al.* 2004b). Time-series analysis has confirmed a seasonal pattern to cases of EFE in a UK hospital population (Archer *et al.* 2006). Twelve- and six-month cyclical patterns were identified consistently over a 10 year period with cases of EFE peaking over the winter months, consistent with the findings of Archer *et al.* (2004b).

Studies that have investigated the epidemiology of EFE to date have used other colic cases as a comparison, which introduces selection bias, and have not explored other horse- or management-level risk factors for this condition. The aim of this study was to identify horse- and management-level risk factors for EFE using a population of healthy horses as controls.

An unmatched case-control study design was used to explore the apparent seasonality of this condition. The *a priori* hypotheses were that horses exhibiting certain behaviours and those exposed to particular management practices that vary during different times of the year e.g. stabling and turnout practices and quantity of feed would be at increased risk of EFE.

Materials and methods

Study Design

A multi-centre, unmatched case-control study was conducted to identify associations between horse- and management-level variables and EFE (outcome variable). Nine equine clinics located in the UK participated in the study. These clinics were selected based on colic caseload, surgeons experienced in the diagnosis and treatment of surgical colic, geographical location and willingness to participate in the study. Data from cases and controls were collected over a 24 month period between 1st May 2004 - 30th April 2006.

Sample size estimation was performed using Win Episcope 2.0 (www.clive.ed.ac.uk/winepiscope). For crib-biting / windsucking as the exposure of interest (OR for association with EFE = 8, Archer *et al.* 2004b) a study with 62 cases and 3 controls per case, assuming 2% exposure in controls, has greater than 90% power to detect odds ratios of 8 or higher with 95% confidence. If an exposure of interest has 10% exposure in controls, a study with 61 cases and 3 controls per case would have 80% power to detect odds ratios of 3.0 or greater with 95% confidence. Based on retrospective data obtained from the collaborating clinics, it was estimated that 72 cases of EFE would be recruited over the 2 year period. To ensure that cases and controls were unmatched on time, 9 controls were recruited during each of the 24 months of the study.

Case definition

Cases of EFE diagnosed at laparotomy or post-mortem examination at any of the collaborating clinics during the 24 months under investigation were recruited onto the study. Recruitment of cases from clinicians experienced in the diagnosis and treatment of surgical colic avoided problems associated with potential case misclassification. The owner or carer of the horse was informed about the study and asked if they were willing to participate. Once owner / carer consent had been obtained, telephone contact was made with the client to arrange a convenient time to conduct the questionnaire as soon as possible after surgery (depending on individual clinic requests and client wishes).

Control definition and selection

Controls were randomly selected from the list of clients seen at each of the collaborating clinics in the previous calendar year. Because the caseloads varied between clinics, to ensure that selection of controls was proportional to number of clients seen at each clinic, the client lists were pooled together and treated as a single population. The study population was therefore all horses owned / cared by clients seen in the previous 12 months at the 9 collaborating clinics. Random numbers were generated and a client was selected at random from this potential control population. The majority of controls were contacted initially by post followed by a telephone call to ask if they would be willing to participate in the study. Some clinics preferred to contact these clients directly to obtain consent prior to telephone contact by the principal investigator. To maximise client compliance, owners were informed that this study was investigating colic in the horse and that we wished to collect general information about horses and their daily care. Owners were unaware of the hypotheses being tested. At initial contact a 'horse' (defined as a horse or pony) in the care of the client of was randomly selected. The horse had to fulfil the following inclusion criteria: i) it must not have suffered from colic in the previous 4 weeks and ii) surgery for colic would be undertaken on this horse if deemed necessary. The latter criteria was taken to avoid selection bias i.e. the controls would potentially have been eligible to become cases. If the selected horse did not fulfil these criteria, another horse was selected or if none fulfilled the criteria, a new control client was selected (Hillyer *et al.* 2002).

Questionnaire design

The questionnaire was constructed using information from previous epidemiological studies investigating colic and other hypotheses considered to be biologically plausible as risk factors for EFE. These included signalment, a previous episode of colic, carer, whether horses were stabled or had access to pasture, the amount and types of feed that they were currently receiving and if they exhibited stereotypic behaviour (Archer and Proudman 2006). In particular, we wished to explore management-level factors that may vary on a seasonal basis e.g. hours stabled or spent at pasture per week, feed types and quantities, hours exercised per week and recent (i.e. within 28 days) changes in feeding, stabling and exercise routines. Questions were grouped into the following categories: signalment and use, medical history, general premises details, stabling and turnout, nutrition, exercise and transport, behaviour and preventive healthcare.

Data collection

The questionnaire was conducted over the telephone by the principal investigator. Data were entered onto a data-capture form and an Access database was created using a data entry scanner (Fujitsu fi-4120C2) and software (TeleForm v9, Verity Inc.). Scanned data were verified using the software programme to identify values out-with pre-defined ranges and confirm the correct entry in instances where there were multiple instead of single data entries in tick boxes before committing the scanned data into the database.

Sample collection and analysis

Faecal samples were collected from the cases during hospitalisation. The owners / carers were asked to collect a faecal sample from the selected control horse within 4 weeks after the questionnaire had been administered and prior to the next administration of an anthelmintic. To maximise compliance, owners were offered the results of the faecal worm egg count free of charge and were provided with sample pots and pre-paid envelopes for sample return. A faecal egg count test was performed using the McMaster's method.

Statistical Analysis

Screening of all variables was performed using a univariable logistic regression model with EFE as the dependent variable. The statistical package Stata (Stata Corp. LP) was used for data analysis. Categorical variables with small numbers of observations in one or more categories, or where the reference category contained relatively few individuals, were re-coded to create fewer categories or to create a different reference category. Continuous variables were examined in their continuous state and were categorised into quintiles, quartiles or other biologically plausible categories. The functional form of the relationships between the continuous explanatory variables and binary outcome (EFE) were explored using generalised additive models (GAM). These are an extension of generalised linear models where variables are included additively via the link function and are not assumed to take a linear form, replacing the usual linear function of a covariate with a cubic spline smoothing function (Hastie and Tibshirani 1990). The GAM models were fitted in the statistical package S-plus (Insightful Corp.). If the relationship between the continuous variables and outcome was considered to be significantly non-linear, other polynomial relationships were explored to see if they significantly improved the fit of the model. To reduce the effects of collinearity, continuous variables were centred by subtracting the mean of the variable from all recorded observations (Kleinbaum *et al.* 1988) prior to producing higher order terms.

Variables with a univariable P-value <0.2 were considered for subsequent inclusion in a multivariable model. Variables with >20% of missing values were excluded from the initial model-building procedure. To avoid problems associated with collinearity, where variables were considered to be measuring the same exposure or were shown to be highly correlated (Pearson correlation coefficient >0.9), the most statistically significant or biologically plausible variable was selected.

The model was built using a backwards stepwise approach where variables were retained in the model if their manual exclusion resulted in a likelihood ratio test statistic (LRTS) of P<0.05. A change in the coefficient of >25% was considered to be indicative of confounding. Four submodels were initially created: signalment and medical history, behaviour, nutrition and other management factors. The variables identified in each of these models were pooled and used to develop the final effects model (Reeves 1996). All the remaining variables considered for inclusion were then forced back into the model to ensure that no significant or confounding variables had been excluded. Variables with >20% missing values were also re-tested in the model at this stage. The effect of biologically plausible interaction terms was tested in the model. The fit of the model was assessed using the Hosmer-Lemeshow test statistic (Hosmer and Lemeshow 2000) and model stability was assessed by examination of the standardised delta-betas for all of the variables in the final model using the computer programme Egret (Cytel Software Corp.). The model was considered to be stable if removal of individual cases or controls altered the odds ratio by <25% and did not affect the significance of individual variables. The predictive ability of the model was assessed by computing the sensitivity and specificity of the model at various cut-off points and by generating a receiver operating characteristic (ROC) curve.

Population attributable fraction

Assuming a causal relationship, the population attributable fraction (AF_p) indicates the proportion of disease in the whole population that is attributable to the exposure and would be avoided if the exposure were removed from the population (Dohoo *et al.* 2003). It has variously been termed the population attributable proportion, population aetiological fraction, aetiological fraction, attributable fraction, attributable risk, attributable risk percent and population attributable risk (Thrusfield 2005). This is a function of the strength of the association and the prevalence of exposure and can be estimated from unmatched data in a case-control study using the equation:

$$AF_p = AF_e [a_1 / m_1]$$

Where $AF_e \approx (OR - 1) / OR$

a_1 = number of cases in the exposed group
m_1 = total number of cases

Continuous variables were converted to categorical variables and all categorical variables were ordered by ascending odds ratios. The model was re-run to obtain adjusted odds ratios which were then used to calculate the AF_p's for all the potentially modifiable variables in the final model.

Results

Descriptive statistics and univariable analysis

During the 24 month study period a total of 81 cases of EFE were identified and 77 of these were recruited onto the study; 2 were not recruited at the request of the collaborating clinic, notification of 1 case occurred too late for collected data to be considered valid and 1 owner was unable to be contacted. A total of 216 control owners were selected at random and recruited onto the study. The questionnaires took a mean of 23 minutes to complete (range 12 - 49 minutes) and faecal samples were obtained from 49 % of the control horses and 65% of the cases.

Cases were identified throughout the 24 month recruitment period with the greatest number (17 % of all cases) identified in the month of January (Figure 1). Month of the year and season were not significant overall in the univariable analysis

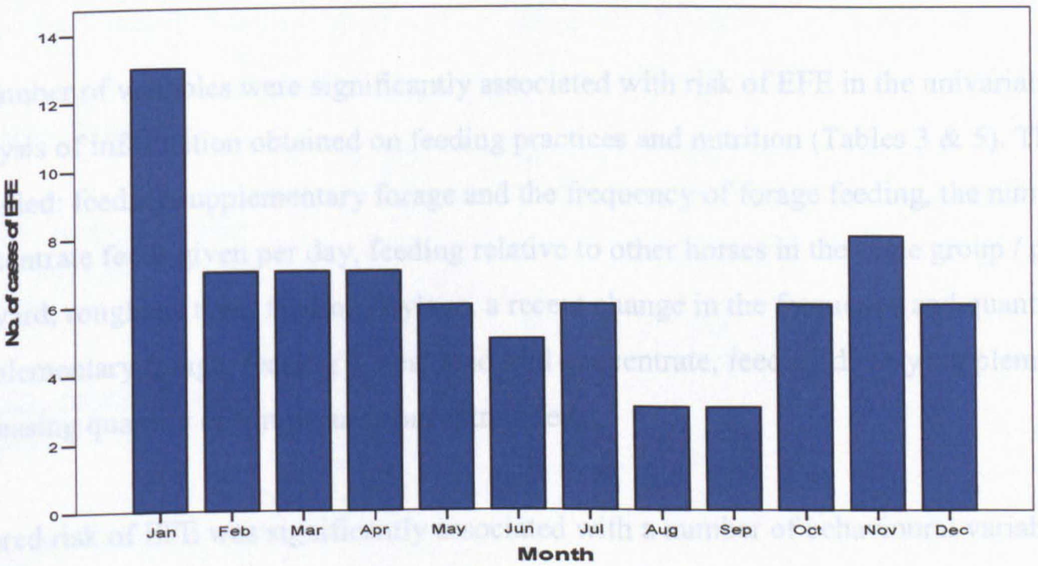


Figure 1. Seasonal distribution of the 77 cases of epiploic foramen entrapment (EFE) recruited onto the study from 9 collaborating clinics in the U.K. over a 24 month duration (May 2004 – April 2006).

Univariable analysis of signalment and medical history (Table 1) revealed significant associations between gender, dental / gastrointestinal problems or a history of colic in the previous 12 months and risk of EFE. Increasing height and weight were shown to be significantly associated with an increased risk of EFE in univariable analysis of continuous variables (Table 5). Age was not significantly associated with risk of EFE (P=0.24).

Examination of GAM plots for the variables height and weight (Figure 2) indicated that a linear fit was appropriate and both variables were found to fit the model best in a linear form. These variables were highly correlated (Pearson correlation coefficient >0.8) and so height was chosen for inclusion into the model as it was considered that these data were more accurate.

A number of management-level variables were significantly associated with EFE in the univariable analysis of information obtained on premises, stabling, pasture turnout and exercise (Table 2). These variables included carer, current management, current access to pasture and current stabling, increased stabling in the previous 28 days and exercise location. Univariable analysis of continuous variables revealed a significantly increased risk of EFE with increasing hours stabled per week and significantly decreased risk of EFE with increasing number of hours turned out at pasture per week (Table 5). GAM plots of these variables are shown in Figure 2 and both variables were found to fit the model best in a linear form.

A number of variables were significantly associated with risk of EFE in the univariable analysis of information obtained on feeding practices and nutrition (Tables 3 & 5). These included: feeding supplementary forage and the frequency of forage feeding, the number of concentrate feeds given per day, feeding relative to other horses in the same group / part of the yard, roughage type, feeding haylage, a recent change in the frequency and quantity of supplementary forage, feeding a local feed mill concentrate, feeding dietary supplements, increasing quantity of forage and concentrate fed.

Altered risk of EFE was significantly associated with a number of behavioural variables (Table 4). These included response to a frightening stimulus and feeding behaviour when stressed (e.g. competing or moving premises). Horses exhibiting stereotypic behaviour were at increased risk of EFE and crib-biting or windsucking behaviour was significantly associated with increased risk of EFE. Other forms of stereotypic behaviour including woodchewing, weaving and box-walking were not significantly associated with EFE

Table 1. Results of univariable logistic regression analysis of categorical variables with P-value <0.2 obtained from information on signalment and medical history.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Breed					
TB	23 (18)	20 (42)	Ref.		
TBx	22 (17)	21 (45)	0.88	0.40 – 1.93	
WB / WBx	22 (17)	11 (24)	1.65	0.72 – 3.79	0.050
Pony / miniature horse	8 (6)	14 (30)	0.47	0.16 – 1.31	
Cob / Cob x	4 (3)	12 (25)	0.28	0.07 – 1.05	
Other horse	21 (16)	23 (49)	0.76	0.35 – 1.68	
Gender					
Male	75 (58)	58 (126)	Ref.		
Female	25 (19)	42 (90)	0.46	0.26 – 0.82	0.007
Principal use					
Pleasure	42 (32)	42 (91)	Ref.		
Competition (local / regional)	19 (15)	14 (31)	1.38	0.66 – 2.87	
Competition (national / international)	12 (9)	13 (29)	0.88	0.38 – 2.06	
Working horse	6 (5)	4(8)	1.78	0.54 – 5.83	0.122
Pet / retired	3 (2)	9 (20)	0.28	0.06 – 1.29	
Broodmare / breeding stallion	10 (8)	5 (10)	2.27	0.83 – 6.27	
Unbroken / recently broken / injured	8 (6)	13 (27)	0.63	0.24 – 1.67	
Orthopaedic problem in previous 12 months					
No	76 (55)	65 (136)	Ref.		
Yes	24 (17)	35 (73)	0.57	0.31 – 1.06	0.071
Dental / gastrointestinal problems in previous 12 months					
No	77 (55)	91 (188)	Ref.		
Yes	23 (16)	9 (19)	2.88	1.39 – 5.97	0.005
NSAIDs administered in previous 28 days					
No	92 (59)	83 (121)	Ref.		
Yes	8 (5)	17 (24)	0.43	0.15 – 1.18	0.078
Colic episode in previous 12 months					
No	75 (53)	94 (196)	Ref.		
Yes	25 (18)	6 (13)	5.12	2.35 – 11.12	<0.0001

Table 2. Results of univariable logistic regression analysis of categorical variables with P-value <0.2 obtained from information on premises, carer, stabling, pasture turnout and exercise.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Premises type					
Private yard	48 (37)	56 (121)	Ref.		
Working / competition yard /	19 (15)	10 (21)	2.34	1.09 – 4.98	
Livery yard	31 (24)	31 (66)	1.19	0.66 – 2.16	0.114
Stud farm	1 (1)	4 (8)	0.41	0.05 – 3.38	
Carer					
Owners(s) / relative or spouse involved in daily care	53 (41)	77 (166)	Ref.		
Owner / relative / spouse not involved in daily care	47 (36)	23 (49)	2.97	1.72 – 5.15	0.0001
Current management					
Stabled with 2 / >2hrs turnout every day	54 (40)	54 (115)	Ref.		
Stabled all the time / stabled apart from when exercised	19 (14)	7 (15)	2.68	1.19 – 6.05	
Stabled with <2h turnout daily / irregular turnout	13.5 (10)	10 (22)	1.30	0.57 – 3.00	0.005
Not stabled – turned out all the time	13.5 (10)	29 (61)	0.47	0.22 – 1.00	
Current stabling					
No	14 (10)	29 (61)	Ref.		
Yes	86 (64)	71 (152)	2.57	1.24 – 5.33	0.007
Access to straw bedding					
No	70 (53)	79 (170)	Ref.		
Yes	30 (23)	21 (45)	1.64	0.91 – 2.96	0.105
Current access to pasture					
No	17 (13)	7 (16)	Ref.		
Yes	83 (64)	93 (199)	0.40	0.18 – 0.87	0.023
Increased stabling within the previous 28 days					
No	69 (51)	83 (171)	Ref.		
Yes	31 (23)	17 (36)	2.14	1.16 – 3.94	0.016
Increased stabling within the previous 14 days					
No	80 (55)	88 (178)	Ref.		
Yes	20 (14)	12 (25)	1.81	0.88 – 3.73	0.113
Increased stabling within the previous 7 days					
No	84 (58)	91 (185)	Ref.		
Yes	16 (11)	9 (18)	1.95	0.87 – 4.36	0.113
Increased pasture turnout in the previous 28 days					
No	97 (72)	91 (189)	Ref.		
Yes	3 (2)	9 (18)	0.29	0.07 – 1.29	0.059
Location of exercise					
Not applicable	19.5 (15)	23 (49)	Ref.		
Arena / school only	19.5 (15)	7 (15)	3.27	1.30 – 8.20	0.014
Other	61 (47)	70 (150)	1.02	0.53 – 1.99	

Table 3. Results of univariable logistic regression analysis of categorical variables with P-value <0.2 obtained from information on feeding practices and nutrition.

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Feeding of hay / haylage						
	No	8 (6)	21 (45)	Ref.		
	Yes	92 (70)	79 (171)	3.07	1.25 – 7.52	0.006
Supplementary forage feeding						
	None	8 (6)	21 (45)	Ref.		
	Once daily	21 (16)	28 (61)	1.97	0.71 – 5.42	
	Twice daily	37 (28)	31 (68)	3.10	1.18 – 8.06	0.006
	Three - four times daily	21 (16)	15 (32)	3.75	1.32 – 10.63	
	Ad libitum	13 (10)	5 (10)	7.50	2.21 – 25.46	
Concentrate currently fed						
	No	5 (4)	12 (26)	Ref.		
	Yes	95 (72)	88 (187)	2.50	0.84 – 7.42	0.070
Concentrate feeding						
	None	5 (4)	12 (26)	Ref.		
	Once daily	12 (9)	25 (54)	1.08	0.30 – 3.85	0.006
	Twice daily	66 (50)	53 (112)	2.90	0.96 – 8.75	
	Three times daily or more	17 (13)	9 (21)	4.02	1.14 – 14.18	
Fed at same time and frequency as horses in group / yard						
	Yes	87 (61)	67 (124)	Ref.		
	No	13 (9)	33 (62)	0.29	0.14 – 0.63	0.0006
Fed at the same time (to within an hour) every day of the week						
	Never varies	71 (51)	55 (103)	Ref.		
	Occasionally varies	11 (8)	11 (21)	0.77	0.32 – 1.86	0.032
	Regularly varies	18 (13)	34 (63)	0.42	0.21 – 0.83	
Roughage type						
	Grass only	8 (6)	21 (44)	Ref.		
	Hay	37 (28)	46 (97)	2.12	0.82 – 5.48	
	Haylage	47 (36)	27 (58)	4.55	1.76 – 11.76	0.003
	Hay & haylage	8 (6)	7 (14)	3.14	0.87 – 11.32	
Currently fed haylage						
	No	45 (35)	67 (144)	Ref.		
	Yes	55 (42)	33 (72)	2.40	1.41 – 4.08	0.001
Change in frequency of forage feeding in previous 28 days:						
	No	88 (61)	74 (131)	Ref.		
	Yes	12 (8)	26 (45)	0.38	0.17 – 0.86	0.012
Change in frequency of forage feeding in previous 14 days						
	No	97 (63)	86 (135)	Ref.		
	Yes	3 (2)	13 (21)	0.20	0.05 – 0.90	0.011
Change in frequency of forage feeding in previous 7 days						
	No	98 (64)	92 (144)	Ref.		
	Yes	2 (1)	8 (12)	0.18	0.02 – 1.47	0.047
Change in quantity of forage fed in previous 28 days						
	No	82 (55)	64 (113)	Ref.		

	Yes	18 (12)	36 (64)	0.38	0.19 – 0.77	0.004
Change in quantity of forage fed in previous 14 days						
	No	95 (58)	81 (124)	Ref.		
	Yes	5 (3)	19 (29)	0.22	0.06 – 0.76	0.004
Change in quantity of forage fed in previous 7 days						
	No	97 (59)	90 (138)	Ref.		
	Yes	3 (2)	10 (15)	0.31	0.07 – 1.41	0.085
Change in type of roughage fed in previous 14 days						
	No	99 (67)	94 (166)	Ref.		
	Yes	1 (1)	6 (10)	0.25	0.03 – 1.97	0.116
Local feed mill concentrate fed						
	No	72 (49)	88 (172)	Ref.		
	Yes	28 (19)	12 (24)	2.78	1.41 – 5.49	0.004
Sugar beet pulp fed						
	No	62 (45)	73 (157)	Ref.		
	Yes	38 (28)	27 (57)	1.71	0.98 – 3.00	0.062
Change in frequency concentrate previous 14 days						
	No	97 (65)	93 (170)	Ref.		
	Yes	3 (2)	7 (13)	0.40	0.09 – 1.83	0.194
Change in quantity of concentrate last 28 days						
	No	81 (54)	70 (133)	Ref.		
	Yes	19 (13)	30 (56)	0.57	0.29 – 1.13	0.097
Change in quantity of concentrate last 14 days						
	No	92 (56)	85 (149)	Ref.		
	Yes	8 (5)	15 (26)	0.51	0.19 – 1.40	0.166
Supplements fed						
	No	21 (16)	11 (24)	Ref.		
	Yes	79 (60)	89 (192)	0.47	0.23 – 0.94	0.037
Garlic / herbal supplement fed						
	No	78 (59)	66 (143)	Ref.		
	Yes	22 (17)	39 (73)	0.56	0.31 – 1.03	0.058
Salt / mineral lick or supplement fed						
	No	75 (57)	65 (140)	Ref.		
	Yes	25 (19)	35 (76)	0.61	0.34 – 1.10	0.098

Table 4. Results of univariable logistic regression analysis of categorical variables with a P-value <0.2 obtained from information on behaviour.

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Easily frightened						
	No	83 (64)	62 (134)	Ref.		
	Yes	17 (13)	38 (81)	0.34	0.17 – 0.65	0.0005
Settle after fright						
	Instantly	71 (55)	54 (117)	Ref.		
	Few minutes / longer than few minutes	29 (22)	46 (99)	0.47	0.27 – 0.83	0.007
Tremble / shake when frightened						
	No	92 (71)	76 (162)	Ref.		
	Yes	8 (6)	24 (52)	0.26	0.11 – 0.64	0.0008
Reaction to surroundings						
	Will watch / Not interested	55 (42)	45 (97)	Ref.		
	Very inquisitive	45 (35)	55 (119)	0.68	0.40 – 1.15	0.146
Behaviour at feed time						
	Interested	74 (57)	82 (175)	Ref.		
	Agitated	26 (20)	18 (39)	1.58	0.85 – 2.92	0.155
Feeding when stressed						
	Eats normally	96 (73)	85 (175)	Ref.		
	Goes off food in full / part	4 (3)	15 (31)	0.23	0.07 – 0.78	0.005
Direct physical contact with other horses						
	Regular	78 (59)	86 (184)	Ref.		
	None / occasional	22 (17)	14 (31)	1.71	0.88 – 3.31	0.118
Stereotypic behaviour						
	No	42 (32)	84 (182)	Ref.		
	Yes	60 (45)	16 (34)	7.53	4.20 – 13.5	<0.0001
Crib-biting / windsucking						
	No	52 (40)	98 (211)	Ref.		
	Yes	48 (37)	2 (4)	48.8	16.5 – 144.5	<0.0001
Weaving						
	No	90 (69)	95 (205)	Ref.		
	Yes	10 (8)	5 (10)	2.38	0.90 – 6.26	0.088
Box walking						
	No	97 (75)	93 (201)	Ref.		
	Yes	3 (2)	7 (14)	0.38	0.08 – 1.72	0.164

Table 5. Continuous variables with a P-value of <0.2 in the univariate analysis of potential horse- and management-risk factors for epiploic foramen entrapment.

Variable	*Unit of measurement*	*Mean / median*	*Coefficient*	*Standard Error*	**P-value**
Horse					
Height	cm	156	0.0490	0.0134	<0.0001
Weight	kg	502	0.0063	0.0015	<0.0001
Housing and grazing					
No. of hours stabled per week	hours	108	0.0099	0.0026	<0.0001
No. of hours grazing per week	hours	56	-0.0095	0.0025	<0.0001
Nutrition					
Supplementary forage weight	kg	5.44	0.1065	0.0280	0.0001
Total weight concentrate / grain	kg	0.42	0.1543	0.0076	0.047

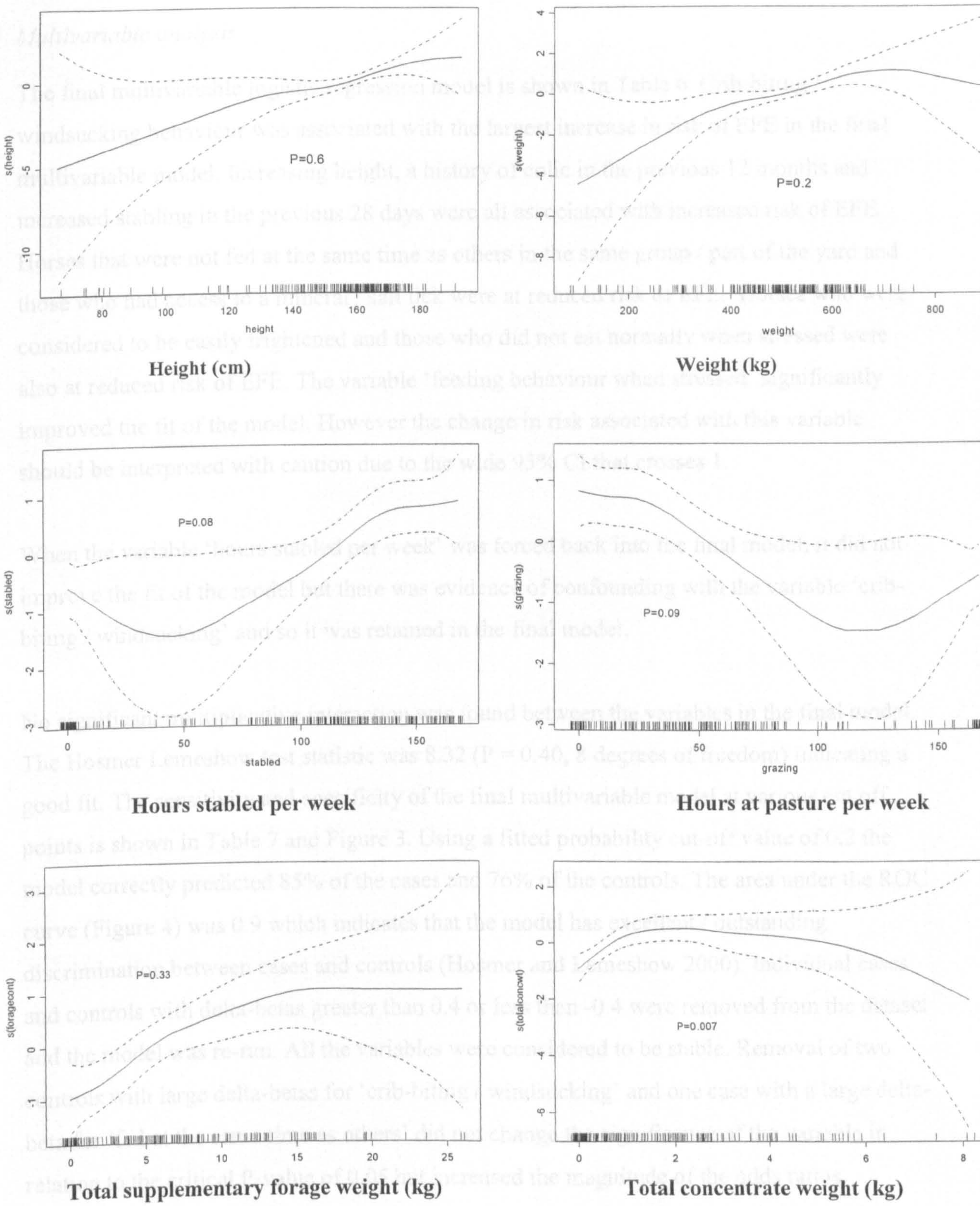


Figure 2. Use of Generalised Additive Models to demonstrate the functional form of the relationship between the predictor variable and the outcome (log odds of EFE). The plots show the fitted curves with 95% confidence intervals (dashed lines) and the rug plots along the x-axis represent the number of data points. The P-value is a chi-square test for non-linearity.

Multivariable analysis

The final multivariable logistic regression model is shown in Table 6. Crib-biting / windsucking behaviour was associated with the largest increase in risk of EFE in the final multivariable model. Increasing height, a history of colic in the previous 12 months and increased stabling in the previous 28 days were all associated with increased risk of EFE. Horses that were not fed at the same time as others in the same group / part of the yard and those who had access to a mineral / salt lick were at reduced risk of EFE. Horses who were considered to be easily frightened and those who did not eat normally when stressed were also at reduced risk of EFE. The variable 'feeding behaviour when stressed' significantly improved the fit of the model. However the change in risk associated with this variable should be interpreted with caution due to the wide 95% CI that crosses 1.

When the variable 'hours stabled per week' was forced back into the final model, it did not improve the fit of the model but there was evidence of confounding with the variable 'crib-biting / windsucking' and so it was retained in the final model.

No significant multiplicative interaction was found between the variables in the final model. The Hosmer Lemeshow test statistic was 8.32 ($P = 0.40$, 8 degrees of freedom) indicating a good fit. The sensitivity and specificity of the final multivariable model at various cut off points is shown in Table 7 and Figure 3. Using a fitted probability cut-off value of 0.2 the model correctly predicted 85% of the cases and 76% of the controls. The area under the ROC curve (Figure 4) was 0.9 which indicates that the model has excellent / outstanding discrimination between cases and controls (Hosmer and Lemeshow 2000). Individual cases and controls with delta-betas greater than 0.4 or less than -0.4 were removed from the dataset and the model was re-run. All the variables were considered to be stable. Removal of two controls with large delta-betas for 'crib-biting / windsucking' and one case with a large delta-beta for 'fed at the same time as others' did not change the significance of the variable in relation to the critical P-value of 0.05 but increased the magnitude of the odds ratios. Inspection of the cases and controls with large delta-betas did not reveal any unusual covariate patterns and so these individuals were retained in the final model.

Table 6. Multivariable logistic regression model of horse- and management-level risk factors for epiploic foramen entrapment. The table shows the coefficients, standard errors, P-values, odd ratios and 95% confidence intervals (CI).

Variable		*Coefficient*	*Standard Error*	*LRS P-value*	*Adjusted Odds ratio*	*95% CI*
Crib-biting /windsucking behaviour exhibited						
	No	Ref.			1.00	
	Yes	4.27	0.82	<0.01	71.58	14.26 – 359.19
Colic in previous 12 months						
	No	Ref.			1.00	
	Yes	1.63	0.66	0.01	5.13	1.39 – 18.85
Increased stabling in the previous 28 days						
	No	Ref.			1.00	
	Yes	1.31	0.49	<0.01	3.70	1.41 – 9.70
Height (per cm increase)		0.06	0.02	<0.01	1.07	1.01 – 1.12
Hours stabled per week (per hour increase)		0.01	<0.01	0.12	1.01	0.98 – 1.01
Easily frightened						
	No	Ref.			1.00	
	Yes	-1.07	0.51	0.03	0.34	0.13 – 0.93
Access to a mineral / salt lick						
	No	Ref.			1.00	
	Yes	-1.07	0.51	0.03	0.34	0.12 – 0.93
Fed at the same time as others in the same group / part of the yard						
	Yes	Ref.			1.00	
	No	-1.40	0.59	0.01	0.25	0.07 – 0.79
Feeding behaviour when stressed						
	Eats normally	Ref.			1.00	
	Goes off food in full / part	-1.63	0.92	0.04	0.20	0.03 – 1.20

Table 7. Sensitivity and specificity of the multivariable logistic regression model at cut-off points between 0.2 – 0.8

Cut-off point	*Sensitivity (% of cases predicted)*	*Specificity (% of controls predicted)*
0.2	85	76
0.3	72	86
0.4	70	93
0.5	63	96
0.6	61	98
0.7	55	99
0.8	42	99

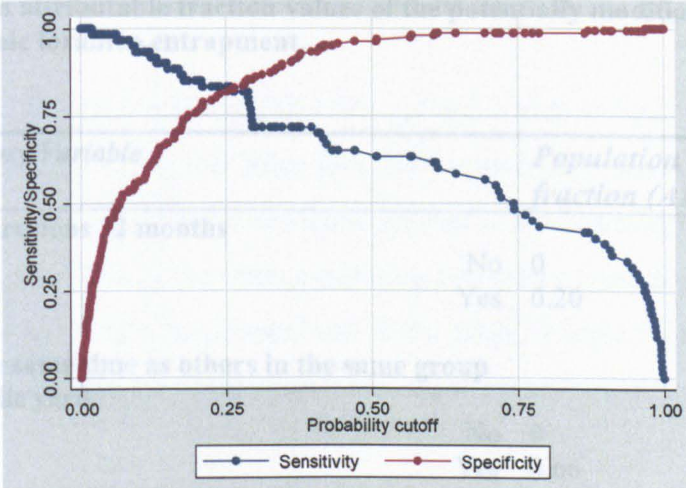


Figure 3. Graph showing the sensitivity and specificity of the multivariable logistic regression model in predicting cases of EFE and controls at various cut-off points for the fitted probability values.

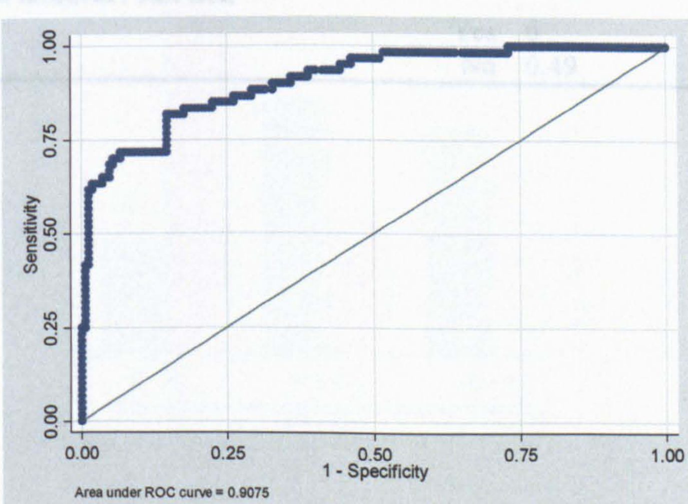


Figure 4. Receiver operating characteristic curve for the final multivariable logistic regression model.

Population attributable fraction

The population attributable fraction (AF_p) was calculated for each of the potentially modifiable explanatory variables included in the final multivariable logistic regression model. The variables 'fed at the same time as others', 'access to mineral / salt lick' and 'crib-biting / windsucking' had the largest AF_p (Table 8).

Table 8. Population attributable fraction values of the potentially modifiable explanatory variables for epiploic foramen entrapment.

Explanatory Variable		*Population attributable fraction (AF_p)*
Colic in previous 12 months		
	No	0
	Yes	0.20
Fed at the same time as others in the same group / part of the yard		
	No	0
	Yes	0.66
Crib-biting /windsucking behaviour exhibited		
	No	0
	Yes	0.47
Increased stabling in previous 28 days		
	No	0
	Yes	0.23
Access to a mineral / salt lick		
	Yes	0
	No	0.49

Crib-biting / windsucking behaviour

The prevalence of crib-biting or windsucking behaviour was 1.8 % in the control population and 48.0 % in the case population. A chi-squared test revealed a significant association between crib-biting / windsucking behaviour and an episode of colic in the previous 12 months (P=<0.001). There was a significant difference between the number of hours stabled per week (two-sample t-test, P=0.001) in horses exhibiting crib-biting / windsucking behaviour (mean 114.6 hours, standard deviation [s.d.] 54.1) compared to horses not exhibiting this behaviour (mean 83.0 , s.d. 60.6) and in the number of hours at pasture per week (P=0.001) between the two groups (crib-biting / windsucking group mean 49.2 hours, s.d. 55.8, non crib-biting / windsucking group mean 81.9 hours, s.d. 62.3).

The small numbers of horses exhibiting this form of behaviour in the control group precluded inclusion of variables describing this behaviour in a multivariable model. When the owner or carer was asked to give a subjective overall assessment of this behaviour as 'mild', 'moderate' or 'severe', 38% of the cases exhibiting crib-biting / windsucking behaviour were considered to be 'severe', 43% 'moderate' and 19% 'mild' (Figure 5). In contrast, none of the control horses exhibiting this behaviour were classified as 'severe' and most (75%) were classified as 'mild'.

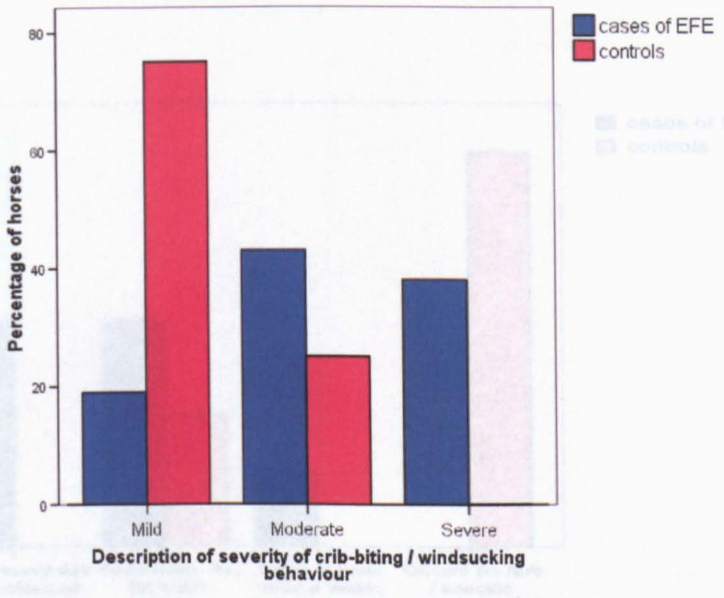
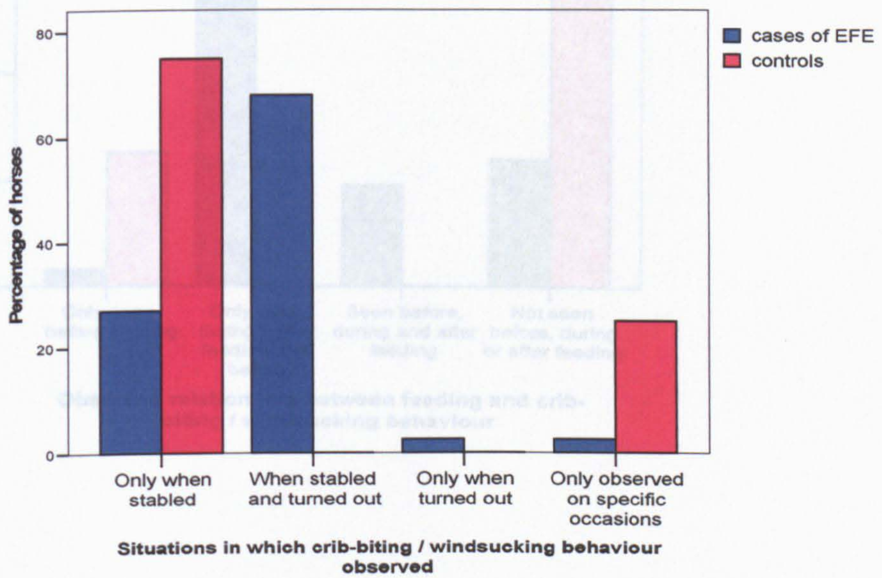


Figure 5. Subjective assessment of the severity of crib-biting / windsucking behaviour by the owner / carer of case and control horses.

More objective assessment included asking if this behaviour was exhibited when in the stable or field (or both) or during specific situations such as being tied up. Sixty-eight percent of the cases that exhibited this behaviour did so when stabled and at pasture and 27% were observed to crib-bite / windsuck only when stabled. None of the control horses that exhibited this behaviour were observed to crib-bite / windsuck when at pasture (Figure 6). Most of the EFE cases exhibiting this behaviour did so every day either for prolonged (43%) or short periods (43%) whereas most (75%) of the control horses were observed to crib-bite / windsuck on rare or specific occasions only (Figure 6).



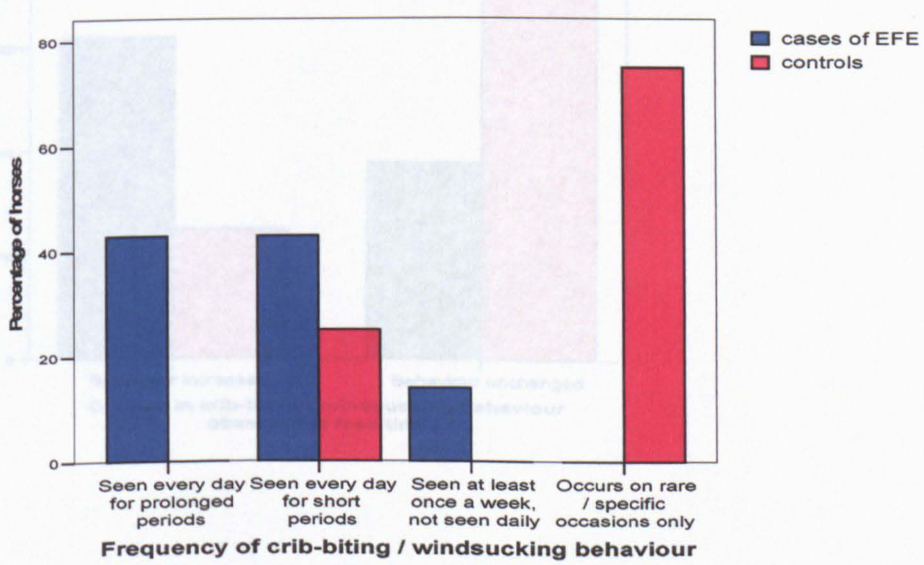
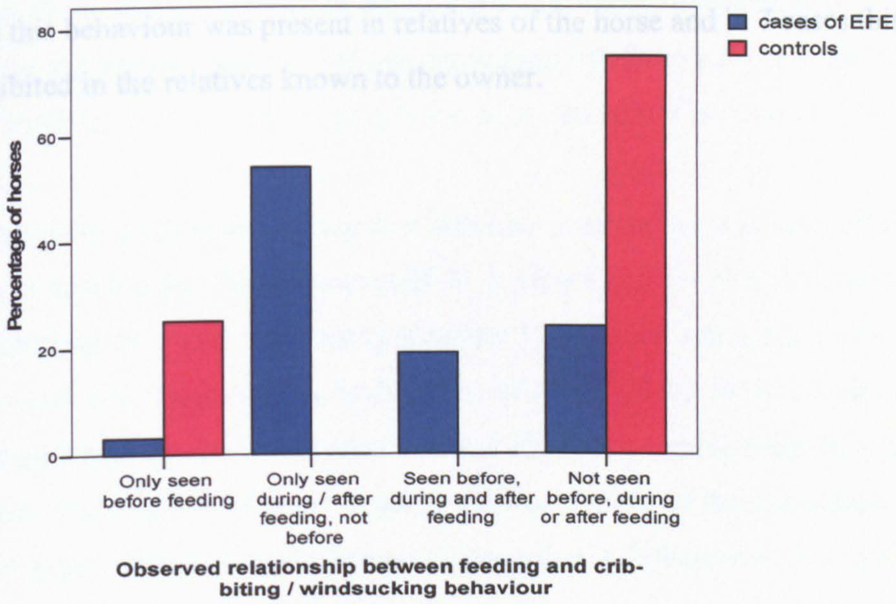


Figure 6. Description of the situations in which crib-biting / windsucking behaviour was observed and the frequency of this behaviour in case and control horses.

When asked to describe when crib-biting / windsucking occurred in relation to feeding, 73% of the cases exhibiting this behaviour did so during and after feeding and 62% were considered to exhibit this behaviour more frequently at feed times (Figure 7). In contrast, of the control horses that exhibited this behaviour, most (75%) were unchanged at feed times.



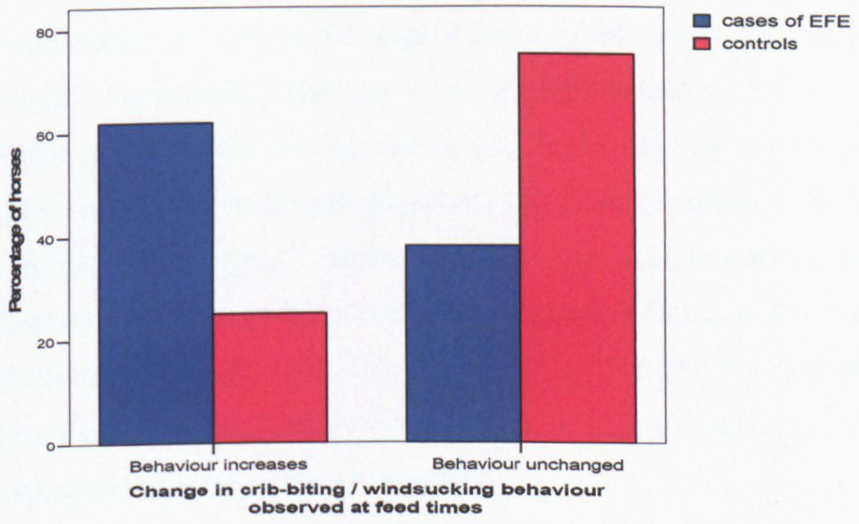


Figure 7. Relationship between feeding and crib-biting / windsucking behaviour in case and control horses.

In 62% of the cases and 100% of the controls that showed crib-biting / windsucking behaviour, measures had previously been taken to try to prevent the behaviour. These measures, which included devices such as crib-biting collars, were reported to have reduced this behaviour in 30% of the cases and 75% of the controls. In the majority of cases (n=23) and in all of the controls (n=4) it was unknown if crib-biting / windsucking behaviour had been exhibited in the sire / dam or siblings. The owners / carers of 7 cases knew for certain that this behaviour was present in relatives of the horse and in 7 cases this behaviour was not exhibited in the relatives known to the owner.

Discussion

Epidemiological studies have identified a number of risk factors for colic in general but few studies have examined risk factors for specific types of colic (Archer and Proudman 2006). In addition, many of the latter studies have used other colic cases as a comparison which introduces selection bias i.e. the controls may have been exposed to factors that predispose to other forms of colic and are so they are not a representative sample of the study population. This is the first unmatched study to investigate risk factors for epiploic foramen entrapment (EFE) using a representative population of at risk horses as controls.

In the present study, crib-biting or windsucking behaviour was associated with the greatest risk of developing EFE (adjusted OR 71.6, 95% CI 14.3 – 359.2). This is in agreement with the findings of the previous study (Chapter 3), in which a matched case-control study design was used, and the studies by Archer *et al.* (2004a; 2004b). In the present study, crib-biting / windsucking behaviour was exhibited in 1.8% of the control population of normal, healthy horses which is similar to previously published reports of the prevalence of this type of stereotypic behaviour in the general UK population (McGreevy *et al.* 1995). In contrast this behaviour was present in 48% of EFE cases in the present study, which is similar to the findings of the matched case-control study and the study conducted by Archer *et al.* (2004a), and is far higher than any reported prevalence of this behaviour in a population of normal horses. In agreement with the findings of the matched case-control study, horses exhibiting crib-biting / windsucking behaviour were also significantly more likely to have suffered from an episode of colic in the previous 12 months. In the study by Hillyer *et al.* (2002) investigating risk factors for simple colonic obstruction distension (SCOD) colic, 46% of the cases exhibited crib-biting / windsucking behaviour compared to 0.01% in their control population and this behaviour was also the largest risk factor for this type of colic in their final multivariable model (OR 70.0, 95% CI 9.59 – 510.96). These findings add to the evidence that crib-biting / windsucking behaviour is associated with colic in general and some specific forms of colic including EFE.

Due to the small numbers of horses exhibiting crib-biting / windsucking behaviour in the control population, it was not feasible to investigate differences between the severity, frequency and situations in which this behaviour was observed in a multivariable model. From the descriptive analysis, it would appear that this behaviour was subjectively assessed by the owners / carers to be more severe in the horses with EFE compared to the control horses. In addition, compared to control horses who exhibited this behaviour, crib-biting / windsucking was exhibited more frequently and increased in frequency at feed times in horses with EFE. If this behaviour is associated with some form of gastrointestinal dysfunction the severity, frequency and relationship to feeding may correlate with the degree of dysfunction. Further work is required to determine if measures of gastrointestinal function e.g. intestinal transit times (McGreevy *et al.* 2001) correlate with subjective and objective measurements of crib-biting / windsucking behaviour.

McGreevy *et al.* (1995) found a positive association between the performance of stereotypy and the amount of time that horses spent within the stable. It has also been proposed that crib-biting / windsucking behaviour helps to retain a digestive function or to meet unsatisfied foraging needs (McGreevy and Nicol 1998). Therefore, in theory, increased time spent at pasture (and hence increased opportunity to forage) might be beneficial to horses that exhibit this behaviour. It is interesting to note that, in the present study, crib-biting / windsucking horses spent significantly more time in a stable and fewer hours at pasture per week compared to horses that did not exhibit this behaviour. This finding is contradictory to the findings of Leuscher *et al.* (1998) and may reflect geographical differences in owners' / carers' opinions on how these horses should be managed.

In the present study, a number of horse-level factors were identified that were associated with an increased risk of EFE in the final multivariable model. These were similar to the findings of the matched case-control study (Chapter Three). An episode of colic in the previous 12 months was associated with increased risk of EFE adding further evidence to the theory that EFE may be associated with some underlying gastrointestinal dysfunction. In agreement with the latter study, there was no interaction between the variables 'colic in the previous 12 months' and 'crib-biting / windsucking' i.e. a history of colic in a horse exhibiting this crib-biting / windsucking behaviour does not increase the risk of EFE further. Increasing height was also identified as a risk factor for EFE. This may be due to anatomical differences in the relative dimensions of the epiploic foramen making entrapment more likely to occur in larger horses and requires further investigation.

Increased stabling in the previous 28 days was significantly associated with increased risk of EFE. This variable was defined as: introduction of stabling in horses that previously spent all their time at pasture, periods of stabling for a number of days / nights in horses that previously spent all their time at pasture and days / nights in which stabled horses were kept in instead of being turned out as normal. Recent change in stabling has also been identified as a risk factor for colic in general (Cohen *et al.* 1995, 1999) and SCOD colic (Hillyer *et al.* 2002). Increased stabling may be a marker for a number of other changes such as reduced access to pasture, increased quantity of supplementary forage and reduction in exercise. There was no evidence of significant confounding by variables measuring access to pasture, exercise, types of feed or feeding routines when these variables were forced back into the final multivariable model. Avoidance of sudden increases in stabling may therefore represent a way in which the risk of EFE can be reduced.

One of the reasons for conducting an unmatched case-control study was to investigate the seasonal pattern identified in cases of EFE (Archer *et al.* 2006b, Chapter 2). In the present study, there was some evidence of a seasonal pattern with more cases of EFE occurring in January than in any other month. This is consistent with the seasonal distribution of EFE cases described by Archer *et al.* (2004b) and Archer *et al.* (2006b, Chapter 2). The variables 'season' and 'month' were not significantly associated with EFE in the univariable model. This may be due to lack of study power to detect a seasonal or monthly effect and an inappropriate statistical approach to investigate seasonality as discussed in Chapter 2. When forced back into the model neither variable had a significant effect. Identification of increased stabling in the previous 28 days as a risk factor for EFE may help to explain the observed seasonal effect due to the fact that sudden increases in stabling may coincide with particular seasonal weather patterns.

Horses that had access to a mineral or salt-lick were found to be at significantly reduced risk of EFE. This variable may be a marker for management practices due to the fact that when introduced into the multivariable model, this variable significantly improved the fit of the model but resulted in the variables 'carer' and 'currently fed haylage' dropping out. There was no difference between provision of a mineral / salt lick between carer (chi-squared test P=0.71) nor between crib-biting / windsucking horses (P=0.47). Interestingly, it has been proposed that crib-biting may function to increase the flow of alkaline saliva (Nicol 1999) and that this behaviour could be a response to an acid stomach condition based on the observation that there is an association between the endoscopic appearance of the stomach mucosa in foals and crib-biting (Nicol *et al.* 2002). If EFE is associated with an underlying gastrointestinal disorder similar to that observed in crib-biting / windsucking horses, a mineral / salt lick could provide a means of compensating for altered gastrointestinal function. This requires further investigation.

A number of behavioural features remained in the final multivariable model. Horses that were considered by their owner / carer not to be easily frightened and those who ate their food normally when exposed to a stressful situation, e.g. change of premises, were identified to be at increased risk of EFE. These findings are consistent with the findings of the matched study (Chapter 3) and may reflect behavioural features that enable these individuals to cope with an environment that induces stress and provides a means of maintaining normal feed patterns to compensate for altered gastrointestinal function.

Horses that were fed at the same time as the others in the same group / part of the yard were also identified to be at increased risk of EFE. There was some correlation between the variable 'fed at the same time as others' and 'behaviour at feed time' whereby one dropped out of the model when the other was introduced. The latter variable only marginally improved the fit of the model (P=0.05) whereas 'fed at the same time as others' significantly improved the fit of the model. This may reflect changes in behaviour related to food anticipation. Bachmann *et al.* (2003) observed an increase in stereotypic behaviour in relation to the frequency of feeding and suggested that management strategies preventing situations that cause food anticipation behaviour should be avoided. The findings of the present study might be explained by worsening of pre-existing gastrointestinal dysfunction in relation to food anticipation and merits further investigation.

So can EFE be prevented? Some of risk factors identified in the present study such as height are non-modifiable and it is unlikely that behavioural characteristics such as an individual's response to a stimulus causing fright can be modified. Calculation of the population attributable fraction (AF_p) for each of the potentially modifiable risk factors that were identified in the present study indicated that feeding horses in the same group / part of the yard at different times, providing a mineral / salt lick and maintaining constant stabling routines (i.e. avoiding sudden periods of increased stabling) may prevent 66, 49 and 23% of the cases of EFE respectively. It is important to note that the AF_p are calculated from multiple logistic regression therefore do not add up to 100% (Rowe *et al.* 2004). In addition calculation of the AF_p assumes a causal relationship between each of these risk factors and

EFE. An intervention study would be required to determine if modification of these factors reduces the risk of EFE.

If a history of colic in the previous 12 months has a direct causal relationship with risk of EFE, 20% of EFE cases could potentially be prevented if this risk factor was removed. Based on information accumulated in a number of epidemiological studies investigating risk factors for colic (Archer and Proudman 2006) owners / carers of horses can be advised of ways in which the risk of colic can be minimised. In addition, practitioners can use this information to determine the likely cause of an episode of colic and provide advice on how the chances of recurrence can be minimised. However, if an inherent disorder of gastrointestinal function is the cause of EFE then it is possible that modification of management-level factors may have no effect. Further research is warranted to determine if this hypothesis is correct.

Calculation of the AF_p for crib-biting / windsucking indicated that 47% of EFE cases would be avoided if this behaviour was removed from the population, assuming a causal relationship between this form of behaviour and EFE. This highlights the importance of trying to prevent this behaviour from developing, given that this behaviour rarely disappears once established in youngstock (McGreevy and Nicol 1998). There is evidence to suggest that crib-biting / windsucking does serve a function in stress reduction or digestive activity and that its prevention by surgical or physical means may compromise welfare (McGreevy and Nicol 1998). Further research is required to determine why this behaviour occurs, including genetic predisposition to this behaviour, and whether the use of pharmacological agents to reduce or stop this behaviour (Rendon *et al.* 2001; McBride and Hemmings 2005) has any beneficial effect on the risk of EFE or colic in general.

In conclusion, this study has identified a number of horse- and management-level factors that place individuals at increased risk of EFE using a population of healthy horses as controls. Crib-biting / windsucking behaviour was associated with the greatest increase in risk of EFE. Risk of EFE also increased as horse height increased. Increased duration of stabling in the previous 28 days was associated with increased risk of EFE and may explain the apparent seasonal pattern of EFE coinciding with times of the year when weather patterns may result in horses being more likely to undergo sudden periods of increased stabling. The results from this study suggest that interventions such as avoiding sudden increases in stabling, not feeding horses in the same group / yard at the same time and provision of a mineral / salt lick, assuming a causal relationship between these risk factors and the outcome, may reduce the risk of EFE. These findings, together with increasing evidence that EFE may be associated with some underlying gastrointestinal dysfunction, merit further investigation.

APPENDIX TO CHAPTER 4

Table 1. Univariable logistic regression analyses of binary and categorical horse- and management-level variables and their relationship with the risk of developing epiploic foramen entrapment (EFE).

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Month	January	17 (13)	8.3 (18)	Ref		
	February	9 (7)	8.3 (18)	0.54	0.17 – 1.66	
	March	9 (7)	8.3 (18)	0.54	0.17 – 1.66	
	April	9 (7)	8.3 (18)	0.54	0.17 – 1.66	
	May	8 (6)	8.3 (18)	0.46	0.14 – 1.48	
	June	6 (5)	8.3 (18)	0.39	0.11 – 1.30	
	July	8 (6)	8.3 (18)	0.46	0.14 – 1.48	0.730
	August	4 (3)	8.3 (18)	0.23	0.06 – 0.95	
	September	4 (3)	8.3 (18)	0.23	0.06 – 0.95	
	October	8 (6)	8.3 (18)	0.46	0.14 – 1.48	
	November	10 (8)	8.3 (18)	0.61	0.20 – 1.84	
	December	8 (6)	8.3 (18)	0.46	0.14 – 1.48	
Season						
	Winter (December – February)	38 (26)	25 (54)	Ref.		
	Spring (March – May)	26 (20)	25 (54)	0.77	0.38 – 1.54	0.399
	Summer (June – August)	18 (14)	25 (54)	0.54	0.25 – 1.14	
	Autumn (September – November)	22 (17)	25 (54)	0.65	0.32 – 1.34	
General horse and management details						
Breed	TB	23 (18)	20 (42)	Ref.		
	TBx	22 (17)	21 (45)	0.88	0.40 – 1.93	
	WB / WBx	22 (17)	11 (24)	1.65	0.72 – 3.79	0.050
	Pony / miniature horse	8 (6)	14 (30)	0.47	0.16 – 1.31	
	Cob / Cob x	4 (3)	12 (25)	0.28	0.07 – 1.05	
	Other horse	21 (16)	23 (49)	0.76	0.35 – 1.68	
Gender	Male	75 (58)	58 (126)	Ref.		
	Female	25 (19)	42 (90)	0.46	0.26 – 0.82	0.007
Principal use	Pleasure	42 (32)	42 (91)	Ref.		

	Competition (local / regional)	19 (15)	14 (31)	1.38	0.66 – 2.87	
	Competition (national / international)	12 (9)	13 (29)	0.88	0.38 – 2.06	
	Working horse	6 (5)	4(8)	1.78	0.54 – 5.83	0.122
	Pet / retired	3 (2)	9 (20)	0.28	0.06 – 1.29	
	Broodmare / breeding stallion	10 (8)	5 (10)	2.27	0.83 – 6.27	
	Unbroken / recently broken / injured	8 (6)	13 (27)	0.63	0.24 – 1.67	
Competition type	None	62 (48)	66 (141)	Ref.		
	Racing (flat / jump / point-to-point)	4 (3)	6 (12)	0.73	0.20 – 2.71	
	Dressage	12 (9)	6 (13)	2.03	0.82 – 5.06	
	Show-jumping	9 (7)	4 (9)	2.28	0.81 – 6.47	0.210
	Eventing	5 (4)	4 (9)	1.31	0.38 – 4.43	
	Other	8 (6)	14 (31)	0.57	0.22 – 1.45	
Medical details						
Veterinary attention in last 12 months (non-routine)	No	48 (34)	40 (83)	Ref.		
	Yes	52 (37)	60 (127)	0.71	0.41 – 1.22	0.218
Type of problem						
Orthopaedic	No	76 (55)	65 (136)	Ref.		
	Yes	24 (17)	35 (73)	0.57	0.31 – 1.06	0.071
Dental / Gastrointestinal / Weight loss	No	77 (55)	91 (188)	Ref.		
	Yes	23 (16)	9 (19)	2.88	1.39 – 5.97	0.005
Received medication (other than anthelmintic or vaccination) in last 12 months	No	56 (40)	47 (98)	Ref.		
	Yes	44 (32)	53 (109)	0.72	0.42 – 1.23	0.230

Currently receiving medication	No	92 (70)	94 (200)	Ref.		
	Yes	8 (6)	6 (12)	1.43	0.52 – 3.95	0.500
NSAIDs in previous 28 days	No	92 (59)	83 (121)	Ref.		
	Yes	8 (5)	17 (24)	0.43	0.15 – 1.18	0.078
Colic episode in previous 12 months	No	75 (53)	94 (196)	Ref.		
	Yes	25 (18)	6 (13)	5.12	2.35 – 11.12	<0.0001
Previous abdominal surgery	No	96 (74)	97 (210)	Ref.		
	Yes	4 (3)	3 (6)	1.42	0.35 – 5.81	0.634
Premises						
Premises type	Private yard	48 (37)	56 (121)	Ref.		
	Working / competition yard /	19 (15)	10 (21)	2.34	1.09 – 4.98	
	Livery yard	31 (24)	31 (66)	1.19	0.66 – 2.16	0.114
	Stud farm	1 (1)	4 (8)	0.41	0.05 – 3.38	
Carer	Owners(s) / relative or spouse involved in daily care	53 (41)	77 (166)	Ref.		
	Owner / relative / spouse not involved in daily care	47 (36)	23 (49)	2.97	1.72 – 5.15	0.0001
No. of premises in last 12 months	1	45 (35)	50 (108)	Ref.		
	2 - 3	38 (29)	28 (60)	1.49	0.83 – 2.67	
	>3	17 (13)	22 (48)	0.84	0.41 – 1.72	0.246
No. of premises changes in last 12 months	0	45 (35)	51 (108)	Ref.		
	1	23 (18)	17 (37)	1.50	0.76 – 2.96	
	2-4	19 (15)	19 (40)	1.16	0.57 – 2.34	0.691
	>4	12 (9)	13 (28)	0.99	0.43 – 2.30	

Premises change in last 12 months	No	45 (35)	50 (108)	Ref.		
	Yes	55 (42)	50 (108)	1.20	0.71 – 2.02	0.493
Premises change in last 28 days	No	89 (67)	92 (192)	Ref.		
	Yes	11 (8)	8 (17)	1.35	0.56 – 3.27	0.514
Housing and grazing						
Current management	Stabled with 2 / >2hrs turnout every day	54 (40)	54 (115)	Ref.		
	Stabled all the time / stabled apart from when exercised	19 (14)	7 (15)	2.68	1.19 – 6.05	
	Stabled with <2h turnout daily / irregular turnout	13.5 (10)	10 (22)	1.30	0.57 – 3.00	0.005
	Not stabled – turned out all the time	13.5 (10)	29 (61)	0.47	0.22 – 1.00	
Current stabling	No	14 (10)	29 (61)	Ref.		
	Yes	86 (64)	71 (152)	2.57	1.24 – 5.33	0.007
Change in stabling / turnout routine in previous 28 days	No	64 (47)	69 (145)	Ref.		
	Yes	36 (27)	31 (65)	1.28	0.73 – 2.23	0.385
Change in stabling / turnout routine in previous 14 days	No	75 (52)	78 (156)	Ref.		
	Yes	25 (17)	22 (44)	1.16	0.61 – 2.20	0.654
Change in stabling / turnout routine in previous 7 days	No	81 (56)	85 (171)	Ref.		
	Yes	19 (13)	15 (29)	1.37	0.67 – 2.81	0.400
Increased stabling in the previous 28 days	No	69 (51)	83 (171)	Ref.		
	Yes	31 (23)	17 (36)	2.14	1.16 – 3.94	0.016

Increased stabling in the previous 14 days	No	80 (55)	88 (178)	Ref.		
	Yes	20 (14)	12 (25)	1.81	0.88 – 3.73	0.113
Increased stabling in the previous 7 days	No	84 (58)	91 (185)	Ref.		
	Yes	16 (11)	9 (18)	1.95	0.87 – 4.36	0.113
Increased pasture turnout in the previous 28 days	No	97 (72)	91 (189)	Ref.		
	Yes	3 (2)	9 (18)	0.29	0.07 – 1.29	0.059
Increased pasture turnout in the previous 14 days	No	97 (72)	94 (191)	Ref.		
	Yes	3 (2)	6 (13)	0.41	0.09 – 1.85	0.201
Increased pasture turnout in the previous 7 days	No	97 (72)	96 (196)	Ref.		
	Yes	3 (2)	4 (8)	0.68	0.14 – 3.28	0.619
Bedding type	Woodshavings	52 (36)	60 (102)	Ref.		
	Straw	33 (23)	27 (45)	1.45	0.77 – 2.72	
	Other	15 (10)	13 (22)	1.29	0.56 – 2.98	0.496
Access to straw bedding	No	70 (53)	79 (170)	Ref.		
	Yes	30 (23)	21 (45)	1.64	0.91 – 2.96	0.105
Bedding change (type / batch) in last 28 days	No	90 (63)	90 (152)	Ref.		
	Yes	10 (7)	10 (16)	1.06	0.41 – 2.69	0.910
Manually filled water supply in stable	No	22 (15)	15 (26)	Ref.		
	Yes	78 (53)	85 (144)	0.64	0.31 – 1.30	0.220
Automatic water supply in	No	78 (53)	83 (141)	Ref.		

stable						
	Yes	22 (15)	17 (29)	1.38	0.68 – 2.77	0.376
Current access to pasture	No	17 (13)	7 (16)	Ref.		
	Yes	83 (64)	93 (199)	0.40	0.18 – 0.87	0.023
Duration on current pasture	< 1 month	16 (10)	22 (41)	Ref.		
	1 – 6 months	51 (31)	51 (95)	1.34	0.60 – 2.98	*0.523*
	> 6 months	33 (20)	27 (50)	1.64	0.69 – 3.89	
Change of pasture in previous 28 days	No	81 (50)	79 (154)	Ref.		
	Yes	19 (12)	21 (42)	0.88	0.43 – 1.80	0.725
Turned out on own	No	78 (50)	76 (153)	Ref.		
	Yes	22 (14)	24 (48)	0.89	0.45 – 1.75	0.740
Pasture treatment within previous 28 days	No	92 (58)	92 (181)	Ref.		
	Yes	8 (5)	8 (15)	1.04	0.36 – 2.99	0.942
Water source when turned out	Manually filled source only	44 (27)	43 (86)	Ref.		
	Automatic water source only	45 (28)	43 (86)	1.04	0.56 – 1.90	0.889
	Pond / stream or more than one water source	11 (7)	14 (27)	0.83	0.32 – 2.11	
Nutrition						
Do the same people feed every day / most days	No	7 (5)	7 (14)	Ref.		
	Yes	93 (66)	93 (184)	1.00	0.35 – 2.90	0.994
No. of people feeding daily	1	44 (32)	55 (109)	Ref.		
	2	36 (26)	36 (71)	1.25	0.69 – 2.27	0.049
	>2	19 (14)	9 (17)	2.80	1.25 – 6.30	

Feeding of hay / haylage	No	8 (6)	21 (45)	Ref.		
	Yes	92 (70)	79 (171)	3.07	1.25 – 7.52	0.006
Supplementary forage feeding	None	8 (6)	21 (45)	Ref.		
	Once daily	21 (16)	28 (61)	1.97	0.71 – 5.42	
	Twice daily	37 (28)	31 (68)	3.10	1.18 – 8.06	0.006
	Three - four times daily	21 (16)	15 (32)	3.75	1.32 – 10.63	
	Ad libitum	13 (10)	5 (10)	7.50	2.21 – 25.46	
Concentrate fed	No	5 (4)	12 (26)	Ref.		
	Yes	95 (72)	88 (187)	2.50	0.84 – 7.42	0.070
Concentrate feeding	None	5 (4)	12 (26)	Ref.		
	Once daily	12 (9)	25 (54)	1.08	0.30 – 3.85	0.006
	Twice daily	66 (50)	53 (112)	2.90	0.96 – 8.75	
	Three times daily or more	17 (13)	9 (21)	4.02	1.14 – 14.18	
Fed at same time and frequency as horses in group / yard	Yes	87 (61)	67 (124)	Ref.		
	No	13 (9)	33 (62)	0.29	0.14 – 0.63	0.0006
Fed at the same time (to within an hour) every day of the week	Never varies	71 (51)	55 (103)	Ref.		
	Occasionally varies	11 (8)	11 (21)	0.77	0.32 – 1.86	0.032
	Regularly varies	18 (13)	34 (63)	0.42	0.21 – 0.83	
Roughage type	Grass only	8 (6)	21 (44)	Ref.		
	Hay	37 (28)	46 (97)	2.12	0.82 – 5.48	
	Haylage	47 (36)	27 (58)	4.55	1.76 – 11.76	0.003
	Hay & haylage	8 (6)	7 (14)	3.14	0.87 – 11.32	
Currently fed hay	No	56 (43)	49 (105)	Ref.		
	Yes	44 (34)	51 (111)	0.75	0.44 – 1.26	0.275

Currently fed haylage	No	45 (35)	67 (144)	Ref.		
	Yes	55 (42)	33 (72)	2.40	1.41 – 4.08	0.001
Change in frequency forage feeding:						
Last 28 days	No	88 (61)	74 (131)	Ref.		
	Yes	12 (8)	26 (45)	0.38	0.17 – 0.86	0.012
Last 14 days	No	97 (63)	86 (135)	Ref.		
	Yes	3 (2)	13 (21)	0.20	0.05 – 0.90	0.011
Last 7 days	No	98 (64)	92 (144)	Ref.		
	Yes	2 (1)	8 (12)	0.18	0.02 – 1.47	0.047
Change in quantity forage feeding:						
Last 28 days	No	82 (55)	64 (113)	Ref.		
	Yes	18 (12)	36 (64)	0.38	0.19 – 0.77	0.004
Last 14 days	No	95 (58)	81 (124)	Ref.		
	Yes	5 (3)	19 (29)	0.22	0.06 – 0.76	0.004
Last 7 days	No	97 (59)	90 (138)	Ref.		
	Yes	3 (2)	10 (15)	0.31	0.07 – 1.41	0.085
Change in type of roughage fed in :						
Last 28 days	No	96 (65)	91 (163)	Ref.		
	Yes	4 (3)	9 (16)	0.47	0.13 – 1.67	0.209
Last 14 days	No	99 (67)	94 (166)	Ref.		
	Yes	1 (1)	6 (10)	0.25	0.03 – 1.97	0.116
Last 7 days	No	100 (68)	98 (172)	Ref.		
	Yes	0 (0)	2 (4)	-		
Change in batch roughage in:						
Last 28 days	No	70 (38)	78 (117)	Ref.		
	Yes	30 (16)	22 (33)	1.49	0.74 – 3.00	0.267
Last 14 days	No	84 (43)	86 (126)	Ref.		
	Yes	16 (8)	14 (21)	1.11	0.46 – 2.70	0.809
Last 7 days	No	88 (45)	94 (138)	Ref.		

	Yes	12 (6)	6 (9)	2.04	0.69 – 6.06	0.209
Proprietary concentrate diet fed	No	36 (25)	38 (75)	Ref.		
	Yes	64 (45)	62 (124)	1.09	0.62 – 1.92	0.768
Local feed mill concentrate fed	No	72 (49)	88 (172)	Ref.		
	Yes	28 (19)	12 (24)	2.78	1.41 – 5.49	0.004
Grain fed	No	89 (64)	91 (194)	Ref.		
	Yes	11 (8)	9 (20)	1.21	0.51 – 2.89	0.667
Sugar beet pulp fed	No	62 (45)	73 (157)	Ref.		
	Yes	38 (28)	27 (57)	1.71	0.98 – 3.00	0.062
Fibre source fed e.g. grass / chaff / chop	No	22 (16)	27 (58)	Ref.		
	Yes	78 (57)	73 (156)	1.32	0.70 – 2.49	0.376
Change in frequency concentrate in:						
Last 28 days	No	89 (63)	87 (165)	Ref.		
	Yes	11 (8)	13 (24)	0.87	0.37 – 2.04	0.752
Last 14 days	No	97 (65)	93 (170)	Ref.		
	Yes	3 (2)	7 (13)	0.40	0.09 – 1.83	0.194
Last 7 days	No	99 (66)	98 (177)	Ref.		
	Yes	1 (1)	3 (6)	0.45	0.05 – 3.78	0.419
Change in quantity of concentrate in:						
Last 28 days	No	81 (54)	70 (133)	Ref.		
	Yes	19 (13)	30 (56)	0.57	0.29 – 1.13	0.097
Last 14 days	No	92 (56)	85 (149)	Ref.		
	Yes	8 (5)	15 (26)	0.51	0.19 – 1.40	0.166
Last 7 days	No	95 (58)	91 (160)	Ref.		
	Yes	5 (3)	9 (15)	0.55	0.15 – 1.97	0.334

Change in concentrate type / brand in:						
Last 28 days	No	90 (62)	92 (172)	Ref.		
	Yes	10 (7)	8 (15)	1.29	0.50 – 3.32	0.596
Supplements fed	No	21 (16)	11 (24)	Ref.		
	Yes	79 (60)	89 (192)	0.47	0.23 – 0.94	0.037
Vegetables / fruit	No	57 (43)	48 (104)	Ref.		
	Yes	43 (33)	52 (112)	0.71	0.42 – 1.20	0.206
Garlic / herbal	No	78 (59)	66 (143)	Ref.		
	Yes	22 (17)	39 (73)	0.56	0.31 – 1.03	0.058
Chondroitin / glucosamine	No	88 (67)	85 (183)	Ref.		
	Yes	12 (9)	15 (33)	0.74	0.34 – 1.64	0.455
Probiotics	No	95 (72)	94 (203)	Ref.		
	Yes	5 (4)	6 (13)	0.87	0.27 – 2.75	0.807
Salt / mineral lick or supplement	No	75 (57)	65 (140)	Ref.		
	Yes	25 (19)	35 (76)	0.61	0.34 – 1.10	0.098
Oil	No	62 (47)	60 (128)	Ref.		
	Yes	38 (29)	40 (86)	0.91	0.50 – 1.65	0.752
Other supplement	No	62 (47)	60 (128)	Ref.		
	Yes	38 (29)	40 (86)	0.92	0.54 – 1.57	0.756
Supplement added within last 28 days	No	92 (70)	94 (201)	Ref.		
	Yes	8 (6)	6 (12)	1.44	0.52 – 3.97	0.494
Exercise and transport						
No. of days exercised per week	0	21 (16)	24 (52)	Ref.		
	1-2	12 (9)	15 (32)	0.91	0.36 – 2.31	
	3-4	19 (15)	19 (42)	1.16	0.51 – 2.62	0.862
	5-6	35 (27)	31 (68)	1.29	0.63 – 2.64	
	7	13 (10)	10 (22)	1.48	0.58 – 3.76	

Change in exercise routine in previous 28 days	No	74 (57)	70 (149)	Ref.		
	Yes	26 (20)	30 (63)	0.83	0.46 – 1.50	0.531
Type of exercise	None	19 (15)	23 (49)	Ref.		
	Ridden only	32 (25)	43 (92)	0.89	0.43 – 1.84	
	Lunged / treadmill / horsewalker only	5 (4)	3 (7)	1.87	0.48 – 7.26	0.207
	Combination of above / other	43 (33)	31 (67)	1.61	0.79 – 3.28	
Location of exercise	Not applicable	19.5 (15)	23 (49)	Ref.		
	Arena / school only	19.5 (15)	7 (15)	3.27	1.30 – 8.20	0.014
	Other	61 (47)	70 (150)	1.02	0.53 – 1.99	
Transport in previous 28 days	No	64 (48)	65 (138)	Ref.		
	Yes	36 (27)	35 (74)	1.05	0.60 – 1.82	0.865
Transport in previous 14 days	No	75 (55)	71 (145)	Ref.		
	Yes	25 (18)	29 (59)	0.80	0.44 – 1.48	0.482
Transport in previous 7 days	No	84 (61)	80 (164)	Ref.		
	Yes	16 (12)	20 (40)	0.81	0.40 – 1.64	0.547
Behaviour						
General behaviour						
Easily frightened	No	83 (64)	62 (134)	Ref.		
	Yes	17 (13)	38 (81)	0.34	0.17 – 0.65	0.0005
Settle after fright	Instantly	71 (55)	54 (117)	Ref.		
	Few minutes / longer than few minutes	29 (22)	46 (99)	0.47	0.27 – 0.83	0.007

Response to unknown object	Interested / not bothered	80 (61)	71 (153)	Ref.		
	Excited	21 (16)	29 (62)	0.65	0.35 – 1.21	0.163
Sweat up when excited	Never	73 (56)	68 (147)	Ref.		
	Easily, every time / occasionally	27 (21)	32 (69)	0.80	0.45 – 1.42	0.442
Tremble / shake when frightened	No	92 (71)	76 (162)	Ref.		
	Yes	8 (6)	24 (52)	0.26	0.11 – 0.64	0.0008
Reaction to surroundings	Will watch / not interested	55 (42)	45 (97)	Ref.		
	Very inquisitive	45 (35)	55 (119)	0.68	0.40 – 1.15	0.146
Reaction to other horses	Excited	82 (63)	81 (172)	Ref.		
	Interested / not bothered	18 (14)	19 (41)	0.93	0.48 – 1.82	0.837
Restlessness when stabled	No	81 (59)	81 (172)	Ref.		
	Yes	18 (14)	19 (41)	0.88	0.45 – 1.73	0.715
Distressed when stabled alone	No	65 (47)	63 (120)	Ref.		
	Yes	35 (25)	37 (72)	0.89	0.50 – 1.56	0.676
Behaviour at feed time	Interested	74 (57)	82 (175)	Ref.		
	Agitated	26 (20)	18 (39)	1.58	0.85 – 2.92	0.155
Concentrate feeding	Normal / fast	100 (77)	98 (175)	Ref.		
	Doesn't eat all feed, picky	0 (0)	2 (5)	-		
Forage feeding	Normal / fast	92 (68)	89 (180)	Ref.		
	Doesn't eat all forage	8 (6)	11 (22)	0.72	0.28 – 1.86	0.488
Feeding when stressed	Eats normally	96 (73)	85 (175)	Ref.		
	Goes off food in full / part	4 (3)	15 (31)	0.23	0.07 – 0.78	0.005
Aggression towards humans when given food	No	88 (68)	85 (182)	Ref.		

	Yes	*12 (9)*	*15 (32)*	*0.75*	*0.34 – 1.66*	*0.473*
Irritated when handled	Yes – regularly / occasionally	62 (48)	54 (116)	Ref.		
	No	38 (29)	46 (99)	0.71	0.41 – 1.21	0.201
Direct physical contact with other horses	Regular	78 (59)	86 (184)	Ref.		
	None / occasional	22 (17)	14 (31)	1.71	0.88 – 3.31	0.118
Stereotypic behaviour						
Stereotypic behaviour	No	42 (32)	84 (182)	Ref.		
	Yes	60 (45)	16 (34)	7.53	4.20 – 13.5	<0.0001
Crib-biting / windsucking	No	52 (40)	98 (211)	Ref.		
	Yes	48 (37)	2 (4)	48.8	16.5 – 144.5	<0.0001
Woodchewing	No	99 (76)	97 (208)	Ref.		
	Yes	1 (1)	3 (7)	0.39	0.05 – 3.23	0.331
Weaving	No	90 (69)	95 (205)	Ref.		
	Yes	10 (8)	5 (10)	2.38	0.90 – 6.26	0.088
Box walking	No	97 (75)	93 (201)	Ref.		
	Yes	3 (2)	7 (14)	0.38	0.08 – 1.72	0.164
Other oral stereotypic behaviour	No	97 (75)	99 (211)	Ref.		
	Yes	2.6 (2)	1 (3)	1.87	0.31 – 11.4	0.507
Preventative health care						
Frequency of dental care	Every 12 months	52 (37)	47 (98)	Ref.		
	More than 12 monthly	15 (11)	11 (22)	1.32	0.58 – 2.30	0.282
	Less than 12 monthly	32 (23)	42 (87)	0.70	0.39 – 1.27	
Vaccination in previous 28 days	No	88 (51)	90 (173)	Ref.		

	Yes	12 (7)	10 (20)	1.19	0.47 – 2.97	0.716
Last vaccination	Flu & tetanus	64 (35)	67 (118)	Ref.		
	Flu only	25 (14)	23 (41)	1.15	0.56 – 2.35	0.9731
	Tetanus only	7 (4)	6 (11)	1.23	0.37 – 4.09	
	Other	4 (2)	3 (6)	1.12	0.22 – 5.82	
Anthelmintic administration	Every 6 – 13 weeks	70 (50)	73 (155)	Ref.		
	14 weeks – 6 monthly	18 (13)	18 (37)	1.09	0.54 – 2.21	0.835
	> 6 monthly	11 (8)	9 (19)	1.30	0.54 – 3.16	
Anthelmintic administration in previous 7 days	No	93 (64)	89 (164)	Ref.		
	Yes	7 (5)	11 (21)	0.61	0.22 – 1.69	0.322
Anthelmintic administration in previous 14 days	No	83 (57)	79 (147)	Ref.		
	Yes	17 (12)	20 (38)	0.81	0.40 – 1.67	0.571
Anthelmintic administration in previous 28 days	No	71 (49)	63 (117)	Ref.		
	Yes	29 (20)	37 (68)	0.70	0.38 – 1.28	0.243
Last anthelmintic product administered	Ivermectin	13 (8)	19 (32)	Ref.		
	Benzimidazole	6 (4)	11 (18)	0.89	0.23 – 3.37	
	Moxidectin / doramectin	42 (26)	33 (55)	1.89	0.76 – 4.67	0.446
	Pyrantel	13 (8)	16 (27)	1.18	0.39 – 3.58	
	Praziquantel ± avermectin	26 (16)	21 (36)	1.78	0.67 – 4.70	
Penultimate worming product	Ivermectin	15 (8)	17 (22)	Ref.		
	Benzimidazole	10 (5)	8 (11)	1.25	0.33 – 4.73	
	Moxidectin / doramectin	25 (13)	30 (39)	0.92	0.33 – 2.55	0.761
	Pyrantel	29 (15)	20 (26)	1.59	0.57 – 4.44	
	Praziquantel + avermectin	21 (11)	25 (32)	0.94	0.33 – 2.73	

Treated for tapeworms in previous 12 months	Yes	82 (54)	84 (151)	Ref.		
	No	18 (12)	16 (29)	1.16	0.55 – 2.43	0.70
Are specific measures taken to reduce the nos. of parasites on the pasture?	Yes	90 (60)	88 (182)	Ref.		
	No	10 (7)	12 (24)	0.88	0.36 – 2.16	0.786
Worm egg count or tapeworm ELISA performed within last 12 months	No	81 (57)	85 (177)	Ref.		
	Yes	19 (13)	15 (32)	1.26	0.62 – 2.57	0.526
Negative faecal egg count	Yes	82 (41)	81 (86)	Ref.		
	No	18 (9)	19 (20)	0.94	0.40 – 2.25	0.896

Table 2. Univariable logistic regression analyses of categorised continuous horse- and management-level variables and their relationship with the risk of developing epiploic foramen entrapment (EFE).

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
General horse & management details						
Age (years)	≤ 6	17 (13)	26.5 (57)	Ref.		
	7 – 9	27 (21)	23 (50)	1.84	0.84 – 4.05	
	10 – 13	26 (20)	24 (52)	1.68	0.76 – 3.72	0.387
	≥ 14	30 (23)	26.5 (57)	1.77	0.82 – 3.83	
Height (cm)	≤ 151	10 (8)	28 (61)	Ref.		
	152 – 159	18 (14)	20 (43)	2.48	0.96 – 6.43	0.0003
	160 – 164	17 (13)	22 (48)	2.06	0.79 – 5.38	
	≥ 165	55 (42)	30 (64)	5.00	2.17 – 11.51	
Weight (kg)	≤ 449	10 (8)	22 (48)	Ref.		
	450 - 499	8 (6)	16 (35)	1.02	0.33 – 3.23	0.0006
	500 - 569	40 (31)	42 (90)	2.07	0.88 – 4.85	
	≥570	42 (32)	20 (43)	4.46	1.86 – 10.74	
Premises						
No. of horses on premises	1 - 5	28 (21)	40 (85)	Ref.		
	6 - 10	17 (13)	15 (32)	1.64	0.74 – 3.67	
	11 - 20	26 (20)	20 (43)	1.88	0.92 – 3.84	0.293
	>20	29 (22)	26 (55)	1.62	0.81 – 3.22	
Housing and grazing						
Hours stabled per week	0	15 (11)	29 (62)	Ref.		
	1 - 100	9 (7)	23 (50)	0.79	0.28 – 2.18	
	101 - 120	17 (13)	19 (41)	1.79	0.73 – 4.37	0.0001
	121 - 149	33 (25)	16 (34)	4.14	1.82 – 9.44	
	≥ 150	25 (19)	13 (27)	3.97	1.66 – 9.46	

Hours grazing per week	0 – 15	27 (20)	16 (35)	Ref.		
	16– 48	36 (27)	16 (35)	1.35	0.64 – 2.84	
	49 – 69	13 (10)	17 (37)	0.47	0.19 – 1.15	0.0002
	70 – 165	11 (8)	12 (45)	0.31	0.12 – 0.79	
	165 – 168	13 (10)	29 (62)	0.28	0.12 – 0.67	
Stocking density	<0.5 acre / horse	22 (12)	26 (48)	Ref.		
	0.5 – 0.74 acres / horse	29 (16)	19 (36)	1.78	0.75 – 4.22	
	0.75 – 1.4 acres / horse	24 (13)	26 (48)	1.08	0.45 – 2.61	0.514
	≥1.5 acres / horse	25 (14)	29 (54)	1.04	0.44 – 2.46	
Nutrition						
Total daily supplementary forage weight	None / <3kg	12 (6)	36 (61)	Ref.		
	3 – 7 kg	33 (16)	35 (59)	2.76	1.01 – 7.53	0.0005
	≥ 8 kg	55 (27)	29 (49)	5.60	2.14 – 14.65	
Total concentrate / grain weight	None	23 (14)	46 (86)	Ref.		
	<2.0 kg	34 (21)	30 (55)	2.34	1.10 – 5.00	
	2.0 – 3.9 kg	30 (18)	15 (28)	3.95	1.74 – 8.95	0.005
	≥4.0 kg	13 (8)	9 (16)	3.07	1.11 – 8.51	
Exercise and transport						
No. of hours exercised per week	< 1	26 (20)	25 (53)	Ref.		
	1 – 3.9	22 (17)	26 (56)	0.80	0.38 – 1.70	0.928
	4 – 5.9	20 (15)	19 (40)	0.99	0.45 – 2.18	
	≥ 6	32 (25)	31 (67)	0.99	0.50 – 1.97	
No. of journeys in last 28 days	0	66 (48)	65 (138)	Ref.		
	1 – 2	15 (11)	10 (22)	1.44	0.65 – 3.18	0.513
	3 – 6	9.5 (7)	15 (32)	0.63	0.26 – 1.52	
	>6	9.5 (7)	9 (19)	1.06	0.42 – 2.68	

No. of hours being transported in previous 28 days	0	68 (48)	65 (138)	Ref.		
	1 – 2	14 (10)	15 (32)	0.90	0.41 – 1.96	0.978
	3 – 7	11 (8)	13 (27)	0.85	0.36 – 2.00	
	>7	7 (5)	7 (14)	1.03	0.35 – 3.00	

Table 3. Univariable logistic regression analyses of continuous horse- and management-level variables and their relationship with the risk of developing epiploic foramen entrapment (EFE).

Variable	*Unit of measurement*	*Mean / median*	*Coefficient*	*Standard Error*	**P-value**
Horse					
Age	years	10.2	0.3209	0.0273	0.240
Height	cm	156	0.0490	0.0134	<0.0001
Weight	kg	502	0.0063	0.0015	<0.0001
Premises					
No. horses on premises		10	0.0004	0.0041	0.918
Housing and grazing					
No. of hours stabled per week	hours	108	0.0099	0.0026	<0.0001
No. of hours grazing per week	hours	56	-0.0095	0.0025	<0.0001
Stocking density	horses / acre	0.75	0.0600	0.0880	0.455
Nutrition					
Supplementary forage weight	kg	5.44	0.1065	0.0280	0.0001
Total weight concentrate / grain	kg	0.42	0.1543	0.0076	0.047
Exercise and transport					
No. of days exercised per week		3.5	0.0688	0.0636	0.197
Duration of exercise each week	hours	3.9	0.0051	0.0378	0.893
No. journeys in last 28 days		0	-.02713	0.0364	0.444
Duration of transport in last 28 days	hours	0	-0.0214	0.0411	0.593

CHAPTER 5

Case-control studies to investigate risk factors for idiopathic focal eosinophilic enteritis

Abstract

Idiopathic focal eosinophilic enteritis (IFEE) is an uncommon cause of colic but one that appears to be increasingly recognised. To date, no studies have investigated the epidemiology of this condition. The aim of this study was to identify horse- and management-level risk factors for IFEE using a healthy population of horses as controls.

Matched and unmatched case-control studies were conducted concurrently between 2004 – 2006. The matched study was conducted in the UK, Ireland and USA and data on 31 cases and 93 controls were collected. Controls were matched to cases on clinic and time in order to control for differences in management between different geographic regions. Conditional logistic regression was used to identify associations between a number of horse- and management-level variables and the risk of IFEE. Cases of IFEE identified at 9 clinics in the UK between 1st May 2004 – 30th April 2006 were recruited onto an unmatched case-control study. Data on 18 cases and 216 controls were collected over the 24 month study period and logistic regression was used to analyse these data.

Both studies identified young horses and horses with access to a pond / stream / stagnant pool at pasture to be at increased risk of IFEE. A history of colic in the previous 12 months and the number of horses on the premises were identified as additional risk factors for IFEE in the matched study. In the unmatched study, a history of treatment for tapeworms in the previous 12 months and an increasing number of horses on the pasture reduced the risk of IFEE. The findings from the present study provide clues to the potential pathogenesis of this condition and areas that require further investigation.

Introduction

Idiopathic focal eosinophilic enteritis (IFEE) is an uncommon cause of colic but is one that appears to be increasing in frequency (Archer et al. 2006a; Perez Olmos et al. 2006). To date, published studies of this condition have not identified any common aetiologies and the pathogenesis of this disease in the horse is unknown.

Eosinophilic infiltration of the equine gastrointestinal tract may be a manifestation of a more diffuse infiltrative eosinophilic disease affecting multiple organs including the skin (Nimmo-Wilkie *et al.* 1985; Gibson and Alders 1987). Alternatively, eosinophilic infiltration may be localised to the gastrointestinal tract. Diffuse eosinophilic infiltration, affecting differing regions of the gastrointestinal tract, results in clinical signs of weight loss, hypoalbuminaemia, diarrhoea and occasionally recurrent colonic impactions (Pass and Bolton 1982; Lindberg 1984; Bassage *et al.* 1997; Roberts 2000).

In contrast IFEE is characterised by focal lesions of the small intestine which contain a massive infiltration of eosinophils in the absence of a known aetiologic cause such as fungal lesions (Allison and Gillis 1990) or encapsulated nematodes (Cohen *et al.* 1992). These visibly striking hyperaemic, thickened, circumferential or plaque-like lesions result in colic due to obstruction of ingesta at the site of one or more lesions. The resultant clinical signs are consistent with other forms of simple, non-strangulating, obstructions of the small intestine.

The precise role of the eosinophil in the gastrointestinal tract of the horse is not fully understood and currently little is known about the precise mechanisms of eosinophil stimulation, adherence and migration to the intestine (Hubert 2006). In humans, primary eosinophilic gastrointestinal disorders (EGID) are being increasingly recognised and an allergic cause for these diseases has been proposed (Rothenberg 2004).

The aim of the present study was to identify horse- and management-level risk factors for IFEE using a population of normal horses as controls. Knowledge of risk factors for this disease is important in furthering our understanding of the pathogenesis of this uncommon condition and could potentially enable us to develop strategies to reduce the chances of these lesions developing in high-risk individuals.

Materials and Methods

Matched case-control study design

An international, multi-centre matched case-control study was conducted between January 2004 – September 2006 to identify associations between various horse- and management-level risk variables and IFEE (outcome variable).

Controls were matched to cases on clinic to control for horse and management differences between different geographic locations. Three controls were randomly selected from the same clinic population for each case using a list of clients seen at the same collaborating clinic in the previous calendar year. Control selection took place within 2 - 4 weeks of notification of a case. The majority of controls were contacted initially by post followed by a telephone call to ask if they would be willing to participate in the study. To maximise client compliance, owners were informed that this study was investigating colic in the horse and that we wished to collect general information about horses and their daily care. Owners were unaware of the hypotheses being tested. At initial contact a 'horse' (defined as a horse or pony) in the care of the client of was randomly selected. The horse had to fulfil the following inclusion criteria: i) it must not have suffered from colic in the previous 4 weeks and ii) surgery for colic would be undertaken on this horse if deemed necessary. The latter criteria was taken to avoid selection bias i.e. the controls would potentially have been eligible to become cases. If the selected horse did not fulfil these criteria, another horse was selected or if none fulfilled the criteria, a new control client was selected (Hillyer *et al.* 2002).

Unmatched case-control study design

IFEE cases diagnosed at nine clinics in the UK were also recruited onto the unmatched case-control study. This study was conducted over a 24 month period (1st May 2004 – 30th April 2006). To ensure that cases and controls were unmatched on time, 9 controls were recruited during each of the 24 months of the study as part of an unmatched case-control study also investigating the epidemiology of epiploic foramen entrapment (Chaper 4). Controls were randomly selected from the list of clients seen at each of the collaborating clinics in the previous calendar year. Because the caseloads varied between clinics, to ensure that selection of controls was proportional to the number of clients seen at each clinic in the previous year, the list of clients were pooled together and treated as a single population. Random numbers were generated and a client was selected from this control population.

Case definition and recruitment

Cases were defined as horses with hyperaemic, thickened, focal, circumferential or plaque-like lesions of the small intestine causing colic due to impaction of ingesta at the site of one or more lesions. A diagnosis of IFEE was made based on histological examination of resected or biopsied intestines or was considered highly likely on the basis of visual and palpable examination of affected intestine. Surgeons' were asked to take photographic images of lesions that did not undergo histological examination and cases were excluded if they did not fulfil the gross characteristics already described. Histological examination was performed by experienced equine pathologists and had to fulfil the criteria that: i.) eosinophils constituted the majority of inflammatory cells at the site of the lesion and ii.) they were present in numbers that greatly exceeded the low numbers of this cell that are present in the intestinal mucosa and submucosa of normal horses and horses with other intestinal lesions (Meschter *et al.* 1986; Packer *et al.* 2005; Archer *et al.* 2006a). Cases of diffuse eosinophilic infiltration of small intestine causing clinical signs of weight loss or hypoalbuminaemia were excluded from the study.

Surgeons' experienced in the diagnosis and treatment of surgical colic based at clinics in the UK, Ireland and USA were asked if they would be willing to participate in the study and to notify the principal investigator if they identified any cases. These surgeons were visited by the principal investigator to describe the case criteria or they were sent detailed information in order to avoid misdiagnosis or non-recognition of lesions. Surgeons were asked to submit samples for histopathologic examination if their clinical judgement indicated that intestinal resection was necessary. Histological examination was offered free of charge for any suspected lesions. When a case of IFEE was identified, the owner or carer of the horse was informed about the study by the collaborating clinic and they were asked if they were willing to participate in the study. Once owner / carer consent had been obtained, telephone contact was made by the principal investigator with the client to arrange a convenient time to conduct the questionnaire as soon as possible after surgery (depending on individual clinic requests and client wishes).

Study power

Sample size estimation was performed using Win Episcope 2.0 (www.clive.ed.ac.uk/winepiscope). An unmatched study with 42 cases and 3 controls per case, assuming 40% exposure in controls (e.g. high parasite burden), has 95% confidence and 80% power to detect odds ratios of 2.75 or higher.

Questionnaire design

The questionnaire was constructed using information from previous epidemiological studies investigating colic and hypotheses considered to be biologically plausible as risk factors for IFEE. General questions included signalment, a history of previous colic, stabling and turnout routines, feed types and changes in management routines which are known risk factors for colic in general (Archer and Proudman 2006). Specifically we wished to investigate if parasites or dietary allergies were implicated in this condition. Questions were asked about feed types and feeding practices, provision of dietary supplements, recent (i.e. within the previous 28 days) administration of different feed types or supplements, pasture types and turnout routines, recent changes in pasture and methods of parasite control including the last and penultimate anthelmintic products administered and pasture management for parasites. Questions were grouped into the following categories: signalment and use, medical history, general premises details, stabling and turnout, nutrition, exercise and transport, behaviour and preventive healthcare.

Data collection

The questionnaire was conducted over the telephone by the principal investigator. Data were entered onto a data-capture form and an Access database was created using a data entry scanner (Fujitsu fi-4120C2) and software (TeleForm v9, Verity Inc.). Scanned data were verified using the software programme to identify values out-with pre-defined ranges and multiple instead of single data entries in tick boxes before committing the scanned data into the database.

Sample collection and analysis

Faecal and serum samples were collected from the cases during hospitalisation for parasitological examination. The owners / carers of control horses were asked to collect a faecal sample from the selected control horses within 4 weeks following completion of the questionnaire and prior to the next administration of an anthelmintic. Serum samples were not collected from control horses. To maximise compliance, owners were offered the results of the faecal worm egg count free of charge and were provided with sample pots and pre-paid envelopes for sample return. A faecal egg count test was performed using the McMaster method. The serum samples were assayed for anti- 12/13 kDA antigens to the tapeworm *Anoplocephala perfoliata* using an ELISA test (Proudman and Trees 1996b). Serum optical densities (O.D) of these antigens have been shown to correlate with the intensity of tapeworm infection (Proudman and Trees 1996a). Tapeworm burdens were defined as negative / low (OD <0.200), moderate (OD 0.200 – 0.600) or high (OD > 0.600).

Statistical Analysis

Screening of all variables was performed using a univariable logistic or conditional logistic regression model for the unmatched or matched studies respectively with IFEE as the dependent variable. The statistical package Stata (Stata Corp. LP) was used for data analysis. Categorical variables with small numbers of observations in one or more categories were re-coded to create fewer categories or to create a different reference category. Continuous variables were examined in their continuous state and were categorised into quintiles, quartiles or other biologically plausible categories. If the relationship between the continuous variables and outcome was considered to be significantly non-linear, other polynomial relationships were explored to see if they significantly improved the fit of the model. To reduce the effects of collinearity, continuous variables were centred by subtracting the mean of the variable from all recorded observations (Kleinbaum *et al.* 1988) prior to producing higher order terms.

The functional form of the relationships between the continuous explanatory variables and binary outcome (IFEE) in the unmatched case-control study were explored using generalised additive models (GAM). These are an extension of generalised linear models where variables are included additively via the link function and are not assumed to take a linear form, replacing the usual linear function of a covariate with a cubic spline smoothing function (Hastie and Tibshirani 1990). The GAM models were fitted in the statistical package S-plus (Insightful Corp.).

Variables with a univariable P-value <0.25 were considered for subsequent inclusion into a multivariable model for each case-control study. Variables with >20% of missing values were excluded from the initial model-building procedure. To avoid problems associated with collinearity, where variables were considered to be measuring the same exposure or were shown to be highly correlated (Pearson correlation coefficient >0.9), the most statistically significant or biologically plausible variable was selected. The model was built using a backwards stepwise approach where variables were retained in the model if their manual exclusion resulted in a likelihood ratio test statistic (LRTS) of $P<0.05$. A change in the coefficient of >25% was considered to be indicative of confounding. The effect of biologically plausible interaction terms was tested in both models. The fit of the model from the unmatched case-control study was assessed using the Hosmer-Lemeshow test statistic (Hosmer and Lemeshow 2000). The predictive ability of this model was also assessed by computing the sensitivity and specificity of the model at various cut-off points and by generating a receiver operating characteristic (ROC) curve. Cases of IFEE that had not been confirmed histologically were removed to assess their effect on both models. Finally, variables with large delta betas were removed to assess model stability. Each model was considered to be stable if removal of individual cases or controls altered the odds ratio by <25% and did not affect the significance of individual variables.

Results

Matched IFEE study

Descriptive results

Thirty one cases of IFEE and 93 matched controls were recruited onto the study over a 32 month study period. Based upon the original power calculations, this resulted in 95% confidence and 80% power to detect odds ratios of 3.25 or greater.

Twenty of the cases (64.5%) were confirmed histologically; 11 cases did not undergo intestinal resection nor was a biopsy taken but their visual appearance at laparotomy was consistent with the other cases. One unusual plaque like lesion was submitted for histopathology as a questionable case of IFEE during the study period but this was diagnosed histologically as a lymphoma and was therefore not recruited onto the study. All the circumferential lesions examined histologically were confirmed to be IFEE lesions. One horse had a circumferential lesion of the small intestine and an additional thickened, hyperaemic plaque-like lesion of the small colon which was confirmed to be an idiopathic focal colitis lesion.

The seasonal distribution of the cases is shown in Figure 1. Cases occurred throughout the study period with 9 of the cases (29%) occurring in the month of June 2005. The distribution of cases recruited from the UK, Ireland and USA is shown in Figure 2. Cases of IFEE were recruited from a total of 8 clinics (Figure 3) and 81% of the cases were submitted from 3 of these clinics (1 in the UK and 2 in Ireland). Four cases were recruited from 2 premises within a few days of each other (i.e. two cases from each of the two premises). The two pairs of horses had been sharing the same pasture with other horses on the same premises but none of these horses were subsequently diagnosed with IFEE during the study period.

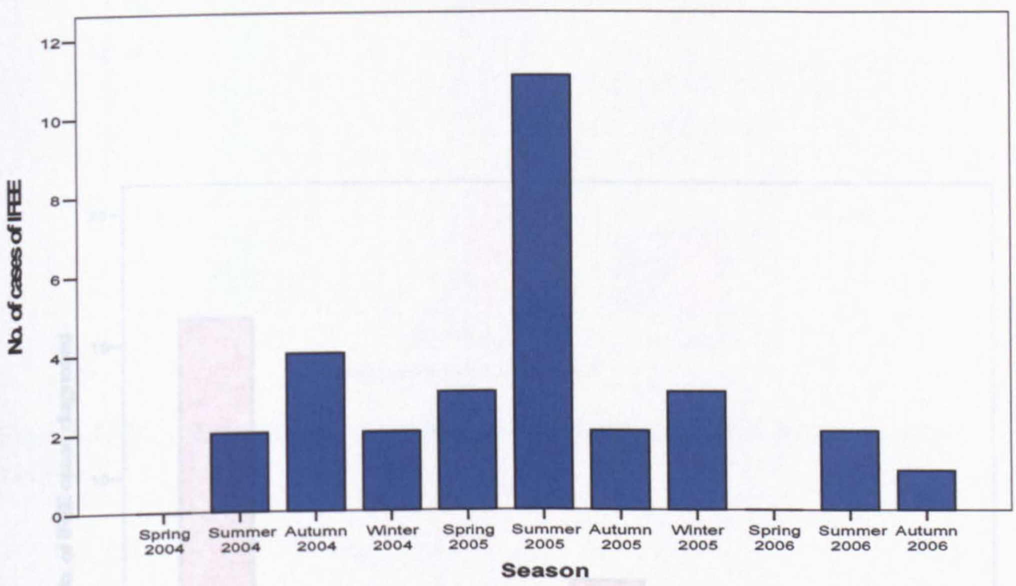


Figure 1. Seasonal distribution of 31 cases of idiopathic focal eosinophilic enteritis (IFEE) recruited onto the matched case-control study between January 2004 – September 2006. Seasons were defined as: Spring (March – May), Summer (June – August), Autumn (September – November) and Winter (December – February).

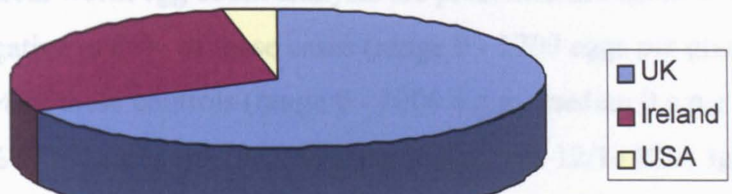


Figure 2. Geographical distribution by country of 31 cases of idiopathic focal eosinophilic enteritis (IFEE) recruited onto the matched case-control study.

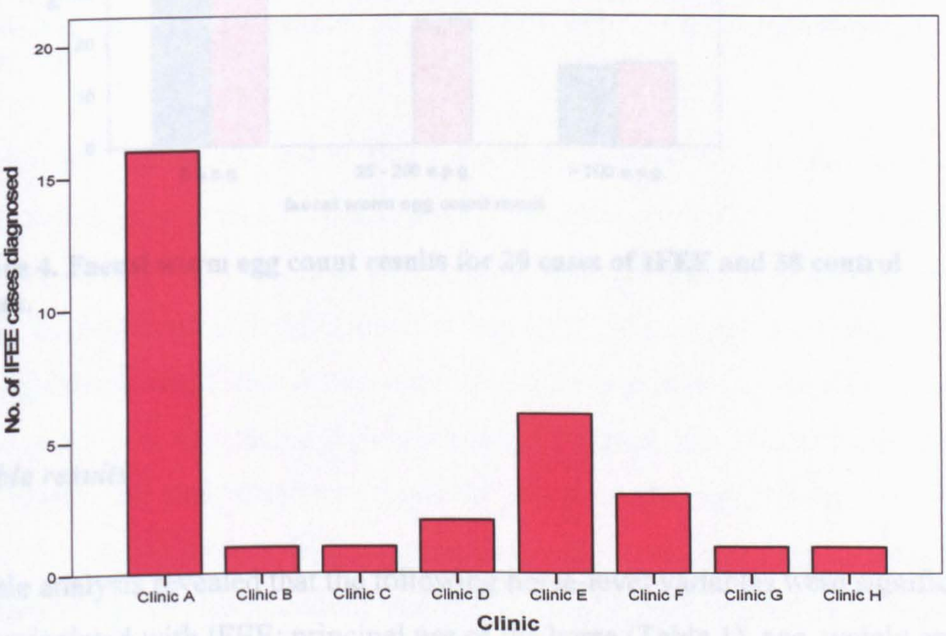


Figure 3. Numbers of cases of idiopathic focal eosinophilic enteritis (IFEE) lesions at the eight clinics that diagnosed these lesions during the study period.

Faecal samples were obtained from 64.5 % of the cases (n=20) and 41% of the controls (n=38). The results of faecal worm egg count analysis are presented in Figure 4. The faecal worm egg count was negative in 85% of these cases (range 0 - 1700 eggs per gram[e.p.g], median 0 e.p.g.) and 60% of these controls (range 0 - 2000 e.p.g., median 0 e.p.g.). Serum was submitted from 58% of the cases (n=18). Measurement of anti 12/13 kDA IgG(T) antibody levels identified tapeworm burdens to be negative / low in 72% of these cases and moderate in 28% (range 0.009 – 0.438 O.D. , median 0.152 O.D.). No cases were identified to have high tapeworm burdens.

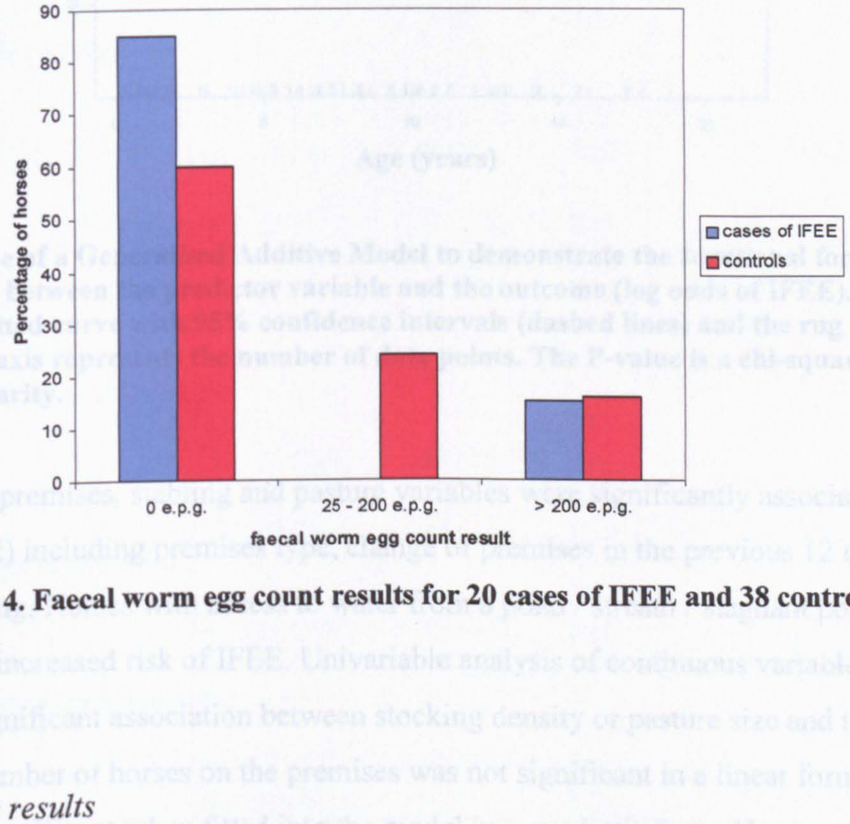


Figure 4. Faecal worm egg count results for 20 cases of IFEE and 38 control horses.

Univariable results

Univariable analysis revealed that the following horse-level variables were significantly ($p<0.05$) associated with IFEE: principal use of the horse (Table 1), age, weight and height (Tables 5 & 6). Age was correlated with height and weight and was chosen for inclusion in the multivariable model based on biological plausibility and statistical significance. Examination of categorised results for age (Table 5) and a GAM plot (Figure 5), with the matching broken, indicated that a piecewise linear function (Parkin *et al.* 2005) with a change point at 2 years of age best described the functional form of the relationship between age and risk of IFEE. A number of other change points were tested in order to identify the one which most reduced the residual deviance of the model; a change point of 2 years was considered to represent the best fit in the model and was highly significant (p < 0.0001).

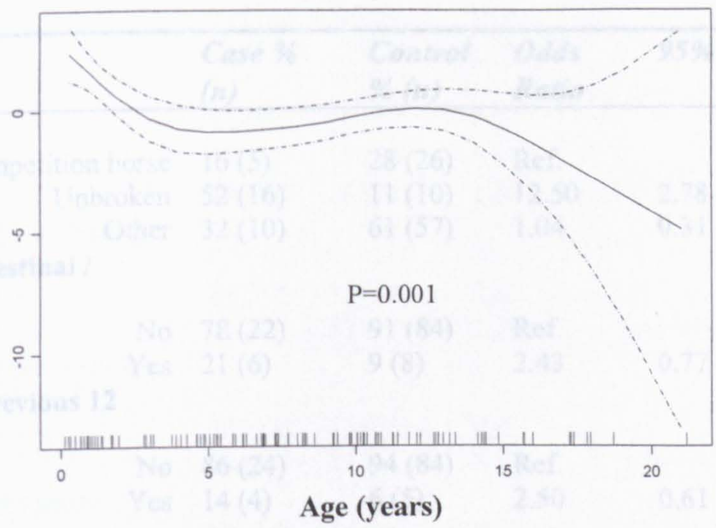


Figure 5. Use of a Generalised Additive Model to demonstrate the functional form of the relationship between the predictor variable and the outcome (log odds of IFEE). The plot shows the fitted curve with 95% confidence intervals (dashed lines) and the rug plot along the x-axis represents the number of data points. The P-value is a chi-square test for non-linearity.

A number of premises, stabling and pasture variables were significantly associated with IFEE (Tables 1 & 2) including premises type, change of premises in the previous 12 months and current stabling. Horses with access to water from a pond / stream / stagnant pool were at significantly increased risk of IFEE. Univariable analysis of continuous variables (Table 5) revealed a significant association between stocking density or pasture size and the risk of IFEE. The number of horses on the premises was not significant in a linear form, but was statistically significant when fitted into the model in a quadratic form. Horses receiving supplementary forage or oil as a dietary supplement, feeding an increasing weight of supplementary forage, horses in current exercise and those who had been transported in the previous 7 days were associated with a significant decrease in risk of IFEE (Table 3). The duration since dental examination had been performed, whether horses were vaccinated on a routine basis and the frequency of anthelmintic administration were also significantly associated with IFEE in univariable analysis of information obtained on preventive healthcare. Univariable analysis of the categorised and continuous results for faecal egg count did not reveal a significant association between this variable and the risk of IFEE.

Table 1. Results of univariable conditional logistic regression analysis of categorical variables with a P-value <0.25 obtained from information on signalment and use, medical history and premises.

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Principal use						
	Competition horse	16 (5)	28 (26)	Ref.		
	Unbroken	52 (16)	11 (10)	12.50	2.78 – 56.50	<0.001
	Other	32 (10)	61 (57)	1.04	0.31 – 3.45	
Dental / Gastrointestinal / Weight loss						
	No	78 (22)	91 (84)	Ref.		
	Yes	21 (6)	9 (8)	2.43	0.77 – 7.72	0.137
Colic episode in previous 12 months						
	No	86 (24)	94 (84)	Ref.		
	Yes	14 (4)	6 (5)	2.50	0.61 – 10.23	0.209
Premises type						
	Private yard	48 (15)	41 (38)	Ref.		
	Livery yard	26 (8)	33 (31)	0.56	0.19 – 1.64	
	Stud farm	23 (7)	10 (9)	2.96	0.50 – 17.49	0.040
	Other	3 (1)	16 (15)	0.19	0.20 – 1.83	
No. of premises in previous 12 months						
	1	32 (10)	57 (53)	Ref.		
	2	39 (12)	29 (27)	2.23	0.87 – 5.71	0.058
	>2	29 (9)	14 (13)	3.15	1.11 – 8.92	
Premises change in previous 12 months						
	No	32 (10)	57 (53)	Ref.		
	Yes	68 (21)	43 (40)	2.57	1.13 – 5.83	0.021
Premises change in previous 28 days						
	No	81 (25)	92 (83)	Ref.		
	Yes	19 (6)	8 (7)	2.56	0.80 – 8.14	0.119

Table 2. Results of univariable conditional logistic regression analysis of categorical variables with a P-value <0.25 obtained from information on stabling and pasture turnout.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Current stabling					
No	52 (16)	30 (28)	Ref.		
Yes	48 (15)	70 (65)	0.32	0.12 – 0.83	0.016
Stable type					
Indoor barn	24 (7)	19 (17)	Ref.		
Outside stable block	41 (12)	57 (50)	0.57	0.17 – 1.86	0.230
Not stabled	34 (10)	24 (21)	1.50	0.37 – 6.10	
Bedding change (type / batch) in previous 28 days					
No	87 (27)	95 (88)	Ref.		
Yes	13 (4)	5 (5)	2.29	0.61 – 8.56	0.230
Bedding change (type / batch) in previous 14 days					
No	90 (28)	97 (98)	Ref.		
Yes	10 (3)	3 (3)	2.81	0.56 – 13.96	0.217
Duration on current pasture					
< 2 months	57 (17)	44 (36)	Ref.		
2 – 6 months	31 (9)	26 (21)	0.91	0.30 – 2.77	0.053
> 6 months	10 (3)	30 (24)	0.25	0.07 – 0.92	
Change of pasture in previous 28 days					
No	52 (15)	69 (63)	Ref.		
Yes	48 (14)	31 (28)	2.14	0.86 – 5.31	0.096
Running water source at pasture					
No	84 (26)	94 (87)	Ref.		
Yes	16 (5)	6 (6)	2.79	0.79 – 9.79	0.117
Stagnant water source at pasture					
No	81 (25)	96 (89)	Ref.		
Yes	19 (6)	4 (4)	5.44	1.34 – 22.01	0.014
Access to water from a stream / pond / stagnant pool					
No	65 (20)	89 (83)	Ref.		
Yes	35 (11)	11 (10)	4.10	1.56 – 10.74	0.004
Other species grazed on current pasture in previous 12 months					
No / Not applicable	39 (12)	57 (52)	Ref.		
Yes	61 (19)	43 (40)	1.92	0.85 – 4.36	0.110
Other species grazing in adjacent pastures					
No / Not applicable	35 (11)	53 (49)	Ref.		
Yes	65 (20)	47 (43)	1.97	0.85 – 4.54	0.103
Soil disturbance in or immediately adjacent to current pasture					
No / Not applicable	83 (24)	92 (83)	Ref.		
Yes	17 (5)	8 (7)	2.30	0.65 – 8.20	0.204

Mineral deficiencies in the soil of pastures currently grazed					
No - tested	42 (5)	71 (22)	Ref.		
Yes - tested	58 (7)	29 (9)	5.61	0.55 – 57.30	0.114

Table 3. Results of univariable conditional logistic regression analysis of categorical variables with a P-value <0.25 obtained from information on feed types and feeding practices, behaviour in relation to feeding, exercise and transport.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Feeding of hay / haylage					
No	42 (13)	23 (21)	Ref.		
Yes	58 (18)	77 (72)	0.31	0.11 – 0.84	0.020
Currently fed haylage					
No	71 (22)	59 (55)	Ref.		
Yes	29 (9)	41 (38)	0.21	0.23 – 1.39	0.212
Change in batch of roughage in previous 14 days					
No	78 (18)	88 (66)	Ref.		
Yes	22 (5)	12 (9)	2.21	0.62 – 7.85	0.227
Change in batch of roughage in previous 7 days					
No	87 (20)	95 (71)	Ref.		
Yes	13 (3)	5 (4)	2.62	0.52 – 13.08	0.248
Local feed mill concentrate fed					
No	93 (28)	82 (75)	Ref.		
Yes	7 (2)	18 (16)	0.32	0.07 – 1.49	0.104
Grain fed					
No	94 (29)	82 (75)	Ref.		
Yes	6 (2)	18 (17)	0.31	0.07 – 1.40	0.084
Increased quantity of concentrate in previous 28 days					
No	81 (25)	91 (79)	Ref.		
Yes	19 (6)	9 (8)	2.22	0.74 – 6.70	0.165
Increased quantity of concentrate in previous 14 days					
No	87 (27)	96 (82)	Ref.		
Yes	13 (4)	4 (3)	5.16	0.92 – 28.83	0.053
Change in concentrate type / brand in previous 28 days					
No	80 (24)	91 (79)	Ref.		
Yes	20 (6)	9 (8)	3.83	0.88 – 16.61	0.066
Currently receives oil in feed					
No	90 (28)	71 (66)	Ref.		
Yes	10 (3)	29 (27)	0.28	0.08 – 0.99	0.024
Other supplement					
No	58 (18)	65 (60)	Ref.		
Yes	42 (13)	35 (33)	1.28	0.56 – 2.94	0.558
Supplement added within previous 28 days					

No	84 (26)	95 (87)	Ref.		
Yes	16 (5)	5 (5)	2.96	0.86 – 10.28	0.094
Feeding behaviour when stressed					
Eats normally	96 (22)	87 (77)	Ref.		
Goes of food in full / part	4 (1)	13 (12)	0.32	0.04 – 2.66	0.230
Current exercise					
No	61 (19)	32 (30)	Ref.		
Yes	39 (12)	68 (63)	0.26	0.10 – 0.66	0.003
Transport in previous 28 days					
No	74 (23)	63 (58)	Ref.		
Yes	26 (8)	37 (34)	0.57	0.22 – 1.48	0.235
Transport in previous 7 days					
No	97 (30)	76 (68)	Ref.		
Yes	3 (1)	24 (21)	0.12	0.02 – 0.95	0.006

Table 4. Results of univariable conditional logistic regression analysis of categorical variables with a P-value <0.25 obtained from information on preventive healthcare and the results of a faecal worm egg count.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Duration since teeth last checked					
Less than 12 months previously	63 (12)	79 (67)	Ref.		
More than 12 months previously / never done	37 (7)	21 (18)	3.74	1.06 – 13.13	0.035
Receives routine vaccinations					
Yes	77 (23)	91 (83)	Ref.		
No	23 (7)	9 (8)	3.80	1.06 – 13.63	0.037
Frequency of anthelmintic administration					
Every 6 – 13 weeks	59 (17)	68 (63)	Ref.		
More than every 6 weeks	21 (6)	5 (5)	6.59	1.23 – 35.40	0.046
Every 14 – 24 weeks or less	21 (6)	27 (25)	0.95	0.34 – 2.68	
Anthelmintic administration in previous 14 days					
No	66 (19)	77 (65)	Ref.		
Yes	31 (10)	23 (19)	1.75	0.70 – 4.35	0.235
Anthelmintic administration in previous 7 days					
No	79 (23)	90 (76)	Ref.		
Yes	21 (6)	10 (8)	2.71	0.87 – 8.44	0.091
Worm egg count or tapeworm ELISA performed within last 12 months					
No	87 (27)	79 (70)	Ref.		
Yes	13 (4)	21 (19)	0.46	0.12 – 1.74	0.227
Faecal worm egg count results negative					
Yes	85 (17)	61 (23)	Ref.		
No	15 (3)	39 (15)	0.23	0.03 – 2.00	0.125

Table 5. Results of univariable conditional logistic regression analysis of categorised continuous variables with a P-value <0.25.

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Age (years)	< 2	52 (16)	52 (16)	Ref.		
	2 - 5	6 (2)	23 (21)	0.01	0.01 – 0.16	
	6 - 8	13 (4)	25 (23)	0.03	0.01 – 0.28	<0.001
	9 - 11	16 (5)	22 (20)	0.03	0.01 – 3.16	
	>11	13 (4)	24 (22)	0.02	0.01 – 0.23	
Height (cm)	< 144	26 (8)	14 (13)	Ref.		
	144 – 155	52 (16)	20 (19)	1.58	0.45 – 5.61	
	156 – 165	6 (2)	37 (34)	0.12	0.02 – 0.62	<0.001
	> 165	16 (5)	29 (27)	0.31	0.07 – 1.34	
Weight (kg)	< 400	39 (12)	15 (14)	Ref.		
	400 – 499	29 (9)	23 (21)	0.49	0.17 – 1.39	
	500 – 549	3 (1)	18 (17)	0.06	0.01 – 0.52	0.004
	> 549	29 (9)	44 (41)	0.21	0.07 – 0.68	
Hours grazing per week	< 22	13 (4)	25 (23)	Ref.		
	22 – 62	26 (8)	28 (26)	1.65	0.44 – 6.25	
	63 – 167	16 (5)	19 (18)	1.52	0.35 – 6.59	0.216
	168	45 (14)	28 (26)	3.54	0.96 – 13.04	
Stocking density (horses per acre)	<0.65	59 (16)	12 (10)	Ref.		
	0.66 – 1.20	15 (4)	28 (22)	0.05	0.01 – 0.37	
	1.21 – 3.9	15 (4)	30 (24)	0.08	0.01 – 0.44	<0.001
	> 3.9	11 (3)	30 (24)	0.05	0.01 – 0.34	
Pasture size (acres)	< 1.0	15 (4)	21 (17)	Ref.		
	1.0 – 2.0	19 (5)	33 (26)	0.96	0.19 – 4.96	
	2.1 – 4.9	22 (6)	22 (18)	1.17	0.22 – 6.13	0.243
	> 4.9	44 (12)	24 (19)	2.97	0.71 – 12.43	
Number of horses with access to current pasture	1 / not currently turned out	17 (5)	29 (22)	Ref.		
	2	67 (11)	18 (16)	3.37	0.85 – 13.43	
	3 – 4	27 (8)	22 (20)	1.78	0.52 – 6.09	0.106
	>4	20 (6)	36 (33)	0.80	0.19 – 3.46	
Supplementary forage weight per day (kg)	0	52 (13)	27 (20)	Ref.		
	0.1 – 6.0	28 (7)	25 (26)	0.24	0.06 – 0.97	0.009
	>6.0	20 (5)	39 (29)	0.10	0.02 – 0.54	

Total weight of concentrate / grain fed per day (kg)	< 0.20	48 (12)	27 (24)	Ref.		
	0.20 – 1.0	28 (7)	36 (32)	0.39	0.12 – 1.23	0.215
	> 1.0	24 (6)	36 (32)	0.49	0.15 – 1.60	

Table 6. Results of univariable conditional logistic regression analysis of continuous variables with a P-value <0.25.

Variable	*Unit of measurement*	*Mean / median*	*Coefficient*	*Standard Error*	P-value
Age (linear)	years	7.6	-0.188	0.059	<0.001
Age (piecewise linear)	years		-2.757	0.007	<0.001
Height	cm	154	-0.259	0.012	0.022
Weight	kg	483	-0.005	0.002	0.003
No. horses on premises (linear)		12	0.008	0.007	0.256
No. horses on premises (quadratic)					
No. horses on premises			-0.035	0.017	0.037
No. horses on premises squared			0.0005	0.0002	0.012
No. of hours stabled per week	hours per week	85	-0.006	0.004	0.118
No. of hours grazing per week	hours per week	88	0.006	0.003	0.086
Stocking density	horses per acre	1.25	-0.394	0.175	0.001
Pasture size	acres	2.5	0.165	0.069	<0.001
No. of horses with current access to pasture		4.7	-0.060	0.055	0.238
Supplementary forage weight per day	kg	4.0	-0.133	0.064	0.014

Multivariable results

The final multivariable model is shown in Table 7. There was a linear decrease in risk of IFEE up to 2 years of age; the risk then levelled out as age increased beyond this point. The relationship between the numbers of horses on the premises and the risk of IFEE was best described by a quadratic curve based on examination of a GAM plot for this variable with the matching broken (Figure 6). The variables 'Colic in the previous 12 months' and 'Access to water from a pond / stream / stagnant pool' significantly improved the fit of the model. However the change in risk associated with these variables should be interpreted with caution due to the wide 95% confidence intervals that cross 1. There was no interaction between any of the variables in the model.

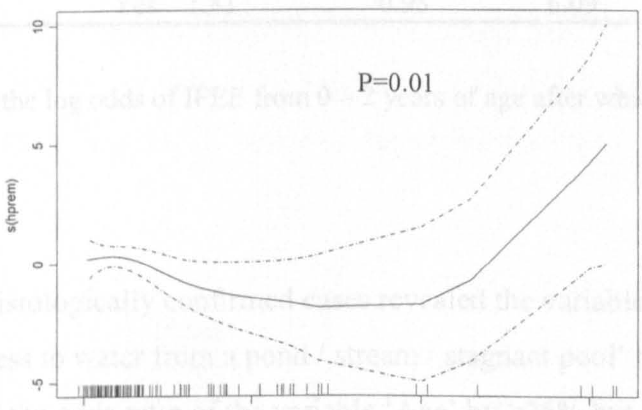


Figure 6. Use of a Generalised Additive Model to demonstrate the functional form of the relationship between the predictor variable and the outcome (log odds of IFEE). The plot shows the fitted curve with 95% confidence intervals (dashed lines) and the rug plot along the x-axis represents the number of data points. The P-value is a chi-square test for non-linearity.

Table 7. Multivariable conditional logistic regression model of horse- and premises-level risk factors for idiopathic focal eosinophilic enteritis.

Variable		*Coefficient*	*Standard Error*	*Adjusted Odds ratio*	*95% CI*	*LRTS P-value*
Age (piecewise linear)*		-3.62	1.26	0.03	0.002 – 0.31	<0.001
No. of horses on premises (quadratic)						
Horses on premises		-0.06	0.03	0.94	0.89 – 0.99	0.256
Horses on premises squared		0.001	0.00	1.001	1.00 – 1.002	0.008
Colic in the previous 12 months						
	No	Ref.		1.00		
	Yes	2.63	1.35	13.90	0.98 – 197.13	0.025
Access to water from a pond / stream / stagnant pool						
	No	Ref.		1.00		
	Yes	1.81	0.98	6.09	0.89 – 41.84	0.049

*linear reduction in the log odds of IFEE from 0 – 2 years of age after which the risk levels off.

Removal of non-histologically confirmed cases revealed the variables 'Colic in previous 12 months' and 'Access to water from a pond / stream / stagnant pool' to be stable. Removal of these cases altered the odds ratio of the variable 'Age' by >25% but did not change the significance of this variable in relation to the critical P-value of 0.05. The variable 'Number of horses on premises' became non-significant when these cases were removed.

Removal of matched sets containing cases and controls with large delta betas revealed the variables 'Number of horses on premises' and 'Access to water from a pond / stream / stagnant pool' to be stable. The magnitude of the odds ratio for the variable 'Colic in the previous 12 months' increased by >25% but did not change the significance of this variable in relation to the critical P-value of 0.05. Removal of 2 cases and a single control (and hence 2 matched sets) with large delta betas for the variable 'Age' altered the magnitude of the odds ratio by >25% and changed the significance of the variable in relation to the critical P-value of 0.05.

Unmatched IFEE study

Descriptive results

Data were obtained from 18 cases of IFEE and 216 controls in the UK over a 24 month period. These cases of IFEE were a subset of the cases described in the matched case-control study. Based on the original power calculations, a study with 18 cases and 220 controls has 80% power and 95% confidence to detect odds ratios of 4.0 or greater.

Samples were submitted for histopathological examination in 15 of the cases (83%) and all were confirmed histologically as IFEE lesions. Faecal samples were submitted from 44% of the cases (n=12) and 49% of the controls (n=106). The results of faecal worm egg count analysis are presented in Figure 7. Serum samples were obtained from 55% of the cases (n=10) for analysis of tapeworm burdens. Measurement of anti 12/13 kDA IgG(T) antibody levels identified tapeworm burdens to be negative / low in 67% of these cases and moderate in 33%. No cases were identified to have high tapeworm burdens.

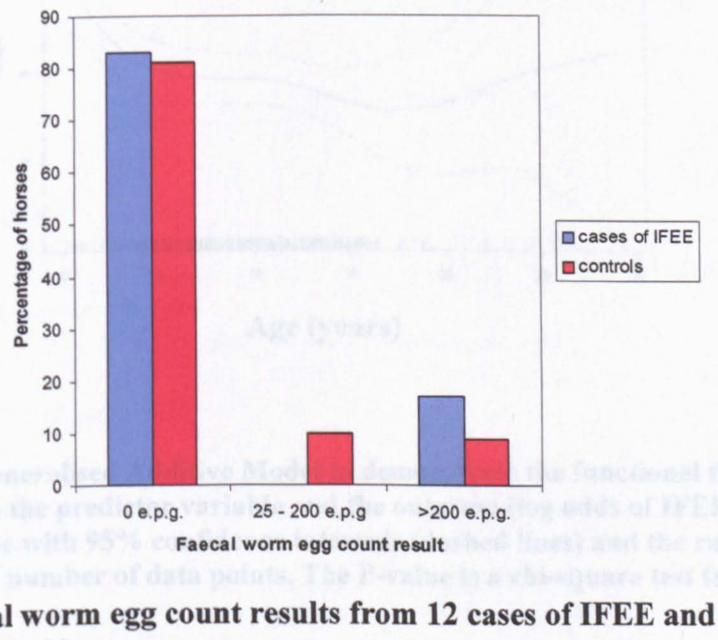


Figure 7. Faecal worm egg count results from 12 cases of IFEE and 99 unmatched control horses.

Univariable analysis

The results of univariable logistic regression analysis of the categorical variables are presented in Table 8. Current use of the horse, horses with current / recent access to a pond / stream / stagnant pool at pasture or those receiving oil as a dietary supplement, the use of a benzimidazole as the last anthelmintic administered and anthelmintic treatment for tapeworms in the previous 12 months were significantly associated with risk of IFEE.

Univariable analysis of continuous variables (Tables 9 & 10) revealed that the risk of IFEE reduced with increasing age. Examination of age in its categorised form and with a GAM (Figure 8) indicated that a piecewise linear term was most appropriate. A cut-off point of 5 years of age provided the best fit in the model.

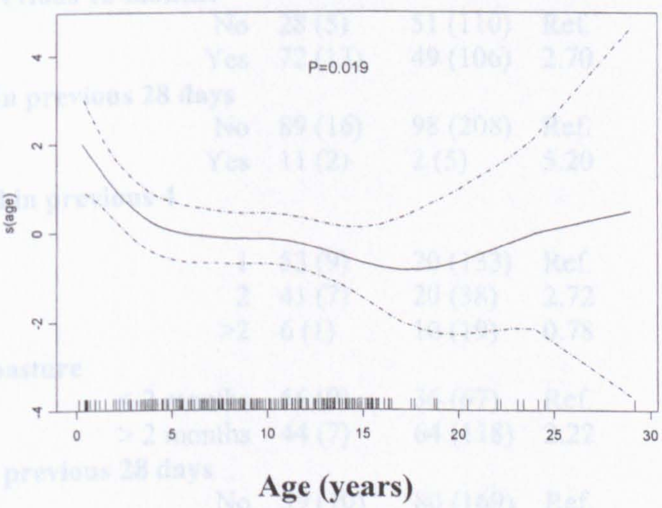


Figure 8. Use of a Generalised Additive Model to demonstrate the functional form of the relationship between the predictor variable and the outcome (log odds of IFEE). The plot shows the fitted curve with 95% confidence intervals (dashed lines) and the rug plot along the x-axis represents the number of data points. The P-value is a chi-square test for non-linearity.

Table 8. Results of univariable logistic regression analysis of categorical variables with a P-value <0.25.

Variable	*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Season					
Winter (December – February)	11 (2)	25 (54)	Ref.		
Spring (March – May)	28 (5)	25 (54)	2.50	0.46 – 13.45	
Summer (June – August)	44 (8)	25 (54)	4.00	0.81 – 19.71	0.238
Autumn (September – November)	17 (3)	25 (54)	1.50	0.24 – 9.34	
Breed					
TB / WB / TBx / WBx	61 (11)	47 (101)	Ref.		
Other breed	39 (7)	53 (114)	0.44	0.16 – 1.22	0.106
Principal use					
Competition horse	22 (4)	36 (77)	Ref.		
Unbroken	45 (8)	7 (15)	10.27	2.74 – 38.49	0.002
Other	33 (6)	57 (124)	0.93	0.25 – 3.41	
Received veterinary treatment for a respiratory problem in the previous 12 months					
No	81 (13)	92 (191)	Ref.		
Yes	19 (3)	8 (16)	2.75	0.71 – 10.68	0.177
Premises change in previous 12 months					
No	28 (5)	51 (110)	Ref.		
Yes	72 (13)	49 (106)	2.70	0.93 – 7.83	0.055
Bedding type change in previous 28 days					
No	89 (16)	98 (208)	Ref.		
Yes	11 (2)	2 (5)	5.20	0.93 – 28.94	0.095
No. of pastures grazed in previous 4 weeks					
1	53 (9)	70 (133)	Ref.		
2	41 (7)	20 (38)	2.72	0.95 – 7.79	0.162
>2	6 (1)	10 (19)	0.78	0.09 – 6.49	
Duration on current pasture					
< 2 months	56 (9)	36 (67)	Ref.		
> 2 months	44 (7)	64 (118)	2.22	0.82 – 6.00	0.119
Change of pasture in previous 28 days					
No	59 (10)	80 (169)	Ref.		
Yes	41 (7)	20 (42)	2.82	1.01 – 7.84	0.056
Current access to water from a pond / stream / stagnant pool					
No	61 (11)	89 (188)	Ref.		
Yes	39 (7)	11 (24)	4.98	1.76 – 14.08	0.004
Feeding of hay / haylage					
No	33 (6)	20 (44)	Ref.		
Yes	67 (12)	80 (172)	0.51	0.18 – 1.45	0.220
Change of batch of roughage in previous 7 days					
No	94 (17)	99 (209)	Ref.		
Yes	6 (1)	1 (3)	3.20	0.62 – 16.52	0.208
Currently receives garlic / herbal feed supplement					

No	50 (9)	66 (143)	Ref.		
Yes	50 (9)	34 (73)	1.96	0.75 – 5.15	0.175
Currently receives oil in feed					
No	94 (17)	73 (158)	Ref.		
Yes	6 (1)	27 (58)	0.16	0.20 – 1.23	0.022
Currently exercised					
No	44 (8)	24 (52)	Ref.		
Yes	56 (10)	76 (164)	0.40	0.15 – 1.06	0.071
Transport in previous 28 days					
No	78 (14)	64 (135)	Ref.		
Yes	22 (4)	36 (77)	0.51	0.16 – 1.57	0.213
Behaviour at feed time					
Some / little interest	61 (11)	82 (175)	Ref.		
Agitated	39 (7)	18 (39)	2.86	1.04 – 7.83	0.051
Benzimidazole = last anthelmintic administered					
No	76 (13)	93 (162)	Ref.		
Yes	24 (4)	7 (12)	4.15	1.17 - 14.71	0.043
Anthelmintic treatment for tapeworms in the previous 12 months					
Yes	57 (8)	85 (156)	Ref.		
No	43 (6)	15 (27)	4.33	1.39 – 13.48	0.016
Faeces removed from the pasture					
No	56 (10)	89 (83)	Ref.		
Yes / not turned out at pasture	44 (8)	61 (130)	0.51	0.19 – 1.35	0.173

Table 9. Results of univariable logistic regression analysis of categorised continuous variables with a P-value of <0.25.

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
Age (years)						
	< 6	56 (10)	22 (48)	Ref.		
	6 - 8	11 (2)	19 (41)	0.23	0.05 – 1.13	0.034
	9 - 12	17 (3)	25 (54)	0.27	0.07 – 1.03	
	> 12	17 (3)	17 (3)	0.20	0.05 – 0.75	
Weight	< 400	44 (8)	14 (30)	Ref.		
	400 – 499	25 (53)	25 (53)	0.14	0.03 – 0.71	
	500 – 565	22(4)	42 (90)	0.17	0.05 – 0.59	0.017
	> 565	22 (4)	20 (43)	0.35	0.10 – 1.26	
Stocking density (horses per acre)	<0.61	56 (9)	22 (41)	Ref.		
	0.61 – 1.10	19 (3)	26 (48)	0.28	0.07 – 1.12	
	1.11 – 1.90	6 (1)	13 (24)	0.19	0.02 – 1.59	0.042
	> 1.90	19 (3)	39 (73)	0.19	0.05 – 0.73	

Table 10. Results of univariable conditional logistic regression analysis of continuous variables with a P-value of <0.25

Variable	*Unit of measurement*	*Mean / median*	*Coefficient*	*Standard Error*	**P-value**
Age (linear)	years	9.6	-0.200	0.061	<0.001
Age (piecewise linear)			-0.531	0.106	<0.001
Weight	kg	481	-0.002	0.002	0.228
Stocking density	horses per acre	1.11	-0.237	0.192	0.112
No. of horses with current access to pasture		2	-0.179	0.125	0.062

Multivariable analysis

The final multivariable model for the unmatched case-control study is shown in Table 11. The risk of IFEE reduced with increasing age until 5 years of age after which there was no change in risk. Horses that had current / recent access to a pond / stream / stagnant pool were at increased risk of IFEE. A protective effect of treating for tapeworms in the previous 12 months was also identified. A linear increase in the number of horses with weekly access to the current pasture was associated with decreased risk of IFEE in the final multivariable model. The latter variable improved the fit of the model but the change in risk associated with this variable should be interpreted with caution due to the wide 95% confidence interval that crosses 1.

No interaction was found between the variables in the final model. The Hosmer-Lemeshow test statistic revealed the model to be a good fit (P-value = 0.386). The sensitivity and specificity of the final multivariable model at various cut-off points is shown in Table 12 and Figure 9. Using a fitted probability cut-off value of 0.2, the model would have correctly predicted 64% of the cases and 95% of the controls. The area under the ROC curve (Figure 10) was 0.86 which indicates that the model has excellent discrimination between cases and controls (Hosmer and Lemeshow 2000). Removal of the 3 cases of IFEE that had not been confirmed histologically (the lesions had not been resected) changed the significance of the variable 'Treatment for tapeworms in the previous 12 months' in relation to the critical P-value of 0.05. The magnitude of the odds ratio of the variable 'Access to water from a pond / stream / stagnant pool' increased but there was no change of this variable in relation to the critical P-value of 0.05. Removal of individual cases and controls with large delta-betas revealed the variables 'Access to water from a pond / stream / stagnant pool' and 'No. of horses with access to pasture' to be stable. The variable 'Treatment for tapeworms in the previous 12 months' was unstable following the removal of a single case. Removal of 2 cases and 1 control with large delta betas for the variable 'Age' increased the magnitude of the odds ratio but did not change the significance of this variable in relation to the critical P-value of 0.05. Inspection of these cases and controls confirmed these data to be correct and so these individuals were retained in the final model.

Table 11. Multivariable logistic regression model of horse- and management-level risk factors for idiopathic focal eosinophilic enteritis. The table shows the coefficients, standard errors, likelihood ratio test statistic P-values, adjusted odds ratios and 95% confidence intervals (95% CI).

Variable		*Coefficient*	*Standard Error*	*Adjusted Odds ratio*	*95% CI*	*LRTS P-value*
Age (piecewise linear)*		-0.542	0.158	0.58	0.43 – 0.79	<0.001
No. of horses with access to pasture		-0.585	0.338	0.56	0.29 – 1.06	0.011
Treatment for tapeworms in the previous 12 months						
	Yes	Ref.		Ref.		
	No	1.597	0.747	4.94	1.17 – 20.75	0.033
Access to water from a pond / stream / stagnant pool						
	No	Ref.		Ref.		
	Yes	2.351	0.767	10.50	2.40 – 45.89	0.002

*linear reduction in the log odds of IFEE from 0 – 5 years of age after which the risk levels off.

Table 12. Sensitivity and specificity of the multivariable logistic regression model at cut-off points between 0.2 – 0.8.

Cut-off point	*Sensitivity (% of cases predicted)*	*Specificity (% of controls predicted)*
0.2	64	95
0.3	57	98
0.4	57	98
0.5	43	99
0.6	42	100
0.7	29	100
0.8	14	100

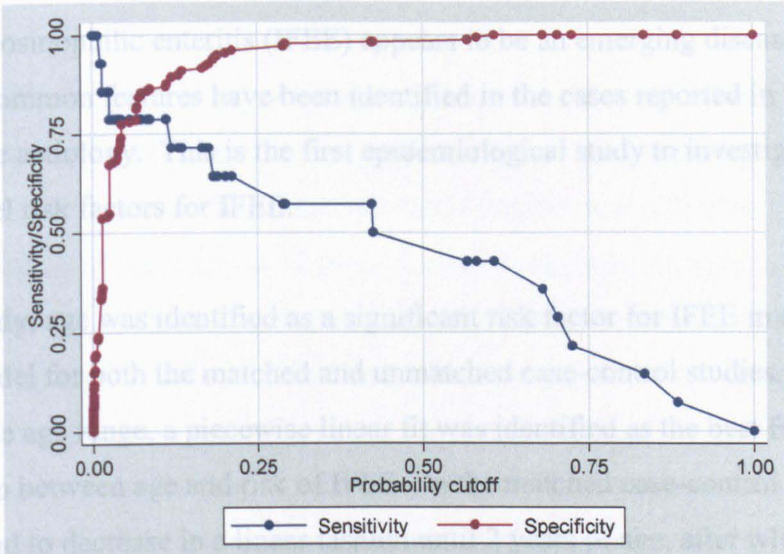


Figure 9. Graph showing the sensitivity and specificity of the multivariable logistic regression model in predicting cases of idiopathic focal eosinophilic enteritis and controls at various cut-off points for the fitted probability values.

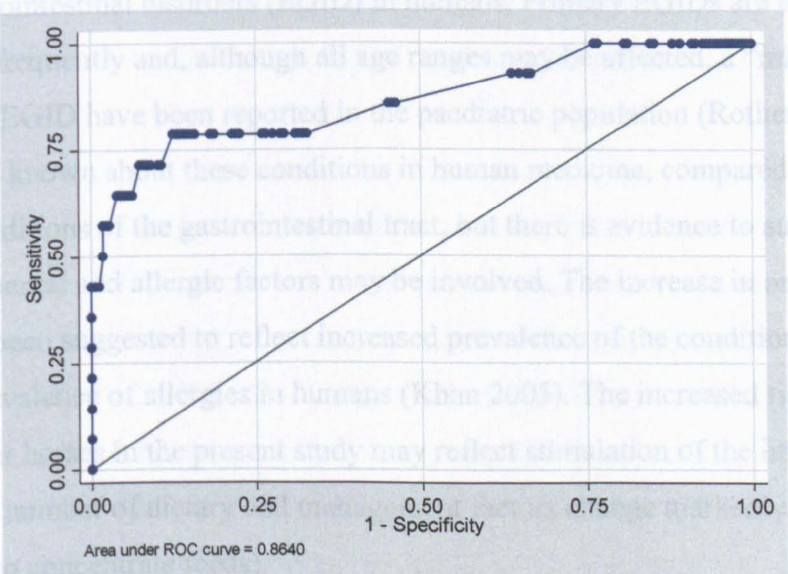


Figure 10. Receiver operating characteristic curve from the final multivariable logistic regression model.

Discussion

Idiopathic focal eosinophilic enteritis (IFEE) appears to be an emerging disease in the horse and, to date, no common features have been identified in the cases reported in the literature to suggest a possible aetiology. This is the first epidemiological study to investigate horse- and management-level risk factors for IFEE.

In the present study, age was identified as a significant risk factor for IFEE in the final multivariable model for both the matched and unmatched case-control studies. Whilst IFEE occurred in a wide age range, a piecewise linear fit was identified as the best functional form of the relationship between age and risk of IFEE. In the matched case-control study, the risk of IFEE was found to decrease in a linear fashion until 2 years of age, after which the risk levelled off. In the unmatched study there was a similar decrease in risk of IFEE with increasing age but the risk levelled off at 5 years of age. These differences in the cut-off points may be explained by the relatively higher proportion of young horses with IFEE that were recruited onto the matched study.

The apparently increasing incidence of IFEE (Proudman and Kipar 2006) and the finding that that younger horses appear to be at increased risk has some interesting parallels with eosinophilic gastrointestinal disorders (EGID) in humans. Primary EGIDs are being recognised more frequently and, although all age ranges may be affected, a "mini-epidemic" of some forms of EGID have been reported in the paediatric population (Rothenberg 2004). Relatively little is known about these conditions in human medicine, compared to other inflammatory conditions of the gastrointestinal tract, but there is evidence to suggest that genetic, environmental and allergic factors may be involved. The increase in recognition of this disorder has been suggested to reflect increased prevalence of the condition that parallels the increasing prevalence of allergies in humans (Khan 2005). The increased risk of IFEE evident in younger horses in the present study may reflect stimulation of the immune system at an age where a number of dietary and management factors change markedly (e.g. weaning and introduction to concentrate feeds).

Eosinophils play a key role in host defence against parasites and encapsulated nematodes have been identified as a cause of focal eosinophilic lesions of the small intestine and colon in the horse (Cohen *et al.* 1992). Therefore it might be reasonable to speculate that parasites play a role in the aetiopathogenesis of the IFEE lesions under investigation and was one of the main hypotheses investigated in the present study.

A number of questions relating to parasite control and pasture management for nematode and cestode parasites were asked but few of these variables were found to be significantly associated with IFEE. Horses that had received praziquantel or a double dose (38mg/kg) of pyrantel for tapeworms in the previous 12 months were found to be at decreased risk of IFEE in the final multivariable model in the unmatched study. However, care should be taken in over-interpreting this finding due to the fact that, whilst inclusion of this variable significantly improved the fit of the model, the 95% confidence intervals crossed the value 1. In addition this variable was unstable in the model when a single case with a large delta-beta for this variable was removed. This question was designed as a proxy measure for tapeworm burdens because it was not feasible in the present study to obtain serum samples from control horses in order to measure anti- 12/13kDA tapeworm antigens and it does not confirm the true tapeworm burdens in the horses under investigation. In addition, the majority of the cases of IFEE for which serum samples were obtained had low optical densities for antibody to tapeworm and none of the cases in the study were classified as having a high tapeworm burden. Therefore there was limited evidence in the present study to implicate nematode or cestode parasites in the aetiopathogesis of IFEE lesions. This finding is supported by the fact that these parasites have not been identified on histological examination of the IFEE lesions reported to date nor were they identified in any of the lesions examined histologically in the present study.

The *a priori* hypotheses for asking about accessible sources of water at pasture was to investigate whether other infectious agents, including parasites other than helminths or cestodes, could be potential aetiologic agents from certain water sources and to rule out water deprivation as a factor (Cohen 2003). The fungus *Pythium* has been identified as a cause of eosinophilic lesions of the small intestine in two horses (Allison and Gillis 1990; Morton *et al.* 1991). Whilst *Eimeria* parasites have been shown to be an incidental finding in normal horses (Hirayama *et al.* 2002) they were noted on histological examination of two IFEE lesions (Scott *et al.* 1999; Archer *et al.* 2006a). These parasites were not identified on any of the lesions examined histologically in the present study.

In the present study, horses that had current or recent (within the previous 28 days) access to water from a pond, stream or stagnant pool were identified to be at increased risk of IFEE in the multivariable model of both studies. If the pasture being grazed had ponds or streams that were fenced off, these were not classified as accessible water sources. There was no significant confounding of this variable by size of pasture or types of pasture management on these premises e.g. faeces removal from pasture. This finding warrants further investigation including analysis of water from these sources (where applicable) in cases of IFEE to identify a potential causal agent or agents.

A history of colic in the previous 12 months was associated with increased risk of IFEE in the final multivariable model in the matched case-control study. However, care should be taken in over-interpreting this finding due to the wide 95% confidence intervals that crossed the value 1. This variable was not found to be significant in the unmatched case-control study but 3 of the 18 cases of IFEE recruited onto the latter study had been owned for less than 12 months and their full medical history, including a previous colic episode, was unknown. A history of previous colic has been identified as a risk factor for colic in general and for some specific types of colic. There is an increasing amount of evidence to suggest that some horses are predisposed to colic. In humans abdominal pain is the most common clinical presentation of EGID and recurrence of the condition may be evident in some patients after discontinuation of steroid therapy (Khan 2005). It is reasonable to speculate that these episodes of colic may have been associated with eosinophilic infiltration of the intestine but it is impossible to confirm this conclusively. Follow-up studies of recurrent colic in cases of IFEE confirmed surgically are complicated by knowledge that laparotomy and small intestinal surgery are known risk factors for recurrent colic (Proudman *et al.* 2002a).

It is unclear why an association was found between the numbers of horses currently resident on the premises (matched case-control study) and between the numbers of horses with current access to the pasture (unmatched case-control study) and the risk of IFEE. The increased risk of IFEE on premises with 6 – 29 horses compared to horses on premises with fewer or greater horses in the matched case-control study may be a marker for management practices on mid-size premises e.g. feeding practices. Whilst a number of management variables were measured, the effect of these factors may have been too small for them to be statistically significant on their own. Alternatively this finding may be due to other, unmeasured factors. In the unmatched case-control study an increasing number of horses with daily / weekly access to the pasture currently being grazed by the horse under investigation were associated with reduced risk of IFEE. Again, care should be taken in over-interpreting this finding due to the wide 95% confidence intervals cross the value 1. This was a surprising finding if one takes the *a priori* hypothesis that parasites may be implicated in the pathogenesis of this condition, the risk of IFEE might be expected to increase as the number of horses grazing on the pasture increased. This finding merits further investigation using a larger number of cases.

The results of the present study provide us with further clues about the aetiopathogenesis of this condition and information about modifiable practices that may be implemented to reduce the risk of IFEE. Based on these results, the risk of IFEE may be reduced by restricting access to water from ponds / streams or stagnant pools and by implementing yearly treatment for tapeworms. Factors such as age and a history of previous colic are not modifiable but the knowledge that younger horses, and horses with a previous history of colic are at increased risk of IFEE assists identification of high-risk individuals.

It is important to note that some of the cases in the present study were not confirmed histologically as IFEE lesions. Histological examination is the only means of confirming the nature of the cell types involved but, on the basis of accumulating evidence in the literature, these distinct lesions appear most often to feature massive eosinophil accumulation. In the present study all the circumferential lesions examined histologically were confirmed as IFEE lesions and only one plaque like lesion would potentially have been misdiagnosed on gross examination alone. Therefore misclassification of IFEE cases should be minimal in the present study. It has been suggested that, depending on the degree of reduction in luminal diameter, intestinal resection may not offer the best prognosis (Perez Olmos *et al.* 2006) and was the reason why some cases of IFEE could not be confirmed histologically. The surgeons who operated on the cases in which lesions were not resected had experienced these lesions previously and so misdiagnosis would seem unlikely. In addition, removal of non-histologically confirmed IFEE cases did not unduly affect either final model.

The small numbers of cases in both studies resulted in relatively low study power. An unmatched study with 32 cases and 3 controls per case, assuming 20% exposure in controls, has 80 power to detect odds ratios of 3 or higher with 95% confidence and a study with 18 cases and 219 controls (assuming 20% exposure in controls) has 80 power to detect odds ratios of 4 or higher with 95% confidence. Therefore, given the low power of the present study, it is possible that other potentially important risk factors may not have been identified. Further work is ongoing to collect data on a larger number of cases to improve study power.

It is interesting to note that the majority of lesions (81%) were recruited from 3 clinics, 2 of which were based in Ireland and 1 in North-West England. This could have occurred due to reporting bias but, given the high degree of co-operation from the same collaborating clinics in concurrent studies investigating the epidemiology of epiploic foramen entrapment (Chapters 3 & 4) this would seem unlikely. In addition, it was hoped that bias due to failure to recognise these lesions was minimised by the principal investigator describing the features of these lesions in detail and providing visual reminders of the lesion in the form of a study booklet and a poster for the surgery area. It is possible, based on the findings from the present study, that there may be geographic clustering of IFEE cases. This may reflect the large numbers of young horses that are resident in certain regions of Ireland. However, this does not help to explain why these lesions are not identified in similar large populations of young horses at stud farms or racing premises in parts of the UK. In addition, the hospital that identified most cases of IFEE in the UK does not have a large population of young horses in its referral population. The short time period over which cases of IFEE were recruited precludes meaningful investigation of the seasonality of this condition. No apparent seasonal patterns were evident but the fact that 29% of these cases occurred in a three month period (June - August 2005) is interesting. Therefore, it is possible that some environmental factors such as climate or soil types may play a part in the pathogenesis of this condition. Space-time clustering has been identified in equine grass sickness (French *et al.* 2005) and further work using larger numbers of cases is required to investigate whether such clustering exists in IFEE.

The IFEE lesions described in the horse appear to resemble the muscular form of the condition in humans, which also commonly results in intestinal obstruction (Uenishi *et al.* 2003; Khan 2005). Given that former lesions are usually diagnosed at exploratory laparotomy to investigate the cause of acute colic, it is possible that the mucosal forms of EGID may be under-diagnosed in the equine population if only mild clinical signs are evident. Further research is required to investigate the true prevalence of EGID in horses. Eosinophil counts have been demonstrated to be higher in the equine small intestine and colon compared to other non-lymphoid tissues in the same animals (Benarafa *et al.* 2000). In addition the normal homing of eosinophils to the equine gastrointestinal tract may be regulated by eotaxin but other cytokines and chemokines have not been measured (Benarafa *et al.* 2002). Further research is also required to investigate these factors in normal horses and those with IFEE in order to more precisely describe the pathogenesis of this disease.

EGID have been reported to be familial in humans and there is evidence that this condition may share some common features with asthma (Rothenberg 2004). It would not have been possible to obtain information about allergic conditions in the sire / dam or siblings for the most of the horses under investigation in the present study given that most owners / carers could not answer questions about stereotypic behaviour in the horses' relatives. Horses with skin or respiratory conditions in the previous 12 months or horses who had received steroids / clenbuterol / antihistaminees in that time were not identified to be at significantly increased risk of IFEE. However, we did not specifically ask if horses had previously been diagnosed with allergic conditions such as sweet itch or recurrent airway obstructive disease and this should be investigated in future studies. In vitro studies have also demonstrated that there are differences in the migration and adherence of blood eosinophils between normal horses and those suffering from sweet itch (Benarafa *et al.* 2002). It is therefore conceivable that some horses may be inherently more susceptible to IFEE given exposure to the same allergens and this requires further research.

Acute eosinophilic pneumonia has been reported in several species including the horse and is suspected to have an immune mediated aetiology (Dixon *et al.* 1992). This rare condition has some parallels with IFEE given that parasitism was ruled out and complete resolution of clinical signs was achieved without recurrence long-term in the latter report. It would be interesting to investigate these cases further to identify possible risk factors and aetiologic agents and to determine if there are any similarities in these factors between the two conditions.

In conclusion, the present study has identified horse- and management-level factors associated with increased risk of idiopathic focal eosinophilic enteritis. The matched and unmatched case-control studies both identified young horses and horses with current or recent access to a pond / stream / stagnant pool at pasture to be at increased risk of IFEE. A history of previous colic and the number of horses on the premises were identified as additional risk factors for IFEE in the matched study. In the unmatched study, a history of treatment for tapeworms in the previous 12 months and an increasing number of horses on the pasture reduced the risk of IFEE. The findings from the present study have provided us with some clues regarding the pathogenesis of this condition and have identified factors that require further investigation.

APPENDIX TO CHAPTER 5

Table 1. Univariable conditional logistic regression analyses of binary and categorical horse- and management-level variables and their relationship with the risk of developing idiopathic focal eosinophilic enteritis (IFEE).

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% Confidence Interval*	*P-value*
General horse and management details						
Breed	TB / WB / TBx / WBx	65 (20)	58 (54)	Ref.		
	Other breed	35 (11)	42 (39)	0.73	0.30 – 1.81	0.500
Gender	Male	55 (17)	62 (58)	Ref.		
	Female	45 (14)	38 (35)	1.37	0.60 – 3.09	0.451
Principal use	Competition horse	16 (5)	28 (26)	Ref.		
	Unbroken	52 (16)	11 (10)	12.50	2.78 – 56.50	<0.001
	Other	32 (10)	61 (57)	1.04	0.31 – 3.45	
Medical details						
Veterinary attention in last 12 months (non-routine)	No	31 (9)	36 (33)	Ref.		
	Yes	69 (20)	64 (59)	1.21	0.51 – 2.92	0.663
Type of problem:						
Respiratory	No	89 (24)	87 (79)	Ref.		
	Yes	11 (3)	13 (12)	0.81	0.21 – 3.11	0.745
Skin	No	89 (24)	88 (81)	Ref.		
	Yes	11 (3)	12 (11)	1.00	0.26 – 3.84	1.000
Dental / Gastrointestinal / Weight loss	No	78 (22)	91 (84)	Ref.		

	Yes	21 (6)	9 (8)	2.43	0.77 – 7.72	0.137
Received medication (other than anthelmintic or vaccination) in last 12 months	No	32 (9)	41 (37)	Ref.		
	Yes	68 (19)	59 (53)	1.62	0.67 – 3.95	0.277
Received clenbuterol / antihistamine / steroid in previous 12 months	No	96 (24)	93 (80)	Ref.		
	Yes	4 (1)	7 (6)	0.53	0.05 – 5.47	0.583
Currently receiving medication	No	97 (30)	93 (85)	Ref.		
	Yes	3 (1)	7 (6)	0.52	0.06 – 4.32	0.513
NSAIDs in previous 28 days	No	92 (22)	94 (75)	Ref.		
	Yes	8 (2)	6 (5)	1.30	0.24 – 7.16	0.765
Colic episode in previous 12 months	No	86 (24)	94 (84)	Ref.		
	Yes	14 (4)	6 (5)	2.50	0.61 – 10.23	0.209
Premises						
Premises type	Private yard	48 (15)	41 (38)	Ref.		
	Livery yard	26 (8)	33 (31)	0.56	0.19 – 1.64	
	Stud farm	23 (7)	10 (9)	2.96	0.50 – 17.49	0.040
	Other	3 (1)	16 (15)	0.19	0.20 – 1.83	
Carer	Owners(s) / relative or spouse involved in daily care	77 (24)	70 (65)	Ref.		
	Owner / relative / spouse not involved in daily care	23 (7)	30 (28)	0.57	0.18 – 1.83	0.331

No. of premises in previous 12 months	1	32 (10)	57 (53)	Ref.		
	2	39 (12)	29 (27)	2.23	0.87 – 5.71	0.058
	>2	29 (9)	14 (13)	3.15	1.11 – 8.92	
Premises change in previous 12 months	No	32 (10)	57 (53)	Ref.		
	Yes	68 (21)	43 (40)	2.57	1.13 – 5.83	0.021
Premises change in previous 28 days	No	81 (25)	92 (83)	Ref.		
	Yes	19 (6)	8 (7)	2.56	0.80 – 8.14	0.119
Premises change in previous 14 days	No	87 (27)	94 (85)	Ref.		
	Yes	13 (4)	6 (5)	2.19	0.59 – 8.20	0.256
Premises change in previous 7 days	No	97 (30)	97 (87)	Ref.		
	Yes	3 (1)	3 (3)	0.81	0.83 – 7.84	0.852
Housing and grazing						
Current management	Stabled with turnout	39 (12)	61 (57)	Ref.		
	Stabled all the time / stabled apart from when exercised	10 (3)	6 (6)	2.65	0.57 – 12.30	0.044
	Not stabled – turned out all the time	52 (16)	32 (30)	3.44	1.23 – 9.61	
Current stabling	No	52 (16)	30 (28)	Ref.		
	Yes	48 (15)	70 (65)	0.32	0.12 – 0.83	0.016
Change in stabling / turnout routine in previous 28 days	No	73 (22)	67 (60)	Ref.		

	Yes	27 (8)	33 (30)	0.70	0.27 – 1.81	0.457
Change in stabling / turnout routine in previous 14 days	No	80 (24)	81 (68)	Ref.		
	Yes	20 (6)	19 (16)	1.04	0.38 – 2.83	0.932
Change in stabling / turnout routine in previous 7 days	No	93 (28)	88 (74)	Ref.		
	Yes	7 (2)	12 (10)	0.58	0.13 – 2.64	0.453
Increased stabling in previous 28 days	No	80 (24)	74 (67)	Ref.		
	Yes	20 (6)	26 (24)	0.66	0.23 – 1.92	0.437
Increased stabling in previous 14 days	No	83 (25)	17 (5)	Ref.		
	Yes	86 (72)	14 (12)	1.18	0.39 – 3.57	0.773
Increased stabling in previous 7 days	No	93 (28)	89 (75)	Ref.		
	Yes	7 (2)	11 (9)	0.64	0.14 – 2.97	0.550
Increased pasture turnout in previous 28 days	No	93 (28)	97 (88)	Ref.		
	Yes	7 (2)	3 (3)	1.84	0.31 – 11.08	0.517
Increased pasture turnout in previous 14 days	No	97 (29)	99 (90)	Ref.		
	Yes	3 (1)	1 (1)	2.45	0.15 – 39.70	0.535
Increased pasture turnout in previous 7 days	No	100 (30)	100 (91)	Ref.		
	Yes	-	-	-	-	-

Stable type	Indoor barn	24 (7)	19 (17)	Ref.		
	Outside stable block	41 (12)	57 (50)	0.57	0.17 – 1.86	0.230
	Not stabled	34 (10)	24 (21)	1.50	0.37 – 6.10	
Bedding type	Straw	22 (5)	29 (21)	Ref.		
	Woodshavings / other	78 (18)	71 (52)	1.10	0.33 – 3.63	0.872
Bedding change (type / batch) in previous 28 days	No	87 (27)	95 (88)	Ref.		
	Yes	13 (4)	5 (5)	2.29	0.61 – 8.56	0.230
Bedding change (type / batch) in previous 14 days	No	90 (28)	97 (89)	Ref.		
	Yes	10 (3)	3 (3)	2.81	0.56 – 13.96	0.217
Bedding change (type / batch) in previous 7 days	No	100 (31)	97 (89)	Ref.		
	Yes	0 (0)	3 (3)	-	-	-
Bedding type change in previous 28 days	No	94 (29)	98 (91)	Ref.		
	Yes	6 (2)	2 (2)	3.00	0.42 – 21.30	0.283
Bedding type change in previous 14 days	No	97 (30)	99 (92)	Ref.		
	Yes	3 (1)	1 (1)	3.00	0.19 – 47.96	0.448
Bedding type in previous 7 days	No	100 (31)	99 (92)	Ref.		
	Yes	0 (0)	1 (1)	-	-	-
Water supply in stable	Automatic	48 (15)	54 (50)	Ref.		
	Manual	23 (7)	24 (22)	1.10	0.34 – 3.61	0.638
	Not applicable	29 (9)	22 (20)	1.75	0.55 – 5.59	

Current access to pasture	No	3 (1)	6 (6)	Ref.		
	Yes	97 (30)	94 (87)	2.04	0.23 – 18.23	0.494
No. of pastures grazed in previous 4 weeks	1	46.5(13)	54 (46)	Ref.		
	2	46.5 (13)	36 (31)	1.51	0.59 – 3.88	0.601
	>2	7 (2)	9 (8)	0.83	0.14 – 4.67	
No. horses with access to pasture	1 / no pasture access	16 (5)	24 (22)	Ref.		
	2 – 5	65 (20)	53 (49)	1.81	0.61 – 5.42	0.511
	>5	19 (6)	23 (21)	1.32	0.30 – 5.78	
Pasture type	Mature	93 (27)	89 (76)	Ref.		
	Reseeded in full / part	7 (2)	11 (9)	0.64	0.13 – 3.15	0.570
Duration on current pasture	< 2 months	57 (17)	44 (36)	Ref.		
	2 – 6 months	31 (9)	26 (21)	0.91	0.30 – 2.77	0.053
	> 6 months	10 (3)	30 (24)	0.25	0.07 – 0.92	
Change of pasture in previous 28 days	No	52 (15)	69 (63)	Ref.		
	Yes	48 (14)	31 (28)	2.14	0.86 – 5.31	0.096
Change of pasture in previous 14 days	No	72 (21)	79 (71)	Ref.		
	Yes	28 (8)	21 (19)	1.52	0.53 – 4.38	0.439
Change of pasture in previous 7 days	No	86 (25)	90 (81)	Ref.		
	Yes	14 (4)	10 (9)	1.33	0.38 – 4.68	0.660
Pasture treatment within previous 28 days	No / no access to pasture	93 (14)	89 (93)	Ref.		

	Yes	7 (1)	11 (10)	0.47	0.05 – 4.19	0.468
Manually filled water source at pasture	No	55 (17)	56 (52)	Ref.		
	Yes	45 (14)	44 (41)	1.05	0.42 – 2.62	0.913
Automatic water source at pasture	No	61 (19)	52 (48)	Ref.		
	Yes	39 (12)	48 (45)	0.61	0.24 – 1.56	0.291
Running water source at pasture	No	84 (26)	94 (87)	Ref.		
	Yes	16 (5)	6 (6)	2.79	0.79 – 9.79	0.117
Stagnant water source at pasture	No	81 (25)	96 (89)	Ref.		
	Yes	19 (6)	4 (4)	5.44	1.34 – 22.01	0.014
Access to water from a stream / pond / stagnant pool	No	65 (20)	89 (83)	Ref.		
	Yes	35 (11)	11 (10)	4.10	1.56 – 10.74	0.004
Other species grazed on current pasture in previous 12 months	No / Not applicable	39 (12)	57 (52)	Ref.		
	Yes	61 (19)	43 (40)	1.92	0.85 – 4.36	0.110
Share grazing on current pasture with cattle / sheep	No / Not applicable	84 (26)	88 (81)	Ref.		
	Yes	16 (5)	12 (11)	1.49	0.44 – 4.99	0.524
Other species grazing in adjacent pastures	No / Not applicable	35 (11)	53 (49)	Ref.		
	Yes	65 (20)	47 (43)	1.97	0.85 – 4.54	0.103
Sheep / cattle rotated onto current pasture	No / Not applicable	67 (20)	70 (63)	Ref.		
	Yes	33 (10)	30 (27)	1.15	0.48 – 2.75	0.749

Manure used to fertilise current pasture	No / Not applicable	82 (23)	78 (69)	Ref.		
	Yes	18 (5)	22 (20)	0.84	0.27 – 2.61	0.761
Wildlife seen on pasture at least once a week	No / Not applicable	26 (8)	24 (22)	Ref.		
	Yes	74 (23)	76 (69)	0.87	0.32 – 2.37	0.791
Soil disturbance in or immediately adjacent to current pasture	No / Not applicable	83 (24)	92 (83)	Ref.		
	Yes	17 (5)	8 (7)	2.30	0.65 – 8.20	0.204
Mineral deficiencies in the soil of pastures currently grazed	No - tested	42 (5)	71 (22)	Ref.		
	Yes - tested	58 (7)	29 (9)	5.61	0.55 – 57.30	0.114
Nutrition						
Feeding of hay / haylage	No	42 (13)	23 (21)	Ref.		
	Yes	58 (18)	77 (72)	0.31	0.11 – 0.84	0.020
Concentrate fed	No	16 (5)	15 (14)	Ref.		
	Yes	84 (26)	85 (79)	0.90	0.25 – 3.19	0.870
Roughage type	Grass only	48 (15)	26 (24)	Ref.		
	Hay	29 (9)	37 (34)	0.39	0.14 – 1.06	0.050
	Haylage	23 (7)	38 (35)	0.29	0.09 – 0.80	
Currently fed hay	No	65 (20)	60 (56)	Ref.		
	Yes	35 (11)	40 (37)	0.82	0.35 – 1.92	0.646
Currently fed haylage	No	71 (22)	59 (55)	Ref.		
	Yes	29 (9)	41 (38)	0.21	0.23 – 1.39	0.212

Increased quantity of supplementary forage fed in :						
Previous 28 days	No	84 (26)	87 (77)	Ref.		
	Yes	16 (5)	13 (12)	1.25	0.41 – 3.84	0.696
Previous 14 days	No	84 (26)	90 (80)	Ref.		
	Yes	16 (5)	10 (9)	1.71	0.53 – 5.53	0.376
Previous 7 days	No	90 (28)	94 (84)	Ref.		
	Yes	10 (3)	6 (5)	1.81	0.39 – 8.31	0.455
Change in batch roughage in:						
Previous 28 days	No	75 (18)	82 (65)	Ref.		
	Yes	25 (6)	18 (14)	1.75	0.57 – 5.41	0.334
Previous 14 days	No	78 (18)	88 (66)	Ref.		
	Yes	22 (5)	12 (9)	2.21	0.62 – 7.85	0.227
Previous 7 days	No	87 (20)	95 (71)	Ref.		
	Yes	13 (3)	5 (4)	2.62	0.52 – 13.08	0.248
Proprietary concentrate diet fed	No	35 (11)	43 (38)	Ref.		
	Yes	65 (20)	57 (51)	1.46	0.58 – 3.71	0.417
Local feed mill concentrate fed	No	93 (28)	82 (75)	Ref.		
	Yes	7 (2)	18 (16)	0.32	0.07 – 1.49	0.104
Grain fed	No	94 (29)	82 (75)	Ref.		
	Yes	6 (2)	18 (17)	0.31	0.07 – 1.40	0.084
Sugar beet pulp fed	No	81 (25)	82 (75)	Ref.		
	Yes	19 (6)	18 (17)	1.02	0.37 – 2.82	0.959
Fibre source fed e.g. grass / chaff / chop	No	42 (13)	48 (44)	Ref.		
	Yes	58 (18)	52 (47)	1.65	0.50 – 5.42	0.402
Increased quantity of concentrate						

in:						
Previous 28 days	No	81 (25)	91 (79)	Ref.		
	Yes	19 (6)	9 (8)	2.22	0.74 – 6.70	0.165
Previous 14 days	No	87 (27)	96 (82)	Ref.		
	Yes	13 (4)	4 (3)	5.16	0.92 – 28.83	0.053
Previous 7 days	No	97 (30)	99 (84)	Ref.		
	Yes	3 (1)	1 (1)	3.00	0.19 – 47.96	0.448
Change in concentrate type / brand in:						
last 28 days	No	80 (24)	91 (79)	Ref.		
	Yes	20 (6)	9 (8)	3.83	0.88 – 16.61	0.066
Change in concentrate type / brand or introduction of new dietary supplement in previous 28 days	No	67 (20)	85 (73)	Ref.		
	Yes	33 (10)	15 (13)	2.98	1.08 – 8.17	0.034
Supplements fed (including fruit / vegetables)	No	19 (6)	18 (17)	Ref.		
	Yes	81 (25)	82 (76)	0.90	0.32 – 2.57	0.851
Supplements fed (excluding fruit / vegetables)	No	23 (7)	30 (28)	Ref.		
	Yes	77 (24)	70 (65)	1.41	0.56 – 3.56	0.455
Vegetables / fruit	No	68 (21)	62 (58)	Ref.		
	Yes	32 (10)	38 (35)	0.78	0.33 – 1.84	0.562
Garlic / herbal	No	68 (21)	72 (67)	Ref.		
	Yes	32 (10)	28 (26)	1.23	0.49 – 3.08	0.660
Chondroitin / glucosamine	No	100 (31)	92 (86)	Ref.		
	Yes	0 (0)	8 (7)	-	-	-

Probiotics	No	100 (31)	97 (90)	Ref.		
	Yes	0 (0)	3 (3)	-	-	-
Salt / mineral lick or supplement	No	61 (19)	63 (59)	Ref.		
	Yes	39 (12)	37 (34)	1.06	0.46 – 2.48	0.885
Oil	No	90 (28)	71 (66)	Ref.		
	Yes	10 (3)	29 (27)	0.28	0.08 – 0.99	0.024
Other supplement	No	58 (18)	65 (60)	Ref.		
	Yes	42 (13)	35 (33)	1.28	0.56 – 2.94	0.558
Supplement added within previous 28 days	No	84 (26)	95 (87)	Ref.		
	Yes	16 (5)	5 (5)	2.96	0.86 – 10.28	0.094
Supplement added within previous 14 days	No	94 (29)	97 (89)	Ref.		
	Yes	6 (2)	3 (3)	1.84	0.31 – 11.08	0.517
Supplement added within previous 7 days	No	97 (30)	98 (90)	Ref.		
	Yes	3 (1)	2 (2)	1.50	0.14 – 16.54	0.747
Exercise and transport						
Current exercise	No	61 (19)	32 (30)	Ref.		
	Yes	39 (12)	68 (63)	0.26	0.10 – 0.66	0.003
Change in exercise routine in previous 28 days	No	74 (23)	76 (69)	Ref.		
	Yes	26 (8)	24 (22)	1.13	0.40 – 3.23	0.816

Transport in previous 28 days	No	74 (23)	63 (58)	Ref.		
	Yes	26 (8)	37 (34)	0.57	0.22 – 1.48	0.235
Transport in previous 14 days	No	77 (24)	71 (63)	Ref.		
	Yes	23 (7)	29 (26)	0.67	0.25 – 1.83	0.427
Transport in previous 7 days	No	97 (30)	76 (68)	Ref.		
	Yes	3 (1)	24 (21)	0.12	0.02 – 0.95	0.006
Behaviour						
Behaviour in relation to feeding						
Behaviour at feed time	Some / little interest	69 (20)	72 (65)	Ref.		
	Agitated	31 (9)	28 (25)	1.07	0.68 – 1.71	0.763
Concentrate feeding	Normal / fast	97 (20)	96 (86)	Ref.		
	Doesn't eat all food / picky	3 (1)	4 (4)	0.76	0.07 – 7.90	0.818
Forage feeding	Normal / fast	100 (24)	88 (76)	Ref.		
	Doesn't eat all forage	0 (0)	12 (10)	-	-	-
Feeding when stressed	Eats normally	96 (22)	87 (77)	Ref.		
	Goes of food in full / part	4 (1)	13 (12)	0.32	0.04 – 2.66	0.230
Stereotypic behaviour						
Stereotypic behaviour	No	87 (26)	85 (79)	Ref.		
	Yes	13 (4)	15 (14)	0.93	0.27 – 3.13	0.902
Oral stereotypic behaviour	No	97 (29)	91 (84)	Ref.		
	Yes	3 (1)	9 (8)	0.44	0.05 – 3.60	0.400
Locomotor stereotypic behaviour	No	93 (28)	92 (86)	Ref.		

	Yes	7 (2)	8 (7)	0.86	0.16 – 4.70	0.865
Preventive health care						
Duration since teeth last checked	Less than 12 months previously	63 (12)	79 (67)	Ref.		
	More than 12 months previously / never done	37 (7)	21 (18)	3.74	1.06 – 13.13	0.035
Duration since last vaccination	> 16 weeks	52 (13)	52 (44)	Ref.		
	9 – 16 weeks	20 (5)	13 (11)	1.69	0.44 – 6.54	0.661
	0 - 8 weeks	28 (7)	35 (29)	0.85	0.30 – 2.41	
Receives routine vaccinations	Yes	77 (23)	91 (83)	Ref.		
	No	23 (7)	9 (8)	3.80	1.06 – 13.63	0.037
Vaccinated in previous 28 days	No	100 (30)	81 (71)	Ref.		
	Yes	0 (0)	19 (17)	-	-	-
Vaccinated in previous 14 days	No	100 (30)	92 (81)	Ref.		
	Yes	0 (0)	8 (7)	-	-	-
Vaccinated in previous 7 days	No	100 (30)	95 (82)	Ref.		
	Yes	0 (0)	5 (4)	-	-	-
Last vaccination	Flu & tetanus	82 (18)	67 (53)	Ref.		
	Flu only	5 (1)	15 (12)	0.35	0.04 – 2.97	
	Tetanus only	9 (2)	9 (7)	0.69	0.12 – 4.01	0.735
	Other	5 (1)	9 (7)	1.08	0.54 – 21.50	
Frequency of anthelmintic administration	Every 6 – 13 weeks	59 (17)	68 (63)	Ref.		
	More than every 6 weeks	21 (6)	5 (5)	6.59	1.23 – 35.40	0.046
	Every 14 – 24 weeks or less	21 (6)	27 (25)	0.95	0.34 – 2.68	

Anthelmintic administration in previous 28 days	No	59 (17)	65 (55)	Ref.		
	Yes	41 (12)	35 (29)	1.27	0.56 – 2.88	0.573
Anthelmintic administration in previous 14 days	No	66 (19)	77 (65)	Ref.		
	Yes	31 (10)	23 (19)	1.75	0.70 – 4.35	0.235
Anthelmintic administration in previous 7 days	No	79 (23)	90 (76)	Ref.		
	Yes	21 (6)	10 (8)	2.71	0.87 – 8.44	0.091
Last anthelmintic product administered	Ivermectin	21 (6)	24 (18)	Ref.		
	Benzimidazole	14 (4)	20 (15)	0.60	0.13 – 2.71	
	Moxidectin / doramectin	28 (8)	25 (19)	1.29	0.37 – 4.47	0.779
	Pyrantel	21 (6)	13 (10)	1.51	0.36 – 6.26	
	Praziquantel ± ivermectin / moxidectin	17 (5)	17 (13)	0.99	0.23 – 4.27	
Type of anthelmintic last administered						
Ivermectin	No	62 (18)	63 (47)	Ref.		
	Yes	35 (11)	37 (28)	1.09	0.45 – 2.61	0.552
Benzimidazole	No	86 (25)	80 (60)	Ref.		
	Yes	14 (4)	20 (15)	0.52	0.16 – 1.70	0.258
Moxidectin / doramectin	No	72 (21)	75 (56)	Ref.		
	Yes	28 (8)	25 (19)	1.33	0.49 – 3.61	0.574
Pyrantel	No	79 (23)	87 (65)	Ref.		
	Yes	21 (6)	13 (10)	1.59	0.48 – 5.18	0.446
Praziquantel ± avermectin	No	83 (24)	83 (62)	Ref.		
	Yes	17 (5)	17 (13)	1.03	0.33 – 3.17	0.962
Penultimate worming product	Ivermectin	42 (10)	24 (13)	Ref.		

	Benzimidazole	12.5 (3)	16 (9)	0.28	0.03 – 2.77	
	Moxidectin / doramectin	12.5 (3)	15 (8)	0.69	0.12 – 4.04	0.817
	Pyrantel	17 (4)	18 (10)	0.81	0.16 – 4.15	
	Praziquantel + avermectin	17 (4)	27 (15)	0.96	0.24 – 3.87	
Treated for tapeworms in previous 12 months	Yes	58 (15)	69 (54)	Ref.		
	No	42 (11)	31 (24)	1.60	0.57 – 4.43	0.369
Are all the horses on the pasture wormed?	Yes	100 (0)	97 (70)	Ref.		
	No	0 (0)	3 (2)	-	-	-
New horses put onto pasture within previous 4 weeks	No	77 (24)	80 (71)	Ref.		
	Yes	23 (7)	20 (18)	1.20	0.45 – 3.21	0.716
Are specific measures taken to reduce the nos. of parasites on the pasture?	Yes	10 (3)	17 (15)	Ref.		
	No	90 (27)	83 (73)	1.83	0.44 – 7.61	0.390
Measures taken to reduce parasites on the pasture:						
Faeces removed from pasture	No	63 (19)	61 (54)	Ref.		
	Yes	37 (11)	39 (34)	0.93	0.38 – 2.27	0.880
Pastures rotated	No	57 (17)	59 (52)	Ref.		
	Yes	43 (13)	41 (36)	1.00	0.38 – 2.65	1.000
Other species grazed on pasture	No	57 (17)	59 (52)	Ref.		
	Yes	43 (13)	41 (36)	1.46	0.51 – 4.16	0.476
Harrowed	No	57 (17)	55 (48)	Ref.		
	Yes	43 (13)	45 (40)	0.92	0.38 – 2.22	0.851
Worm egg count or tapeworm	No	87 (27)	79 (70)	Ref.		

ELISA performed within last 12 months						
	Yes	13 (4)	21 (19)	0.46	0.12 – 1.74	0.227
Faecal worm egg count negative?	Yes			Ref.		
	No			0.23	0.03 – 2.00	0.125

Table 2. Univariable conditional logistic regression analyses of categorised continuous horse- and management-level variables and their relationship with the risk of developing idiopathic focal eosinophilic enteritis (IFEE).

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
General horse & management details						
Age (years)	< 2	52 (16)	52 (16)	Ref.		
	2 - 5	6 (2)	23 (21)	0.01	0.01 – 0.16	
	6 - 8	13 (4)	25 (23)	0.03	0.01 – 0.28	<0.001
	9 - 11	16 (5)	22 (20)	0.03	0.01 – 3.16	
	>11	13 (4)	24 (22)	0.02	0.01 – 0.23	
Height (cm)	< 144	26 (8)	14 (13)	Ref.		
	144 – 155	52 (16)	20 (19)	1.58	0.45 – 5.61	
	156 – 165	6 (2)	37 (34)	0.12	0.02 – 0.62	<0.001
	> 165	16 (5)	29 (27)	0.31	0.07 – 1.34	
Weight (kg)	< 400	39 (12)	15 (14)	Ref.		
	400 – 499	29 (9)	23 (21)	0.49	0.17 – 1.39	
	500 – 549	3 (1)	18 (17)	0.06	0.01 – 0.52	0.004
	> 549	29 (9)	44 (41)	0.21	0.07 – 0.68	
Premises						
No. of horses on premises	1 – 5	26 (8)	25 (23)	Ref.		
	6 – 11	26 (8)	18 (17)	1.52	0.42 – 5.52	
	12 – 29	29 (9)	19 (18)	1.36	0.39 – 4.66	0.181
	> 29	19 (6)	38 (35)	0.42	0.11 – 1.61	

Housing and grazing						
Hours stabled per week	<102	55 (17)	48 (44)	Ref.		
	102 – 132	26 (8)	25 (23)	0.92	0.33 – 2.55	0.673
	> 133	27 (25)	27 (25)	0.63	0.22 – 1.81	
Hours grazing per week	< 22	13 (4)	25 (23)	Ref.		
	22 – 62	26 (8)	28 (26)	1.65	0.44 – 6.25	
	63 – 167	16 (5)	19 (18)	1.52	0.35 – 6.59	0.216
	168	45 (14)	28 (26)	3.54	0.96 – 13.04	
Stocking density (horses per acre)	<0.65	59 (16)	12 (10)	Ref.		
	0.66 – 1.20	15 (4)	28 (22)	0.05	0.01 – 0.37	
	1.21 – 3.9	15 (4)	30 (24)	0.08	0.01 – 0.44	<0.001
	> 3.9	11 (3)	30 (24)	0.05	0.01 – 0.34	
Pasture size (acres)	< 1.0	15 (4)	21 (17)	Ref.		
	1.0 – 2.0	19 (5)	33 (26)	0.96	0.19 – 4.96	
	2.1 – 4.9	22 (6)	22 (18)	1.17	0.22 – 6.13	0.243
	> 4.9	44 (12)	24 (19)	2.97	0.71 – 12.43	
Horses on pasture	1 / not applicable	16 (5)	24 (22)	Ref.		
	2	37 (11)	18 (16)	3.37	0.85 – 13.43	
	3 – 4	27 (8)	22 (20)	1.78	0.52 – 6.09	0.106
	>4	20 (6)	36 (33)	0.80	0.19 – 3.46	
Nutrition						
Forage weight (kg)	0	52 (13)	27 (20)	Ref.		
	0.1 – 6.0	28 (7)	25 (26)	0.24	0.06 – 0.97	0.009
	>6.0	20 (5)	39 (29)	0.10	0.02 – 0.54	
Total weight of	< 0.20	48 (12)	27 (24)	Ref.		

concentrate / grain (kg)						
	0.20 – 1.0	28 (7)	36 (32)	0.39	0.12 – 1.23	0.215
	> 1.0	24 (6)	36 (32)	0.49	0.15 – 1.60	

Table 3. Univariable conditional logistic regression analyses of continuous horse- and management-level variables and their relationship with the risk of developing idiopathic focal eosinophilic enteritis (IFEE).

Variable	*Unit of measurement*	*Mean / median*	*Coefficient*	*Standard Error*	*P-value*
Horse					
Age	years	7.6	-0.188	0.059	<0.001
Age (piecewise linear)	years				
Height	cm	154	-0.259	0.012	0.022
Weight	kg	483	-0.005	0.002	0.003
Premises					
No. horses on premises		12	0.008	0.007	0.256
No. horses on premises (centred)			-0.035	0.017	0.037
No. horses on premises (squared)			0.0005	0.0002	0.012
Housing and grazing					
No. of hours stabled per week	hours per week	85	-0.006	0.004	0.118
No. of hours grazing per week	hours per week	88	0.006	0.003	0.086
Stocking density	horses per acre	1.25	-0.394	0.175	0.001
Pasture size	acres	2.5	0.165	0.069	<0.001
Horses on pasture		4.7	-0.060	0.055	0.238
Nutrition					
Supplementary forage weight	kg	4.0	-0.133	0.064	0.014
Total weight concentrate / grain	kg	0.65	-0.119	0.155	0.422

Table 4. Univariable logistic regression analyses of binary and categorical horse- and management-level variables and their relationship with the risk of developing idiopathic focal eosinophilic enteritis (IFEE).

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% Confidence Interval*	*P-value*
Season						
	Winter (December – February)	11 (2)	25 (54)	Ref.		
	Spring (March – May)	28 (5)	25 (54)	2.50	0.46 – 13.45	
	Summer (June – August)	44 (8)	25 (54)	4.00	0.81 – 19.71	0.238
	Autumn (September – November)	17 (3)	25 (54)	1.50	0.24 – 9.34	
General horse and management details						
Breed	TB / WB / TBx / WBx	61 (11)	47 (101)	Ref.		
	Other breed	39 (7)	53 (114)	0.44	0.16 – 1.22	0.106
Gender	Male	67 (12)	58 (126)	Ref.		
	Female	33 (6)	42 (90)	0.70	0.25 – 1.93	0.485
Principal use	Competition horse	22 (4)	36 (77)	Ref.		
	Unbroken	45 (8)	7 (15)	10.27	2.74 – 38.49	0.002
	Other	33 (6)	57 (124)	0.93	0.25 – 3.41	
Medical details						
Veterinary attention in last 12 months (non-routine)	No	41 (7)	40 (83)	Ref.		
	Yes	59 (10)	60 (127)	0.93	0.34 – 2.55	0.894
Type of problem						
Respiratory	No	81 (13)	92 (191)	Ref.		

	Yes	19 (3)	8 (16)	2.75	0.71 – 10.68	0.177
Skin	No	94 (15)	87 (181)	Ref.		
	Yes	6 (1)	13 (27)	0.45	0.06 – 3.52	0.394
Dental / Gastrointestinal / Weight loss	No	88 (15)	91 (188)	Ref.		
	Yes	12 (2)	9 (19)	1.32	0.28 – 6.21	0.733
Received medication (other than anthelmintic or vaccination) in last 12 months	No	44 (7)	47 (98)	Ref.		
	Yes	56 (9)	53 (109)	1.15	0.41 – 3.22	0.781
Received clenbuterol / antihistamine / steroid in previous 12 months	No	92 (12)	90 (124)	Ref.		
	Yes	8 (1)	10 (14)	0.74	0.09 – 6.11	0.770
Currently receiving medication	No	100 (18)	94 (200)	Ref.		
	Yes	0 (0)	6 (12)	-	-	-
NSAIDs in previous 28 days	No	100 (18)	89 (192)	Ref.		
	Yes	0 (0)	11 (24)	-	-	-
Colic episode in previous 12 months	No	100 (15)	97 (191)	Ref.		
	Yes	0 (0)	7 (14)	-	-	-
Premises						
Premises type	Private yard	61 (11)	61 (132)	Ref.		
	Livery yard	33 (6)	31 (66)	1.09	0.39 – 3.08	0.897

	Other	6 (1)	8 (18)	0.67	0.08 – 5.47	
Carer	Owners(s) / relative or spouse involved in daily care	67 (12)	78 (168)	Ref.		
	Owner / relative / spouse not involved in daily care	33 (6)	22 (47)	1.79	0.64 – 5.02	0.284
No. of premises in previous 12 months	1	29.5 (5)	52 (111)	Ref.		
	2	29.5 (5)	27 (58)	1.91	0.53 – 6.88	0.131
	>2	41 (7)	21 (46)	3.38	1.02 – 11.19	
Premises change in previous 12 months	No	28 (5)	51 (110)	Ref.		
	Yes	72 (13)	49 (106)	2.70	0.93 – 7.83	0.055
Premises change in previous 28 days	No	76 (13)	92 (195)	Ref.		
	Yes	24 (4)	8 (16)	3.75	1.09 – 12.84	0.055
Premises change in previous 14 days	No	82 (14)	96 (203)	Ref.		
	Yes	18 (3)	4 (8)	5.44	1.30 – 22.79	0.039
Premises change in previous 7 days	No	88 (15)	98 (207)	Ref.		
	Yes	12 (2)	2 (4)	6.80	1.17 – 40.77	0.060
Housing and grazing						
Current management	Stabled with turnout	50 (9)	64 (137)	Ref.		
	Stabled all the time / stabled apart from when exercised	11 (2)	7 (15)	2.03	0.40 – 10.28	0.498
	Not stabled – turned out all the time	39 (7)	29 (62)	1.72	0.61 – 4.82	
Current stabling	No	39 (7)	29 (62)	Ref.		

	Yes	61 (11)	71 (152)	0.64	0.24 – 1.73	0.388
Change in stabling / turnout routine in previous 28 days	No	82 (14)	69 (145)	Ref.		
	Yes	18 (3)	31 (65)	0.48	0.13 – 1.72	0.227
Change in stabling / turnout routine in previous 14 days	No	88 (15)	78 (157)	Ref.		
	Yes	12 (2)	22 (44)	0.47	0.10 – 2.16	0.296
Change in stabling / turnout routine in previous 7 days	No	94 (16)	86 (172)	Ref.		
	Yes	6 (1)	14 (29)	0.37	0.05 – 2.90	0.279
Increased stabling in previous 28 days	No	100 (18)	80 (167)	Ref.		
	Yes	0 (0)	20 (41)	-	-	-
Increased stabling in previous 14 days	No	100 (18)	85 (169)	Ref.		
	Yes	0 (0)	15 (29)	-	-	-
Increased stabling in previous 7 days	No	100 (18)	89 (177)	Ref.		
	Yes	0 (0)	11 (21)	-	-	-
Increased pasture turnout in previous 28 days	No	100 (18)	90 (188)	Ref.		
	Yes	0 (0)	10 (20)	-	-	-
Increased pasture turnout	No	100 (18)	93 (185)	Ref.		

in previous 14 days	Yes	0 (0)	7 (14)	-	-	-
Increased pasture turnout in previous 7 days	No	100 (18)	95 (190)	Ref.		
	Yes	0 (0)	5 (9)	-	-	-
Stable type	Indoor barn	27 (3)	26 (40)	Ref.		
	Outside stable block	73 (8)	74 (112)	0.95	0.24 – 3.77	0.945
Bedding type	Straw	14 (2)	27 (45)	Ref.		
	Woodshavings / other	86 (12)	73 (124)	0.98	0.39 – 2.44	0.968
Bedding change (type / batch) in previous 28 days	No	89 (16)	92 (197)	Ref.		
	Yes	11 (2)	8 (16)	1.54	0.32 – 7.29	0.603
Bedding change (type / batch) in previous 14 days	No	94 (17)	95 (201)	Ref.		
	Yes	6 (1)	5 (10)	1.18	0.14 – 9.79	0.879
Bedding change (type / batch) in previous 7 days	No	100 (18)	97 (205)	Ref.		
	Yes	0 (0)	3 (6)	-	-	-
Bedding type change in previous 28 days	No	89 (16)	98 (208)	Ref.		
	Yes	11 (2)	2 (5)	5.20	0.93 – 28.94	0.095
Bedding type change in previous 14 days	No	94 (17)	98 (209)	Ref.		
	Yes	6 (1)	2 (4)	3.07	0.32 – 29.06	0.379

Bedding type in previous 7 days	No	100 (18)	99 (211)	Ref.		
	Yes	0 (0)	1 (2)	-	-	-
Water supply in stable	Automatic	23 (3)	16 (26)	Ref.		
	Manual	77 (10)	84 (14)	0.61	0.16 – 2.39	0.498
Current access to pasture	No	6 (1)	7 (16)	Ref.		
	Yes	94 (17)	93 (99)	1.37	0.17 – 10.94	0.759
No. of pastures grazed in previous 4 weeks	1	53 (9)	70 (133)	Ref.		
	2	41 (7)	20 (38)	2.72	0.95 – 7.79	0.162
	>2	6 (1)	10 (19)	0.78	0.09 – 6.49	
No. horses with access to pasture	1	18 (3)	20 (30)	Ref.		
	2 – 5	82 (14)	61 (121)			
	>5	0 (0)	19 (38)	-	-	
Pasture type	Mature	88 (15)	93 (180)	Ref.		
	Reseeded in full / part	12 (2)	7 (14)	1.71	0.36 – 8.26	0.524
Duration on current pasture	< 2 months	56 (9)	36 (67)	Ref.		
	2 – 6 months	31 (5)	37 (68)	0.55	0.17 – 1.72	0.227
	> 6 months	13 (2)	27 (50)	0.30	0.06 – 1.44	
Change of pasture in previous 28 days	No	59 (10)	80 (169)	Ref.		
	Yes	41 (7)	20 (42)	2.82	1.01 – 7.84	0.056

Change of pasture in previous 14 days	No	75 (12)	82 (152)	Ref.		
	Yes	25 (4)	18 (33)	1.53	0.47 – 5.06	0.494
Change of pasture in previous 7 days	No	88 (14)	89 (165)	Ref.		
	Yes	12 (2)	11 (20)	1.18	0.25 – 5.57	0.838
Pasture treatment within previous 28 days	No	94 (16)	92 (181)	Ref.		
	Yes	6 (1)	8 (15)	0.75	0.09 – 6.08	0.784
Manually filled water source at pasture	No	40 (6)	50 (100)	Ref.		
	Yes	60 (9)	50 (99)	1.51	0.52 – 4.42	0.005
Automatic water source at pasture	No	73 (11)	49 (98)	Ref.		
	Yes	27 (4)	51 (101)	0.35	0.11 – 1.14	0.067
Running water source at pasture	No	73 (11)	93 (185)	Ref.		
	Yes	27 (4)	7 (14)	4.80	1.35 – 17.06	0.028
Stagnant water source at pasture	No	80 (12)	95 (190)	Ref.		
	Yes	20 (3)	5 (9)	5.28	1.26 – 22.07	0.042
Access to water from a stream / pond / stagnant pool	No	61 (11)	88 (190)	Ref.		
	Yes	39 (7)	12 (25)	4.84	1.72 – 13.62	0.005
Other species grazed on	No / Not applicable	53 (9)	67 (133)	Ref.		

current pasture in previous 12 months						
	Yes	47 (8)	33 (66)	1.79	0.66 – 4.85	0.256
Share grazing on current pasture with cattle / sheep	No / Not applicable	89 (16)	94 (200)	Ref.		
	Yes	11 (2)	6 (12)	2.08	0.43 – 10.13	0.397
Other species grazing in adjacent pastures	No / Not applicable	50 (9)	61 (129)	Ref.		
	Yes	50 (9)	39 (84)	1.53	0.58 – 4.03	0.384
Sheep / cattle rotated onto current pasture	No / Not applicable	78 (14)	78 (166)	Ref.		
	Yes	22 (4)	22 (46)	1.03	0.32 – 3.28	0.959
Manure used to fertilise current pasture	No / Not applicable	82 (14)	91 (172)	Ref.		
	Yes	18 (3)	9 (18)	2.05	0.54 – 7.80	0.323
Wildlife seen on pasture at least once a week	No / Not applicable	36 (5)	15 (29)	Ref.		
	Yes	64 (9)	85 (170)	0.31	0.10 – 0.98	0.060
Soil disturbance in or immediately adjacent to current pasture	No / Not applicable	100 (18)	90 (189)	Ref.		
	Yes	0 (0)	10 (21)	-	-	-
Mineral deficiencies in the soil of pastures currently grazed	No - tested	33 (1)	47 (15)	Ref.		
	Yes - tested	67 (2)	53 (17)	1.76	0.14 – 21.47	0.649

Nutrition						
Feeding of hay / haylage	No	33 (6)	21 (45)	Ref.		
	Yes	67 (12)	79 (171)	0.53	0.19 – 1.48	0.239
Concentrate fed	No	11 (2)	12 (26)	Ref.		
	Yes	89 (16)	88 (187)	1.11	0.24 – 5.12	0.890
Roughage type	Grass only	33 (6)	20 (44)	Ref.		
	Hay	22 (4)	45 (97)	0.30	0.08 – 1.12	
	Haylage	33 (6)	28 (60)	0.73	0.22 – 2.43	0.248
	Hay & haylage	11 (2)	7 (14)	1.05	0.19 – 5.79	
Currently fed hay	No	67 (12)	48 (104)	Ref.		
	Yes	33 (6)	52 (111)	0.47	0.17 – 1.29	0.132
Currently fed haylage	No	56 (10)	66 (141)	Ref.		
	Yes	44 (8)	34 (74)	1.52	0.58 – 4.03	0.400
Increased quantity of supplementary forage fed in :						
Previous 28 days	No	89 (16)	90 (190)	Ref.		
	Yes	11 (2)	10 (21)	1.13	0.24 – 5.26	0.877
Previous 14 days	No	89 (16)	93 (194)	Ref.		
	Yes	11 (2)	7 (14)	1.73	0.36 – 8.30	0.516
Previous 7 days	No	94 (17)	97 (201)	Ref.		
	Yes	6 (1)	3 (7)	1.69	0.20 – 14.54	0.653
Change in type of roughage fed in :						
Previous 28 days	No	89 (16)	93 (199)	Ref.		
	Yes	11 (2)	7 (15)	1.66	0.35 – 7.90	0.546
Previous 14 days	No	89 (16)	95 (202)	Ref.		

	Yes	11 (2)	5 (10)	2.52	0.51 – 12.52	0.299
Previous 7 days	No	94 (17)	99 (209)	Ref.		
	Yes	6 (1)	1 (3)	4.10	0.40 – 41.56	0.291
Change in batch roughage in:						
Previous 28 days	No	79 (11)	82 (152)	Ref.		
	Yes	21 (3)	18 (33)	1.26	0.33 – 4.75	0.742
Previous 14 days	No	79 (11)	88 (161)	Ref.		
	Yes	21 (3)	12 (21)	2.09	0.54 – 8.11	0.314
Previous 7 days	No	94 (17)	99 (209)	Ref.		
	Yes	6 (1)	1 (3)	3.20	0.62 – 16.52	0.208
Proprietary concentrate diet fed	No	28 (5)	38 (75)	Ref.		
	Yes	72 (13)	62 (124)	1.57	0.54 – 4.59	0.395
Local feed mill concentrate fed	No	88 (15)	88 (172)	Ref.		
	Yes	12 (2)	12 (24)	0.96	0.21 – 4.44	0.953
Grain fed	No	94 (17)	91 (194)	Ref.		
	Yes	6 (1)	9 (20)	0.57	0.07 – 4.51	0.567
Sugar beet pulp fed	No	72 (13)	73 (157)	Ref.		
	Yes	28 (5)	27 (57)	1.06	0.36 – 3.10	0.916
Fibre source fed e.g. grass / chaff / chop	No	22 (4)	27 (58)	Ref.		
	Yes	78 (14)	73 (156)	1.30	0.41 – 4.11	0.647
Increased quantity of concentrate in:						
Previous 28 days	No	94 (17)	92 (192)	Ref.		

	Yes	6 (1)	8 (17)	0.66	0.08 – 5.30	0.684
Previous 14 days	No	94 (17)	94 (197)	Ref.		
	Yes	6 (1)	6 (12)	0.97	0.12 – 7.88	0.974
Previous 7 days	No	100 (18)	98 (204)	Ref.		
	Yes	0 (0)	2 (5)	-	-	-
Change in concentrate type / brand in:						
last 28 days	No	88 (14)	93 (198)	Ref.		
	Yes	12 (2)	7 (14)	2.02	0.42 – 9.87	0.415
Supplements fed (including fruit / vegetables)	No	17 (3)	11 (24)	Ref.		
	Yes	83 (15)	89 (192)	0.62	0.17 – 2.32	0.500
Supplements fed (excluding fruit / vegetables)	No	22 (4)	20 (44)	Ref.		
	Yes	78 (14)	80 (172)	0.89	0.28 – 2.85	0.553
Vegetables / fruit	No	61 (11)	48 (104)	Ref.		
	Yes	39 (7)	52 (112)	0.59	0.22 – 1.58	0.289
Garlic / herbal	No	50 (9)	66 (143)	Ref.		
	Yes	50 (9)	34 (73)	1.96	0.75 – 5.15	0.175
Chondroitin / glucosamine	No	100 (18)	85 (183)	Ref.		
	Yes	0 (0)	15 (33)	-	-	-
Probiotics	No	100 (18)	94 (203)	Ref.		
	Yes	0 (0)	6 (13)	-	-	-
Salt / mineral lick or	No	67 (12)	65 (140)	Ref.		

supplement						
	Yes	33 (6)	35 (76)	0.92	0.33 – 2.55	0.874
Oil	No	94 (17)	73 (158)	Ref.		
	Yes	6 (1)	27 (58)	0.16	0.20 – 1.23	0.022
Other supplement	No	56 (10)	59 (128)	Ref.		
	Yes	44 (8)	41 (88)	1.16	0.44 – 3.06	0.760
Supplement added within previous 28 days	No	84 (26)	95 (87)	Ref.		
	Yes	16 (5)	5 (5)	2.96	0.86 – 10.28	0.094
Supplement added within previous 14 days	No	94 (17)	94 (201)	Ref.		
	Yes	6 (1)	6 (12)	0.98	0.12 – 8.04	0.989
Supplement added within previous 7 days	No	100 (18)	98 (207)	Ref.		
	Yes	0 (0)	2 (5)	-	-	-
Exercise and transport						
Current exercise	No	44 (8)	24 (52)	Ref.		
	Yes	56 (10)	76 (164)	0.40	0.15 – 1.06	0.071
Change in exercise routine in previous 28 days	No	67 (12)	71 (151)	Ref.		
	Yes	33 (6)	29 (61)	1.24	0.44 – 3.45	0.686
Transport in previous 28 days	No	78 (14)	64 (135)	Ref.		
	Yes	22 (4)	36 (77)	0.51	0.16 – 1.57	0.213

Transport in previous 14 days	No	78 (14)	71 (145)	Ref.		
	Yes	22 (4)	29 (58)	0.71	0.23 – 2.26	0.557
Transport in previous 7 days	No	100 (18)	80 (162)	Ref.		
	Yes	0 (0)	20 (41)	-	-	-
Behaviour						
Behaviour in relation to feeding						
Behaviour at feed time	Some / little interest	61 (11)	82 (175)	Ref.		
	Agitated	39 (7)	18 (39)	2.86	1.04 – 7.83	0.051
Concentrate feeding	Normal / fast	94 (17)	98 (207)	Ref.		
	Does not eat all food / picky	6 (1)	2 (5)	2.43	0.27 – 22.05	0.470
Forage feeding	Normal / fast	100 (16)	89 (180)	Ref.		
	Does not eat all forage	0 (0)	11 (22)	-	-	-
Feeding when stressed	Eats normally	100 (14)	85 (175)	Ref.		
	Goes of food in full / part	0 (0)	15 (31)	-	-	-
Stereotypic behaviour						
Stereotypic behaviour	No	89 (16)	85 (183)	Ref.		
	Yes	11 (2)	15 (33)	0.69	0.15 – 3.16	0.621
Oral stereotypic behaviour	No	94 (17)	93 (200)	Ref.		
	Yes	6 (1)	7 (14)	0.84	0.10 – 6.78	0.867
Preventive health care						
Duration since teeth last	Less than 12 months previously	94 (15)	92 (169)	Ref.		

checked						
	More than 12 months previously / never done	6 (1)	8 (15)	0.75	0.09 – 6.08	0.781
Duration since last vaccination	> 16 weeks	63 (10)	58 (110)	Ref.		
	9 – 16 weeks	12 (2)	15 (29)	0.76	0.16 – 3.65	0.932
	0 - 8 weeks	25 (4)	27 (50)	0.88	0.26 – 2.94	
Receives routine vaccinations	Yes	94 (17)	92 (197)	Ref.		
	No	6 (1)	8 (16)	0.72	0.09 – 5.80	0.751
Vaccinated in previous 28 days	No	94 (15)	89 (169)	Ref.		
	Yes	6 (1)	11 (20)	0.56	0.07 – 4.49	0.559
Vaccinated in previous 14 days	No	94 (15)	95 (180)	Ref.		
	Yes	6 (1)	5 (9)	1.33	0.16 – 11.24	0.798
Vaccinated in previous 7 days	No	100 (16)	98 (186)	Ref.		
	Yes	0 (0)	2 (3)	-	-	-
Frequency of anthelmintic administration	Every 6 – 13 weeks	59 (17)	68 (63)	Ref.		
	More than every 6 weeks	21 (6)	5 (5)	6.59	1.23 – 35.40	0.046
	Every 14 – 24 weeks or less	21 (6)	27 (25)	0.95	0.34 – 2.68	
Anthelmintic administration in previous 28 days	No	65 (11)	64 (121)	Ref.		
	Yes	35 (6)	36 (69)	0.96	0.34 – 2.70	0.933

Anthelmintic administration in previous 14 days	No	71 (12)	78 (149)	Ref.		
	Yes	29 (5)	22 (41)	1.51	0.50 – 4.54	0.470
Anthelmintic administration in previous 7 days	No	88 (15)	88 (167)	Ref.		
	Yes	12 (2)	12 (23)	0.97	0.21 – 4.51	0.967
Last anthelmintic product administered	Ivermectin	18 (3)	18 (32)	Ref.		
	Benzimidazole	24 (4)	7 (12)	3.56	0.69 – 18.28	
	Moxidectin / doramectin	24 (4)	36 (63)	0.68	0.14 – 3.21	0.338
	Pyrantel	18 (3)	17 (29)	1.10	0.21 – 5.90	
	Praziquantel ± ivermectin / moxidectin	18 (3)	22 (38)	0.84	0.16 – 4.64	
Type of anthelmintic last administered						
Ivermectin	No	65 (11)	67 (116)	Ref.		
	Yes	35 (6)	33 (58)	1.09	0.38 – 3.10	0.871
Benzimidazole	No	76 (13)	93 (162)	Ref.		
	Yes	24 (4)	7 (12)	4.15	1.17 – 14.71	0.043
Moxidectin / doramectin	No	76 (13)	64 (112)	Ref.		
	Yes	24 (4)	36 (62)	0.56	0.17 – 1.78	0.303
Pyrantel	No	82 (14)	83 (145)	Ref.		
	Yes	18 (3)	17 (29)	1.07	0.29 – 1.78	0.303
Praziquantel ± avermectin	No	82 (14)	78 (136)	Ref.		
	Yes	18 (3)	22 (38)	0.77	0.21 – 2.81	0.681
Penultimate worming product	Ivermectin	33 (4)	18 (25)	Ref.		
	Benzimidazole	17 (2)	6 (9)	1.39	0.22 – 8.93	
	Moxidectin / doramectin	25 (3)	29 (41)	0.46	0.09 – 2.21	0.390

	Pyrantel	17 (2)	23 (32)	0.39	0.07 – 2.31	
	Praziquantel + avermectin	8 (1)	24 (33)	0.19	0.02 – 1.80	
Treated for tapeworms in previous 12 months	Yes	57 (8)	85 (156)	Ref.		
	No	43 (6)	15 (27)	4.33	1.39 – 13.48	0.016
All the horses on the pasture are wormed	Yes	100 (14)	97 (168)	Ref.		
	No	0 (0)	3 (5)	-	-	-
All the horses on the pasture are wormed at the same time	Yes	86 (12)	88 (151)	Ref.		
	No	14 (2)	12 (21)	1.20	0.25 – 5.73	0.824
New horses put onto pasture within previous 4 weeks	No	83 (15)	86 (163)	Ref.		
	Yes	17 (3)	17 (34)	0.96	0.26 – 3.49	0.949
Specific measures taken to reduce the numbers. of parasites on the pasture	Yes	88 (15)	90 (185)	Ref.		
	No	12 (2)	10 (20)	1.23	0.26 – 5.79	0.795
Measures taken to reduce parasites on the pasture:						
Faeces removed from pasture	No	56 (10)	89 (83)	Ref.		
	Yes	44 (8)	61 (130)	0.51	0.19 – 1.35	0.173
Pastures rotated	No	76 (13)	64 (132)	Ref.		
	Yes	24 (4)	36 (73)	0.56	0.17 – 1.77	0.300
Other species grazed on	No	82 (14)	82 (168)	Ref.		

pasture						
	Yes	18 (3)	18 (37)	0.97	0.27 – 3.56	0.967
Harrowed	No	59 (10)	53 (108)	Ref.		
	Yes	41 (7)	47 (97)	0.78	0.28 – 2.13	0.625
Worm egg count or tapeworm ELISA performed within last 12 months	No	83 (15)	82 (171)	Ref.		
	Yes	17 (3)	18 (38)	0.90	0.25 – 3.26	0.871
Faecal worm egg count negative	Yes	83 (10)	81 (86)	Ref.		
	No	17 (2)	19 (20)	0.86	0.17 – 4.23	0.851

Table 5. Univariable logistic regression analyses of categorised continuous horse- and management-level variables and their relationship with the risk of developing idiopathic focal eosinophilic enteritis (IFEE).

Variable		*Case % (n)*	*Control % (n)*	*Odds Ratio*	*95% CI*	*P-value*
General horse & management details						
Age (years)	< 6	56 (10)	22 (48)	Ref.		
	6 – 8	11 (2)	19 (41)	0.23	0.05 – 1.13	
	9 – 12	17 (3)	25 (54)	0.27	0.07 – 1.03	0.034
	> 12	17 (3)	34 (73)	0.20	0.05 – 0.75	
Height (cm)	< 152	44 (8)	28 (61)	Ref.		
	152 – 162	28 (5)	31 (66)	0.58	0.18 – 1.86	0.338
	> 162	28 (5)	41 (89)	0.43	0.13 – 1.37	
Weight (kg)	< 400	44 (8)	14 (30)	Ref.		
	400 – 499	11 (2)	25 (53)	0.14	0.03 – 0.71	
	500 – 565	22 (4)	42 (90)	0.17	0.05 – 0.59	0.017
	> 565	22 (4)	20 (43)	0.35	0.10 – 1.26	
Premises						
No. of horses on premises	>4	11 (2)	24 (51)	Ref.		
	4 – 8	39 (7)	25 (53)	3.37	0.67 – 16.98	
	9 – 19	33 (6)	21 (46)	3.33	0.63 – 17.30	0.194
	> 19	17 (3)	30 (65)	1.18	0.19 – 7.31	
Housing and grazing						
Hours stabled per week	<78	39 (7)	39 (83)	Ref.		
	78 – 112	11 (2)	21 (45)	0.53	0.10 – 2.64	0.721
	113 – 131	22 (4)	19 (40)	1.18	0.33 – 4.29	

	> 131	28 (5)	21 (46)	1.23	0.39 – 4.29	
Hours grazing per week	< 28	17 (3)	19 (41)	Ref.		
	28 – 49	33 (6)	17 (37)	2.22	0.52 – 9.50	
	49 – 83	11 (2)	21 (45)	0.61	0.10 – 3.82	0.401
	84 - 155	6 (1)	13 (29)	0.47	0.05 – 4.76	
	> 155	33 (6)	27 (29)	1.32	0.30 – 5.41	
Stocking density (horses per acre)	<0.61	56 (9)	22 (41)	Ref.		
	0.61 – 1.10	19 (3)	26 (48)	0.28	0.07 – 1.12	0.042
	1.11 – 1.90	6 (1)	13 (24)	0.19	0.02 – 1.59	
	> 1.90	19 (3)	39 (73)	0.19	0.05 – 0.73	
Pasture size (acres)	< 1.0	18 (3)	27 (55)	Ref.		
	1.0 – 3.0	41 (7)	40 (80)	1.60	0.40 – 6.47	0.626
	> 3.1	41 (7)	33 (66)	1.94	0.48 – 7.88	
No. of horses on pasture	1 / none	22 (4)	25 (53)	Ref.		
	2 – 3	29 (7)	28 (59)	1.57	0.44 – 5.67	0.621
	> 3	29 (7)	47 (100)	0.93	0.26 – 3.31	
Nutrition						
Forage weight (kg)	< 2.0	40 (6)	33 (55)	Ref.		
	2.0 – 7.0	27 (4)	33 (56)	0.65	0.17 – 2.45	0.815
	> 7.0	33 (5)	34 (5)	0.79	0.23 – 2.74	
Total weight of concentrate / grain (kg)	<0.2	40 (6)	32 (61)	Ref.		
	0.2 – 1.4	40 (6)	33 (62)	0.98	0.30 – 3.22	0.487
	> 1.4	20 (3)	35 (65)	0.47	0.11 – 1.96	

Table 6. Univariable logistic regression analyses of continuous horse- and management-level variables and their relationship with the risk of developing idiopathic focal eosinophilic enteritis (IFEE).

Variable	*Unit of measure ment*	*Mean / median*	*Coefficient*	*Standard Error*	*P-value*
Horse					
Age	years	9.6	-0.201	0.061	<0.001
Height	cm	153	-0.008	0.010	0.459
Weight	kg	481	-0.002	0.002	0.228
Premises					
No. horses on premises		9	-0.172	0.0018	0.256
Housing and grazing					
No. of hours stabled per week	hours per week	82	-0.0001	0.004	0.983
No. of hours grazing per week	hours per week	86	0.0002	0.004	0.995
Stocking density (linear)	horses per acre	1.1	-0.237	0.192	0.112
Stocking density (piecewise fit)	horses per acre		-3.420	1.411	0.0024
Pasture size	acres	2.0	0.029	0.025	0.288
No. of horses on pasture		2	-0.179	0.125	0.062
Nutrition					
Supplementary forage weight	kg	4.5	-0.008	0.052	0.871
Total weight concentrate / grain	kg	0.6	0.198	0.205	0.279

CHAPTER 6

Concluding discussion

CONCLUDING DISCUSSION

Work performed in this thesis has identified a seasonal pattern to specific types of equine colic and has identified a number of horse- and management-level risk factors for epiploic foramen entrapment (EFE) and idiopathic focal eosinophilic enteritis (IFEE). The results of the present study provides a further understanding of the underlying causes of colic and assists identification of horses who may be at high-risk of certain forms of colic with the ultimate aim of prevention.

Seasonality of colic

For many years there have been anecdotal reports that colic may be seasonal but, until now, it has not been possible to confirm this scientifically. Some case-control studies have identified particular months of the year to be associated with increased risk of certain types of colic. However the latter approach does not provide information about consistent seasonal patterns over time. In Chapter 2, a novel, model-based statistical technique has enabled us to provide formal evidence of a seasonal pattern to specific forms of colic admitted to a UK hospital over a 10 year period.

The seasonal patterns identified varied between different types of colic supporting the hypothesis that different risk factors may be associated with specific types of colic. In addition, these seasonal patterns appeared to coincide with periods of more intensive management or times of management change. Further research is required to investigate more precisely the management changes that occur at these times e.g. changes in dietary dry matter and protein intake, and duration of time spent stabled. It is possible that horse-level factors e.g. changes in the bacterial population of the gastrointestinal tract, which have been identified in other species (Mathiesen *et al.* 1987), and gastrointestinal metabolic function also vary seasonally (Fuller *et al.* 2001). It would be interesting to investigate if these changes occur and whether they mirror the seasonal patterns of colic identified in this thesis. Further work is also required to investigate the seasonal patterns of colic in other hospital and non-hospital based populations located in different geographic locations.

Epiploic Foramen Entrapment

In Chapters 3 and 4, the results of the first case-control studies to investigate horse- and management-level risk factors for EFE using a population of healthy horses as controls are presented. Horses that exhibited crib-biting / windsucking behaviour were associated with the greatest increase in risk of EFE in the matched (adjusted OR 67.2 95% CI 15.3 – 296.5) and unmatched (adjusted OR 71.6, 95% CI 14.3 – 359.2) case-control studies and confirms the findings of previous studies that used horses with other forms of colic as controls (Archer *et al.* 2004a; Archer *et al.* 2004b). In addition both studies identified a history of colic in the previous 12 months and increasing height to be associated with increased risk of EFE.

In Chapter 2, 6- and 12- month cyclical components were identified to EFE cases admitted to a UK hospital. The main peak occurred in the winter (November, December and January) with a secondary less pronounced peak in the months of April, May and June. In Chapter 4, an unmatched study design was used to investigate risk factors that might explain the observed seasonal effect in the UK. Increased stabling in the previous 28 days was associated with increased risk of EFE and this may help to explain the main seasonal peak given that in the UK horses are more likely to undergo periods of increased stabling during the winter months due to adverse weather conditions.

The risk factors identified in Chapters 3 and 4 suggest that a sub-population of horses exists that has some form of underlying gastrointestinal dysfunction and associated behavioural patterns which, together with possible variations in the relative anatomic dimensions of the epiploic foramen, make them inherently predisposed to EFE. It is possible that risk factors that vary seasonally then act to further increase the risk of EFE i.e. cumulative effect. Further research is required to investigate gastrointestinal function at a molecular level in these horses in order to investigate the underlying reasons for such dysfunction. Bacterial populations in the gastrointestinal tract may have some relationship with abnormal oral behaviours exhibited by horses (Johnson *et al.* 1998) and this also requires further investigation to determine whether this is a factor in these horses.

The behavioural features identified to place horses at increased risk of EFE are based on the owner / carers' assessment of their horses' behaviour in response to defined situations. Further research is required to validate these findings based on the direct observation of horses' behaviour using trained assessors.

Relatively few modifiable risk factors were identified in this thesis limiting the advice that can be given to owners / carers about management practices that can be implemented to reduce the risk of EFE. The evidence from the work performed in this thesis suggests that the risk of EFE can be reduced in high-risk horses by:

- Avoiding sudden increases in the duration of time that horses are stabled
- Developing feeding routines that avoid feed anticipation
- Providing access to a mineral / salt lick

Further work is required to determine why altered risk of EFE was associated with the person caring for the horse on a daily basis. This would involve further investigation of management factors that may be common to certain carers or other factors that were not measured in this study. The apparent protective effect of providing a salt / mineral lick may be associated with increased salivary flow. Nicol *et al.* (2002) hypothesised that the production of additional saliva by crib-biting, perhaps due to stimulation of the parotid gland by the muscular contraction that accompanies this behaviour, may be a means by which horses ameliorate visceral discomfort. It may be possible that provision of a salt lick to horses at high risk of EFE may serve to compensate for some inherent gastrointestinal dysfunction. The former hypothesis has not been proven and further work is required to investigate the findings from the present study.

In addition, further research is required to investigate the anatomic differences in the relative dimensions of the epiploic foramen in a wide range of breeds to determine if this is why larger horses are at increased risk of EFE. It is conceivable that reducing the dimensions of the foramen surgically may reduce the risk of EFE developing. This may be hindered by the anatomical location of the foramen making surgical access via a conventional laparotomy difficult and dangerous due to the vital structures (e.g.

hepatic portal vein) that form its borders. However, laparoscopic techniques provide better access to the epiploic foramen and techniques that have been used to prevent herniation of intestine into other anatomic locations (Marien 2001) may have the potential to be modified to encourage adhesion formation and subsequent reduction in the dimensions of the foramen.

Crib-biting / windsucking behaviour

Ancecdotally, crib-biting / windsucking behaviour has been associated with colic (Frauenfelder 1981). However, this has been disputed (McGreevy & Nicol 1998) and the overall clinical effects of crib-biting have been stated to be negligible (McBride & Long 2001). Work performed in this thesis has confirmed a strong association between crib-biting / windsucking behaviour and EFE. This work has also demonstrated that horses exhibiting this behaviour are significantly more likely to have suffered from colic in the previous 12 months compared to horses that do not exhibit this behaviour. Therefore, the evidence from work presented in this thesis and studies by Archer *et al.* (2004a; 2004b) and Hillyer *et al.* (2002) suggests that crib-biting / windsucking behaviour is associated with specific forms of colic, and possibly with colic in general, and supports the theory that this behaviour is associated with some form of underlying gastrointestinal dysfunction. This finding has important implications for equine welfare and further research is required to determine why this association exists.

Some workers have questioned the association between colic and crib-biting / windsucking based on the findings of McGreevy *et al.* (1995) who demonstrated that this behaviour is not related to deglutition and that air is not swallowed into the stomach (Bracher & Stohler 1998). It is possible that crib-biting / windsucking behaviour is a manifestation of visceral discomfort and this has been supported by recent research (Hemmings *et al.* 2006).

Intestinal function in horses exhibiting this type of behaviour has been investigated at a gross level by measuring intestinal transit times using radio-opaque markers and measures of digestive efficiency (McGreevy *et al.* 2001). Further research is required to investigate intestinal function at a more molecular level in horses exhibiting this behaviour. In addition, based on work presented in Chapter 4, it would be interesting to determine whether measures of intestinal function at a gross and molecular level or bacterial populations in the gastrointestinal tract correlate with subjective and objective measurements of the severity of crib-biting / windsucking behaviour.

If this type of behaviour is associated with underlying gastrointestinal dysfunction the link between crib-biting / windsucking behaviour and colic in general might be easy to explain. However, it is more difficult to explain why this form of behaviour is associated with a large increase in risk of EFE given the location of the foramen in the dorsal abdomen in a region where small intestine is not normally found. It is possible that there may be a direct causal association between crib-biting / windsucking behaviour and EFE. It would be interesting to assess changes in intra-abdominal pressures that occur during crib-biting / windsucking behaviour to determine if there is a mechanical reason why this behaviour is strongly associated with the development of EFE.

Based on the findings of the work presented in Chapter 3, further research is also required to determine if the type of carer influences how horses that exhibit this behaviour are managed. McBride and Long (2001) investigated the management of horses exhibiting different forms of stereotypic behaviour and how this behaviour was perceived by owners. However, the latter study limited this research to horses resident in racing stables, riding schools or competition establishments. Further studies are required to investigate the management of horses that exhibit crib-biting / windsucking behaviour in pleasure and competition / working horse populations and to determine if the type of carer (e.g. owner / professional yard staff) influences the way in which they are managed. It would also be interesting to investigate how horses exhibiting crib-biting / windsucking behaviour are managed based on the primary carer(s) perception of why this behaviour occurs and their feelings towards these horses.

Idiopathic Focal Eosinophilic Enteritis (IFEE)

In Chapter 5 the results of a multicentre, international collaborative study to investigate the epidemiology of IFEE are presented. This is the first case-control study to investigate risk factors for this apparently emerging disease. This work has some interesting parallels with eosinophilic gastrointestinal disorders (EGID) in humans in which the epidemiology of these conditions is also poorly understood. Animal models of this condition could potentially offer an insight into the causes and treatment of EGID in humans.

The study described in Chapter 5 was limited by the small number of IFEE cases recruited onto the study during the defined recruitment period resulting in relatively low study power. This was not unexpected given that these lesions are rare and data could only be collected over a relatively short time-period. However, the findings from the present study provide us with further clues about the underlying aetiology and pathogenesis of these unusual lesions and work is ongoing to collect data from a larger number of cases.

In humans, EGID are suspected to be allergic in nature arising as a result of an interplay between genetic and environmental factors (Rothenberg 2004). In the present study, horses were identified to be at greatest risk of IFEE between the ages of 0 – 5 years. This is a time when the immune system of the horse faces challenges due to marked dietary and other management changes which may expose them to potential allergens. Further research is required to investigate if there is an allergic component to IFEE.

Eosinophils are known to play a key role in host defence against parasites and based on the results presented in this thesis there was limited evidence to implicate nematode or cestode parasites in the pathogenesis of IFEE. This finding is consistent with previous studies describing case series of horses diagnosed with IFEE, the majority of which had been on regular anthelmintic programmes (Archer *et al.* 2006a, Perez Olmos *et al.* 2006). In addition, at a cellular level the lack of mast cells and the infiltration pattern in cases of IFEE and diffuse eosinophilic enteritis were considered to make a typical IgE-mediated reaction to parasites seem unlikely (Mäkinen *et al.* 2005; Proudman and Kipar 2006).

The finding that horses that had access to water from a pond / stream / stagnant pool were at increased risk of IFEE in both case-control studies requires further investigation to determine if this may be a source of a potential aetiologic agent / allergen. In addition, it was surprising to find that the majority of cases were recruited from 3 clinics, and that these lesions were not diagnosed at all in many of the collaborating clinics. It is possible that there may be some spatial and / or temporal clustering in this disease and this requires further investigation using a larger number of cases.

Study design & data collection

Most studies investigating the epidemiology of colic to date have been observational in nature, using case-control, cohort and longitudinal study designs to identify risk factors for colic. Cohen (2003) stated the need for new statistical and epidemiological models to address some of the deficiencies in our knowledge regarding the causes of colic. The novel, model based approach used in Chapter 2 has provided a more valid and elegant means of investigating the seasonality of colic. This technique enables us to approach the investigation of disease causality in a different way and can assist generation of new hypotheses as to why the different types of colic studied exhibit these specific seasonal patterns. This statistical technique has many applications beyond the field of equine colic and may be used to investigate the seasonality of other relatively rare diseases in the horse and in other species.

In this thesis, data were collected on a number of nutritional and behaviour variables which were incorporated into multivariable logistic regression analysis. Use of other statistical methods utilising multivariate methods such as principle components analysis or factor analysis may assist future research investigating the relationship between nutrition or behaviour and colic. These techniques have been used to study the associations between different food types in humans in order to identify underlying dimensions in the data (Northstone *et al.* 2005) and have been used in behavioural studies in many species including the horse (Seaman *et al.* 2002, Momozawa *et al.* 2003). Work will be ongoing to analyse data collected in this thesis on behaviour and nutrition variables using these methods.

Case control studies

Case-control studies provide the most economical means of investigating the epidemiology of rare diseases (Schlesselman 1982), and was the predominant study design used in this thesis. Observational studies are subject to a number of biases with selection bias, misclassification (a form of information bias) and confounding being considered the most important (Thrusfield 2005).

Selection bias was minimised in this study by using a population of non-colic controls. In addition strict study inclusion criteria were used to ensure that control horses were representative of the population at risk and that these horses would have become cases if the outcome had occurred (Dohoo *et al.* 2003). By randomly selecting a horse owned / cared for by the selected client, this avoided selection bias that might result if the client chose the control horse e.g. selecting one that had previously suffered colic if they felt it might be of interest to the study or not selecting a horse that they might consider less useful to the study or one that they felt embarrassed about e.g. a horse that exhibited stereotypic behaviour.

Response rates are important due to the fact that the more these rates decline, the more likely that sample bias will be a problem (Kozlowski *et al.* 2002). It was not possible to determine the response rate for all the clients contacted about the study due to the fact that some clinics preferred to contact their own clients directly. Of 624 clients selected at random as potential controls from 9 of the collaborating clinics, 12.6% (n=81) could not be contacted by telephone by the principle investigator e.g. moved house, telephone number changed or no answer was obtained on repeated occasions. Of the 561 clients who could be contacted, 3.2% (n=18) did not wish to participate in the study and 5.9% (n=33) were willing to participate but did not have an eligible control horse. The high response rate in this study should therefore minimise selection bias. The high response rate achieved in this study may have been due to postal contact describing the study followed by a telephone call (to avoid 'cold calling'), calling at different times of the day if there was no answer to an initial telephone call and by informing the owners that this was a study investigating colic in the horse. Horse owners perceive colic to be an important disease of the horse (Mellor *et al.* 2001) and this knowledge may have made them more willing to participate.

The high questionnaire completion rates in this study are comparable to a study by Murray et al (2006) in which postal contact was followed by a questionnaire administered over the telephone and resulted in completion of questionnaires in 96.1% of cases and 93.1% of controls. Acceptable completion rates of 71 % have been achieved following mailing of questionnaires to horse owners (Mellor *et al.* 2001). However, in human health studies the completion rates have been shown to be higher in telephone compared to postal surveys (Siemiatycki 1979). Given the length of the questionnaire in the present study, and the detailed information required in some questions, administration of the questionnaire by telephone was considered to maximise both the validity of the data obtained and the questionnaire completion rates.

Based on 817 questionnaires for which the time of questionnaire was recorded, 49.7% were conducted between 9am – 5pm (GMT) and 50.3% after 5pm (GMT). This information is important; studies in which questionnaires are only scheduled to take place between the working hours of 9am – 5pm may not be convenient for many horse owners resulting in reduced rates of participation. This would also result in bias e.g. if the owners that did not participate were those that worked during the day due to the fact that these horses may be managed differently compared to owners that were able to look after their horses during the day.

Another bias that might be identified to be problematic in studies of this type may be due to misclassification of cases. Misclassification bias was minimised by recruiting surgeons experienced in the diagnosis and treatment of surgical colic to collaborate with the study in order to ensure that cases were correctly classified. As discussed in Chapter 5, ideally histopatholgical confirmation of IFEE would have been performed in all these cases; it is possible that some of the cases of IFEE may have been misclassified, although accumulated evidence would suggest that this should be minimal.

Recall bias was minimised by conducting the questionnaires with the owners / carers as soon as possible after the date of surgery (or date of interest for controls) to avoid time-related memory decay (Murray *et al.* 2004). In addition, most of the questions related to the horse's health and management in previous 4 weeks which, together with the way in which questions were designed (e.g. prompts) should have minimised this type of bias.

Matching

Matched and un-matched case-control study designs were used in this thesis.
In Chapters 3 and 5, controls were matched to cases on clinic and time to control for the potential confounding effects of geographical location and management practices that may vary seasonally. One disadvantage of the matched study design was that, by matching on time, the seasonality of these types of colic could not be investigated. However, this study design facilitated collection of controls and this factor made the matched studies much easier to conduct.

Collaborative studies

The results presented in this thesis are based on data collected in an international, multi-centre collaborative research study involving 23 equine clinics and hospitals based in the UK, Ireland and USA. This approach was taken to maximise the number of cases collected within the study period and to make the results applicable to a wide range of equine populations. To the author's knowledge this is the first study to investigate risk factors for colic in more than one country.

There are a number of advantages to conducting a multi-centre collaborative study including increasing the amount of data collected and the sharing and development of research skills. However collaborative studies can be a more complex and time consuming mode of research than individual efforts and specific issues such as ownership and the accurate and complete recording of data need to be addressed (Rolfe *et al.* 2004). Senior *et al.* (2006) demonstrated some of the difficulties encountered when the personnel involved in data recording were not directly involved with the study e.g. missing data. The study conducted in this thesis did not encounter the problems associated with collection of data due to the fact that the principle investigator conducted the questionnaires directly with the owner / carer of the case and control horses and was responsible for data entry. However, additional time and effort was required to ensure that all cases occurring over the study period were reported to the principle investigator (e.g. allowing collaborating clinics to notify the principle investigator about cases by whatever means they considered easiest).

Client confidentiality is an important issue and care was taken to ensure that the collaborating clinics had obtained permission from the owners / carers of cases for these horses to be recruited onto the study and for their contact details to be given to the principle investigator. Clients selected as potential owners / carers of controls were also informed that this was a study based at Liverpool University and that they were being contacted on behalf of the relevant collaborating clinic to see if they would be willing to participate with the study.

International collaborative research activities may carry increased 'power' in terms of their value to research but additional problems need to be overcome in order for them to run successfully (Rolfe *et al.* 2004). These studies are associated with additional funding issues (e.g. increased expense), are more complex (e.g. working in different time zones) and are more time-consuming due to geographical distances involved. The advent of email and teleconferencing, in addition to more traditional forms of communication (face-to-face meetings and telephone conversations) can facilitate the running of these studies.

In this study, collaborating clinics were limited to countries in which English was spoken as the primary language due to the fact the funding for the study limited data collection to the principle investigator. This avoided the additional work associated with translation of the questionnaire to another language and training a bilingual person to collect data. However, the wording of questions and in particular the terminology used were discussed with American colleagues to ensure that the questions were not ambiguous or confusing.

In conclusion, work performed in this thesis has identified seasonal patterns to specific forms of colic in a UK hospital population. These seasonal patterns are consistent with risk factors already identified for some forms of colic and suggest hypotheses to be tested in future epidemiological studies. This thesis has also identified a number of risk factors for EFE and IFEE assisting identification of high-risk individuals and providing owners with advice about ways in which the risk of either form of colic can be minimised. Importantly, key areas for future research have also been identified. The work presented in this thesis is based upon data collected in a multi-centre, international collaborative study making the results applicable to a large number of horses in different geographical locations.

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GENERAL APPENDIX

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Review

Epidemiological clues to preventing colic

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Abstract

Colic remains a significant problem in the horse in terms of welfare and economics; in some equine populations it is the single most common cause of death. Many causes of colic are cited in the equestrian and veterinary literature but little scientific evidence exists to substantiate these theories. Recent epidemiological investigations have confirmed that colic is complex and multi-factorial in nature. Studies have identified a number of factors that are associated with increased risk of colic including parasite burden, certain feed types, recent change in feeding practices, stabling, lack of access to pasture and water, increasing exercise and transport. These findings are reviewed together with examples of management practices that may be altered to reduce the incidence of specific types of colic. This is an opinionated, not a systematic, review focusing on those areas that are considered most relevant to the practitioner.

Keywords: Horse; Colic; Epidemiology; Risk-factors; Parasites; Nutrition; Management

1. Introduction

Colic, a term used to describe abdominal pain, usually gastrointestinal in origin, has been recognised as a disease of the horse for centuries. It is a significant disease due to compromise of equine welfare and its economic impact; in the USA the annual cost of colic has been estimated at $115.3 million, losses due to death accounting for 66% of this figure (Traub-Dargatz et al., 2001).

Colic is reported to be the single most common cause of death in some horse populations, representing over a quarter of all deaths in one study (Tinker et al., 1997a). There are many anecdotal reports of causes, and prevention, of colic in the veterinary and equestrian literature but little scientific evidence to substantiate these theories. Recent epidemiological studies have shown that colic, like most non-communicable diseases, is complex and multi-factorial in nature (Reeves, 1997). Identification of risk factors, particularly those that are modifiable, may enable disease-prevention strategies to be developed. The results of these epidemiological studies form the basis of best, current, evidence-based advice that can be given to horse owners on prevention of colic in the horse.

An electronic search for papers was conducted using MEDLINE pubmed (http://www.pubmed.gov) using a variety of search words such as equine, horse, colic, epidemiology, anthelmintic and gastrointestinal. Papers that were not identified on these searches but referenced to in other papers were selected in addition to papers in journals not referenced on MEDLINE and proceedings of equine conferences known to the authors. In this article we review the risk-factors for colic identified in some of these studies. This is not a systematic or comprehensive review of the epidemiology of colic, which is a large subject area, and we acknowledge that there may be personal and cultural bias in the papers we have selected to review. Instead this is an opinionated review that highlights those

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areas that we consider to be most relevant to the practitioner.

Many papers report odds ratios from observational studies. An odds ratio (OR) is defined as the odds of disease in exposed individuals relative to the odds of disease in the unexposed (Schlesselman, 1982). An OR of 1 suggests that there is no association between exposure (e.g., feed type) and disease (i.e., colic), OR < 1 suggests that exposure reduces the risk of colic and OR > 1 suggests that exposure increases the risk of colic.

2. Incidence, types of colic and mortality rates

The reported incidence of colic in different horse populations varies from 3.5 to 10.6 colic episodes per 100 horses per year (Kaneene et al., 1997; Tinker et al., 1997b; Traub-Dargatz et al., 2001; Hillyer et al., 2001). Within a horse population, incidence rates can vary considerably, influenced by variables between and within horse establishments. Tinker et al. (1997b) reported between-farm variations from 0 to 30 episodes per 100 horse years. It has been suggested that investigations should be undertaken in horse populations with more than 20 colic episodes per 100 horse years to identify preventative measures that could be undertaken (White, 1997).

In many cases of colic, the exact gastrointestinal dysfunction or lesion is unknown. A diagnosis of spasmodic/gas colic or colic of unknown cause was diagnosed in 69–72% of cases seen within the general equine population and only 7–9% of cases in two of these studies were surgical in nature (Proudman, 1991; Hudson et al., 2001; Mair, 2004). Risk factors may be different for specific types of colic and studies looking at colic of any cause could miss some disease specific findings (Reeves et al., 1996; Hudson et al., 2001). However, it is important to note that these specific types of colic represent only a small minority of horses and most cases of colic within the general equine population fall into the 'spasmodic/gas/unknown' category.

Overall, reports of estimated case fatality rates as a result of colic vary from 6.7% to 15.6% depending on the population studied and the type of lesion (Tinker et al., 1997b; Kaneene et al., 1997; Mair, 2004). In one study, medical colics were reported to have a case fatality rate of 9% compared to 31% in horses with surgical lesions (Kaneene et al., 1997) highlighting the importance of preventing colic, particularly those forms that may require surgical intervention. Acute and subacute forms of equine grass sickness (EGS) are invariably fatal making prevention of this disease a key area of current equine gastrointestinal research in the UK.

2.1. Geography

Traub-Dargatz et al. (2001) did not identify any association between incidence of colic and geographic location in the USA. However, it must be emphasised that data were derived from a national equine survey that was conducted over a limited time period only (Spring 1998–Spring 1999). It is recognised that horses living in or originating from a particular geographic area are at increased risk for developing specific types of colic (White, 1997). One example is EGS which occurs predominantly in the UK, Northern Mainland Europe and South America (McCarthy et al., 2001). Other examples of types of colic that exhibit geographical clustering include sand colic, which is common in regions with sandy soils, and enterolithiasis (Ragle et al., 1989; Hassel et al., 1999).

Obstruction of the gastrointestinal tract by enteroliths is uncommonly seen in the UK but is particularly common in certain geographical regions such as California, USA. Reasons for clustering of this disease may include mineral content of soil, feed and water in individual regions but, given that all horses within these regions are not affected, it is likely that the disease is multi-factorial in nature (Hassel et al., 1999). The prevalence and severity of duodenitis-proximal jejunitis (also known as proximal or anterior enteritis) is reported to vary depending on geographic location. California would appear to have a lower prevalence of the condition than other regions of the USA and Europe. A more severe form of this condition has been reported in Southeastern USA compared to Northeastern regions of the country and generally the less severe form of the condition is reported in the UK (Edwards, 2000; Freeman, 2000).

2.2. Season

The incidence of colic may be seasonal in some horse populations and for specific types of colic. Proudman (1991) reported an increased incidence of colic of any type during the months of spring and autumn in the UK. This pattern of colic incidence was also reported in Thoroughbred horses in training yards in the UK (Hillyer et al., 2001).

In two separate studies conducted over a 12 month period in the USA, Traub-Dargatz et al. (2001) reported a higher percentage of colic cases in spring compared to summer or autumn, whereas Tinker et al. (1997a,b) reported highest incidence density in the months of December, March and August of the study year. EGS can occur at any time of the year but peak incidence of this condition in the UK is reported in the months of spring and early summer and the month of May in particular (Doxey et al., 1991; Wood et al., 1998). In addition there is strong evidence that, in the UK, grass sickness exhibits space-time clustering particularly within 5 km and 20 days of an arbitrary case (French et al., 2002).

Over a 10 year period, in one referral horse population in the UK, epiploic foramen entrapment of the small intestine (EFE) was consistently more prevalent in the months of December, January and February (Archer et al., 2004b). Despite many suggestions that weather-related factors may be associated with the development of colic, there is no statistical proof of this and the precise conditions predisposing to colic remain ill defined (Cohen, 1997; Goncalves et al., 2002; McCarthy et al., 2001). It is important to consider that seasonal incidence of colic may not be associated with weather factors alone but other potentially alterable management factors common to that time of the year such as stabling, quantities of feed or exercise levels (Hillyer et al., 2001; Archer et al., 2004b).

3. Horse-level risk factors

A variety of horse-level factors may put an individual at increased or decreased risk of suffering from colic. Measures to limit exposure to such risk factors are difficult to conceive, but knowledge of these factors can assist in the diagnosis of certain types of colic. Horse owners or carers may also be more likely to observe for signs of colic, identifying the disease at an earlier stage, in individuals known to be at significantly increased risk of developing colic.

3.1. Signalment

Some types of colic may be gender-specific in nature (e.g., inguinal herniation in stallions, and uterine torsions in mares) but overall there is no clear association between gender and colic. Whereas some studies have reported geldings to be at increased risk of suffering colic associated with pedunculated lipomas (Blikslager et al., 1992; Edwards and Proudman, 1994), others have reported geldings to be at reduced risk of developing colic of any cause (Kaneene et al., 1997) or have found no significant association between gender and incidence of colic (Reeves et al., 1989, 1996; Tinker et al., 1997a; Cohen et al., 1999; Traub-Dargatz et al., 2001). Associations between gender and risk of colic may be confounded by other factors such as use of horse and associated management practices. Foaling (Kaneene et al., 1997) or the 60–150 day period after foaling (White, 1997) has been associated with increased risk of colic in mares.

Studies investigating the association between age of the horse and colic have also yielded conflicting results. Foals <6 months old were found to be at decreased risk of suffering from colic in one study (Traub-Dargatz et al., 2001) but certain types of colic such as surgical lesions of the small colon (Reeves et al., 1989), intussusceptions (Cohen, 1997) and ascarid impactions (Southwood et al., 2002) are reportedly more prevalent in this age group. Horses between 2–10 years old were reported to be at increased risk in another study (Tinker et al., 1997b) but the authors noted that there may have been other confounding factors to explain this or the age group may have been a marker for use of horse, training, exercise or nutritional factors. Conversely, in other studies, horses >8 years (Cohen and Peloso, 1996), 10 years (Cohen et al., 1999) or horses of increasing age (Reeves et al., 1989; Kaneene et al., 1997) were found to be at increased risk of suffering colic.

Although the previously held belief that older horses were more likely to suffer from EFE has been refuted (Freeman and Schaeffer, 2001), older horses and ponies are at increased risk of suffering from colic associated with pedunculated lipomas (Blikslager et al., 1992; Edwards and Proudman, 1994). Young horses have been shown to be at increased risk of EGS in a number of studies (Gilmour and Jolly, 1974; Doxey et al., 1991) and horses aged 3–5 years old (Wood et al., 1998) or 4–5 years (McCarthy et al., 2004b) are reported to be at maximal risk.

The association between breed of horse and colic varies between studies. Thoroughbreds were more likely to develop colic in studies by Traub-Dargatz et al. (2001) and Tinker et al. (1997a). The latter study also identified Arab horses to be at reduced risk of colic whereas other studies (Cohen et al., 1995, 1999; Cohen and Peloso, 1996; Reeves et al., 1996) found Arab horses to be at significantly increased risk. Some studies have identified no association between breed and colic (Kaneene et al., 1997). It is important to consider other factors that may explain these findings. For example breed may be confounded by use and related management practices or, in hospital based studies, there may be bias in the breeds referred to clinics for colic. Specific types of colic are seen more frequently in certain types or breeds of horses such as dorsal colon displacement in large Warmblood breeds (White, 1997) or small colon impactions in ponies, Arab and American miniature horses (Dart et al., 1992). Enterolithiasis is particularly prevalent in certain breeds such as Arab horses and Morgans making a genetic predisposition to the disease possible (Cohen et al., 2000; Hassle, 2004).

3.2. Crib-biting/windsucking behaviour

Horses exhibiting crib-biting/windsucking behaviour have been identified to be at significantly increased risk of suffering from simple colonic obstruction and distension (SCOD) colic (OR 70.0, 95%CI 9.59–510.96) (Hillyer et al., 2002) and EFE in two hospital populations

(Illinois OR 34.7, 95%CI 6.2–194.6 and Liverpool OR 8.2, 95%CI 4.5–15.1) (Archer et al., 2004a). Crib-biting or windsucking behaviour may not play a direct role in the aetiology of these types of colic but may be a marker for management practices, temperament or other factors that predispose to colic. An epidemiological contribution to the gastric ulceration story was made by Nicol et al. (2002) who reported an intervention study performed in foals showing crib-biting behaviour. The addition of an antacid supplement to the diet of some foals resulted in decreased crib-biting behaviour and improvement in the severity of gastric ulceration.

3.3. History of previous colic

Horses with a history of colic have been identified to be at increased risk of suffering further episodes (Cohen et al., 1995, 1999; Reeves et al., 1996; Tinker et al., 1997b). In a study by Traub-Dargatz et al. (2001), 43.5% of horses suffering from colic were reported to have had colic previously, 11% of these within 1 year of the colic event. Horses previously suffering colic have also been significantly associated with SCOD colic (Hillyer et al., 2002).

Histological studies of the intestinal nervous system of horses undergoing surgery for large colon disorders have identified reduced density of interstitial cells of Cajal (Fintle et al., 2004). This is further evidence to support the hypothesis that a sub-population of horses exists with abnormal intestinal physiology that predisposes them to recurrent colic episodes. Individuals with a history of recurrent colic and previous identification of enteroliths in the faeces are indicators that an individual may be at increased risk of suffering an obstruction due to enterolithiasis and are candidates for implementation of preventative measures (Hassel et al., 1999). Horses that have previously undergone surgery for colic are at significantly increased risk of further colic episodes (Cohen et al., 1995, 1999; Cohen and Peloso, 1996). Surgical or therapeutic methods to prevent ileus, minimise the formation of adhesions or prevent recurrence of specific types of colic following surgery are ways in which future episodes of colic may be prevented; these are outwith the scope of this paper and will not be reviewed.

4. Parasites

4.1. The role of parasites and colic

Parasites are a well-documented cause of colic in the horse. Motility disturbances, arteritis, thromboembolism and peritonitis caused by migrating larvae of *Strongylus vulgaris* were once thought to cause up to 90% of all colic episodes in the horse (White, 1997). The availability of modern anthelmintics has resulted in reports of *S. vulgaris*-associated colic now being rare.

More recently, the tapeworm *Anoplocephala perfoliata* has been implicated as a cause of colic. Proudman et al. (1998) demonstrated a strong association between intensity of infection with *A. perfoliata* and ileal impaction and spasmodic colic, and this finding has been supported by a further epidemiological study (Little and Blikslager, 2002). The development of a serological assay to quantify the level of infection by *A. perfoliata* has improved detection of these parasites (Proudman and Trees, 1999; Proudman and Holdstock, 2000).

Uhlinger (1990) reported that a high proportion of colics in one population of horses were likely to have been a result of cyathostominae due to the fact that the incidence of colic was significantly reduced by anthelmintic schedules designed to control these particular parasites. This study confirms the protective effects of intervention strategies to decrease intestinal parasite burden. Caecocaecal and caecocolic intussusceptions have been reported to have clinical and/or pathological evidence of concurrent larval cyathostominosis (Mair et al., 2000), and the intestinal phase of ascarids can be associated with intestinal obstruction, rupture, peritonitis, intussusception or abscessation in foals; these cases usually have a grave prognosis (Southwood et al., 2002).

4.2. Administration of anthelmintics

Despite the availability and frequent use of anthelmintic drugs, parasitic infections are still common in horses. In a study performed in the UK, 69.5% of horses screened were infected with parasites. Of these horses, 30% were infected solely by strongyles, 32% only with tapeworms and 38% had mixed infections (Barrett et al., 2004). However studies relating parasite infestation and anthelmintic control with colic have yielded conflicting results.

Some studies have identified either no association of colic with the type of anthelmintic administered or the parasite control programme (Cohen et al., 1995; Hillyer et al., 2001; Traub-Dargatz et al., 2001), increased risk if horses were not on a regular de-worming programme (Cohen et al., 1999) or a decreased risk of colic associated with worming (Uhlinger, 1990; Reeves et al., 1996), particularly within 14 days after administration (Hudson et al., 2001). Failure to administer a pyrantel salt in the three months prior to admission was a risk factor for development of ileal impaction in one study (Little and Blikslager, 2002), supporting the role of *A. perfoliata* in the aetiology of this specific type of colic. Absence of administration of moxidectin/ivermectin anthelmintic in the previous 12 months was associated with SCOD in another study (Hillyer et al., 2002); the precise reason for this was unclear.

Some studies have identified increased risk of colic associated with anthelmintic administration although it is possible that this is associated with better management practices including closer observation for colic (Kaneene et al., 1997). Cohen et al. (1999) reported increased risk of colic in the seven day period following anthelmintic administration. This phenomenon has been investigated by Barrett et al. (2005) who found serological evidence of large tapeworm burdens in horses suffering from post-dosing colic. The authors suggested that colic was caused by the sudden and rapid death of existing tapeworms and it has been suggested that this situation might be avoided by preventing large burdens becoming established.

The relationship between frequency of anthelmintic administration (Wood et al., 1998) or administration of ivermectin on the ultimate and penultimate treatments (McCarthy et al., 2004a) and the development of EGS is unclear and requires further investigation. Recent administration of an anthelmintic has been identified as a risk factor for larval cyathostominosis (Reid et al., 1995). Anthelmintics may also result in colic due to intestinal obstruction as a result of rapid death of intraluminal ascarids in younger horses (Southwood et al., 2002). Strategies to minimise infection intensity of these parasites would therefore seem prudent. Current evidence suggests that a properly implemented, appropriate, parasite control programme should decrease the incidence of gastro-intestinal disorders among horses but, although parasite control probably reduces the risk of colic, many other sufficient causes of colic also exist (Cohen et al., 1999).

4.3. Other strategies to reduce parasite burden

In many management systems, parasite control depends primarily on frequent administration of anthelmintic drugs and under these conditions it is important to administer these frequently enough to maximise the animals health status. Anthelmintic schedules designed to minimise faecal egg counts may be expected to reduce the risk of colic but other policies such as strategic treatments may be expected to do the same thing (Uhlinger, 1990).

Drug resistance in cyathostominae (small strongyles) has emerged as an impediment to effective parasite control in the horse. Although moxidectin and fenbendazole have been shown to be effective against the encysted larval stages of the parasites, drug resistance is reported to all classes of drugs except the macrocyclic lactones (ivermectin and moxidectin) and is a limiting factor in the control of these parasites (Lyons et al., 2000). It is also recognised that in any group of horses there are always individuals that are more prone to parasitic infections (Barrett et al., 2004). Therefore it is important for horse owners to consider other ways in which the parasite populations on the pasture can be reduced including rotation or co-grazing with ruminants, removal of faeces from pastures and composting of stable manure and bedding before spreading it on pastures (Lyons et al., 2000).

5. Feed types and feeding practices

Certain feed types and feeding practices have long been identified as a cause of colic, Gamgee (1857) stating "too much hay and an excessive quantity of corn may induce violent indigestion and gripes...new hay and new oats combined are proverbially known to be injurious". Diets with an imbalance of roughage to concentrate, feeding certain feedstuffs such as coastal Bermuda grass hay, spoiled feed, young protein-rich grass, coarse poor quality roughage, pelleted feeds, overfeeding, underfeeding and feeding on the ground have also previously been implicated but these findings were anecdotal or based on observations of case populations without any comparable control population (Tinker et al., 1997b).

5.1. Forage

Traub-Dargatz et al. (2001) reported no association of colic with types of dried forage or frequency of feeding forage. In contrast horses with a history of being fed coastal grass hay were significantly associated with previous colic and recurrent colic in one study (Cohen and Peloso, 1996), whereas Hudson et al. (2001) reported feeding hay from round bales and hay other than alfalfa, coastal or Bermuda types to be significantly associated with colic. These findings were thought to have been related to poor quality of hay or the presence of mould, making hay less digestible, or to the percentage of fibre and protein; the types of hay associated with increased risk were of high fibre and low protein content and hence may have been less digestible, predisposing horses to colic (Cohen et al., 1999; Hudson et al., 2001). The latter finding may be surprising given than the equine gastrointestinal tract is adapted to a very high fibre diet.

Tinker et al. (1997b) reported decreased risk of colic in horses with less easily digested, more complex or varied diets with a high proportion of forage in the form of either hay or pasture. There is a need for investigation into the relationship of specific nutrients such as fibre, and measurements of these in feeds, in relation to colic (White, 1997). Feeding of coastal Bermuda grass hay in the USA has been associated with the development of ileal impactions; a reduced risk was identified in horses, in high-risk areas, given pelleted feed in addition to forage (Little and Blikslager, 2002). In Texas, USA, horses with enterolithiasis were demonstrated to be at increased risk if fed alfalfa hay (Cohen et al., 2000).

5.2. Concentrates

Two studies reported no association between colic and feeding a particular type of concentrate (Cohen et al., 1999; Traub-Dargatz et al., 2001) whereas feeding of >2.7 kg oats/day was significantly associated with colic in another study (Hudson et al., 2001). Tinker et al. (1997b) found higher concentrate intakes to be associated with the highest risk of colic, this risk increasing 6-fold in horses being fed the greatest quantities of concentrate (>5 kg/day) compared to horses on pasture receiving no concentrates. In this study, feeding whole grain decreased the risk of colic and feeding of more processed feeds such as pellets or sweet feeds increased the risk. In comparison, colic risk was increased in horses fed whole-grain corn but when all non-roughage concentrate feeds were combined, colic risk was found to decrease with increased intake of concentrates (Reeves et al., 1996). However this association was considered more likely to be a result of confounding by physical exercise, which could not be controlled for in their analysis.

Concentrate type, quantity and frequency of feeding do appear to be important in the aetiopathogenesis of colic and require further investigation. Equine Gastric Ulcer Syndrome (EGUS) can cause overt signs of colic (Vatistas et al., 1999b) and a number of dietary risk factors, including the feeding of a high concentrate diet, have been implicated as risk-factors for this condition (Buchanan and Andrews, 2003).

5.3. Feeding practices

Intermittent feeding has been used as a model to consistently produce EGUS (Murray, 1994) and in a separate study ulcers developed when feed was withheld (Vatistas et al., 1999a). The greater severity and prevalence of gastric ulceration in stall confined horses, compared to those turned out to pasture, was considered to be a result of altered eating behaviour in the former (Murray and Eichorn, 1996). Hudson et al. (2001) identified feeding a new batch of hay in the preceding two weeks to be most strongly associated with increased risk of colic (OR 4.9, 95%CI 2.1–11.4). Increased risk following a change in hay was also significantly associated with colic in another study (Cohen et al., 1999).

An increased risk of colic was reported in horses with more than the expected one change/year of hay (Tinker et al., 1997b) and a recent change in type or amount of grain or concentrate fed was also significantly associated with increased risk (Tinker et al., 1997b; Hudson et al., 2001). Diet change in the two week period prior to examination was significantly associated with colic in general (Cohen et al., 1995, 1999) and increased risk of SCOD colic was associated with increased concentrate feeding in the 14 days after change (Hillyer et al., 2002). Change in feed type or quality in the previous 14 days was also found to be associated with increased risk of EGS in a study by McCarthy et al. (2004a). These studies demonstrate that change in feeding practices is significantly associated with increased risk of colic, supporting historical belief that change to new types or amounts of feed should be gradual.

5.4. Dietary modifications to prevent specific types of colic

Knowledge of dietary risk factors can be used to formulate strategies to prevent particular types of colic from developing or recurring. Nadeau et al. (2000) found that the number and severity of gastric ulcers was significantly lower in horses fed alfalfa-grain diets compared to those receiving bromegrass hay. In conjunction with pharmacologic therapy (Andrews et al., 1999) pasture turnout has been advocated as the best dietary method of treating and preventing recurrence of EGUS. Provision of continual supplies of good quality grass or alfalfa hay, minimising feeding of concentrates and substitution of barley or oats are recommended in horses that must be kept stabled (Buchanan and Andrews, 2003). The feeding of preserved forage (hay or haylage) to horses at high risk of developing EGS may be protective (McCarthy et al., 2004a) although Wood et al. (1998) reported no evidence that the feeding of hay and/or forage was associated with decreased risk.

Recurrence of enterolithasis in 7.7% of previously affected horses (Hassel et al., 1999) makes implementation of preventative strategies important. Current recommendations for horses at high risk include elimination of alfalfa from the diet, grass hay supplementation, daily feeding of concentrates, daily exercise with access to pasture grass and apple cider vinegar supplementation to promote colonic acidification (Hassle, 2004).

Accumulation of sand in the large colon may result in obstruction and possible torsion of the large colon, although the exact quantity of sand that needs to accumulate to cause colic and an individual's tolerance to sand may vary (Bertone et al., 1988; Ragle et al., 1989). The use of psyllium mucilloid to encourage expulsion of sand from the large intestine has been advocated (Bertone et al., 1988) but was shown in one study to have no effect on sand evacuation from the large intestine (Hammock et al., 1998). In the latter study a reduction of intra-colonic sand was seen when sand intake was prevented. Preventative measures involve not feeding horses off the ground, limiting access to sandy yards and paddocks and the feeding of a high-bulk diet.

6. Other management factors

6.1. Exercise

Cohen et al. (1999) reported an increased risk of colic in horses being exercised at least once a week compared to those turned out with no ridden exercise (OR 1.6, 95%CI 1.2–2.2). Hillyer et al. (2001) suggested that the incidence of colic may have been associated with stage of training or level of activity in horses on National Hunt or Flat racing premises based on the seasonal pattern of colic in these two groups. However, this study did not control for factors such as nutrition, transport and use, which confound the relationship between exercise and colic. SCOD was also associated with a recent change in a regular exercise programme, particularly in the week following change (Hillyer et al., 2002). This effect remained significant when feeding and housing practices were taken into account in the final multivariable model.

Since Hammond et al. (1986) first reported a high prevalence (66%) of gastric ulcers in a population of Thoroughbred racehorses in Hong Kong, many researchers have documented the prevalence of EGUS in other groups of horses, primarily in North America, including Thoroughbred and Standardbred racehorses and horses used for endurance riding or showing (Murray, 1989; Murray et al., 1996; Vatistas et al., 1999b; McClure et al., 1999; Rabuffo et al., 2002; Begg and O'Sullivan, 2003; Nieto et al., 2004). The prevalence of EGUS in some of these studies has been as high as 93% (Murray et al., 1996; Vatistas et al., 1999b). In one study of Standardbred racehorses actively racing horses were more likely to have gastric ulceration than those being rested (Dionne et al., 2003). Simulated race-training has been used as a model to induce and maintain gastric ulceration supporting the role of intense exercise in the development of this condition (Vatistas et al., 1999a).

It has been hypothesised that development or worsening of squamous lesions when horses are in intensive training is due to increased intra-abdominal pressure and subsequent gastric compression pushing acidic contents into the squamous lined portion of the stomach. In addition the duration of acid exposure may be directly related to daily duration of exercise (Lorenzo-Figueras and Merritt, 2002). Knowledge of the high prevalence and recurrence rates of EGUS in these populations is important and, although there is limited opportunity to modify the management of horses in race training, dietary changes and pharmacologic therapy may be instituted (Buchanan and Andrews, 2003).

6.2. Stabling and access to pasture

Horses that spend 100% of their time in the stable have been reported to be at increased risk of colic when compared to horses that spent no time in a stable (Hudson et al., 2001). However, mild episodes of colic may be more likely to be detected in stabled horses compared to those turned out at pasture for long periods of time (Kaneene et al., 1997) and stabled horses may experience other management factors that predispose to colic. In addition, horses that are predominantly stabled may have less opportunity for exercise. Cohen et al. (1995, 1999) identified a change in stabling within the previous two weeks to be associated with increased risk of colic, although these studies did not examine which particular stabling changes predisposed horses to colic.

Increased number of hours spent in the stable was also associated with increased risk of SCOD, particularly in the 14 days following change in housing, and a large increase in risk (OR 7.58 95%CI 2.46–23.34) was found in horses stabled between 19 and 24 h per day (Hillyer et al., 2002). Owners should be aware of these factors particularly when horses that are usually turned out for significant periods of the day are confined to the stable. In these situations owners should be advised to monitor levels of feed intake and faecal output enabling early recognition of colic problems.

Decreased exposure to pasture, either a decrease in acreage or time at pasture, was a significant risk-factor for colic in one study (Hudson et al., 2001). Traub-Dargatz et al. (2001) reported no association between colic and type of pasture, pasture quality, percentage of pasture with edible vegetation or stocking density. In another study, stocking density of <0.5 horses/acre was associated with significantly increased risk of colic (Cohen and Peloso, 1996). Further investigations are required to define what types of pasture exposures and management predispose to colic (Reeves et al., 1996).

Access to pasture and duration of access have been associated with increased risk of EGS (Gilmour and Jolly, 1974) and in one study more than 95% of EGS cases had access to grazing (Wood et al., 1998). For many years EGS has been associated with horses grazing certain pastures and increased risk of disease has been identified in horses that have changed pasture in the preceding two weeks (Wood et al., 1998; McCarthy et al., 2001). McCarthy et al. (2004b) identified an association between EGS and increased soil nitrogen content, pasture disturbance and previous occurrence of EGS on the premises. In a separate study recurrence of EGS was associated with loam and sand soils and mechanical removal of droppings whereas chalk soil, co-grazing of ruminants, grass cutting on pastures and removal of droppings by hand was associated with reduced recurrence (Newton et al., 2004). Based on these two studies, current best advice is that young horses should avoid grazing pastures associated with previous EGS cases and that pasture disturbance and excavation should be avoided. In addition good pasture management, co-grazing of ruminants and avoidance of pasture sweepers may potentially reduce recurrence of EGS.

6.3. Access to water

Horses with access to ponds have been shown to be at decreased risk of suffering colic (Cohen et al., 1995). This is in agreement with the findings of Kaneene et al. (1997) where provision of water to groups of horses from sources other than buckets, troughs or tanks was associated with decreased risk. Hudson et al. (2001) found no significant association between the type of watering practice and colic but none of the horses in their study had access to water denied for longer than 4 h. An increased risk of colic was identified in another study in horses without access to water in outdoor enclosures (Reeves et al., 1996).

Water deprivation may be associated with increased risk of large colon impactions (White, 1997) and could partially explain the large increase in risk of horses suffering SCOD following transportation (Hillyer et al., 2002). In summary, provision of fresh palatable water is critical in prevention of colic in the horse and, although this may appear obvious, owners should be made aware of the importance of providing continual access to fresh water and regularly cleaning water sources (Cohen, 2003). Evaluation of mineral components of the water supply may be recommended in horses suffering from enterolithiasis (Hassle, 2004).

6.4. Transport

The association between colic and transport is inconsistent; Cohen et al. (1995) did not find any association whereas White (1997) reported increased risk of colic following transport. Transportation has also been implicated as a risk factor for EGUS (Buchanan and Andrews, 2003). Hillyer et al. (2002) reported that transport in the previous 24 h was associated with a large increase in risk for SCOD (OR 17.48 95%CI 2.16–141.35). This finding may be related to transport itself or may be confounded by simultaneous management changes such as change in premises, physical constraint and deprivation of water and feed. Owners of horses undergoing transport should be aware of these factors and measures taken to minimise such changes e.g., ensuring that horses are regularly offered water.

6.5. Dental prophylaxis

Cohen et al. (1995) did not identify frequency of dental prophylaxis to be associated with decreased risk of colic although both cases (horses with colic) and their controls received dental care making this comparison difficult. Poor dentition is reported to increase the risk of large colon impaction (White, 1997). This is supported by Hillyer et al. (2002) who identified horses that had their teeth checked or treated fewer times per year to be associated with increased risk of SCOD. Owners should be aware of the importance of regular dental examination in the prevention of colic.

6.6. Vaccination

Tinker et al. (1997b), in the USA, identified an increased risk of colic following Potomac horse fever vaccination particularly up to 14 days following vaccination. This association of colic with vaccination has not been found in other studies and merits further investigation to determine if there is a true, increased risk of colic associated with use of this vaccination or if vaccination is a marker for the type of management and health care that the horse receives.

The possibility that EGS may be prevented by vaccination has received renewed interest. A vaccine trial with an antitoxin neutralised botulinum toxin was conducted by Tocher et al. in 1923 and, although there was a significant reduction in mortality following vaccination, the "*B. botulinus* theory" was discounted a few years later (reviewed by McCarthy et al., 2001). It is now hypothesised that EGS results from a *Clostridium botulinum* type C toxicoinfection, due to the strong association between the toxin found in the gastrointestinal tract of horses with the disease (Hunter et al., 1999). Several of the risk factors identified by Newton et al. (2004) may directly or indirectly relate to soil disturbance and consequent soil contamination by grass increasing the rate of exposure of grazing horses to *C. botulinum* which resides in soil. The *C. botulinum* theory has been further supported by the findings of McCarthy et al. (2004a) where EGS was significantly associated with low antibody levels to three clostridial antigens. In future, EGS may potentially be prevented by vaccinating horses, thereby increasing the systemic level of anti-clostridial antibodies; this is an area of current research (Hedderson and Newton, 2004).

6.7. Premises/owner factors and use of horse

Horses whose owners provide their care have been shown to be at decreased risk of colic or recurrence of colic compared to horses cared for by a non-owner (Reeves et al., 1996; Hillyer et al., 2001). Owners may provide better health care for their horses or this finding may be related to other factors such as density of horses on the premises or their exercise level (Cohen, 2003). Traub-Dargatz et al. (2001) reported no association between the gender of person making health care decisions on the operation or the relationship of the person implementing health care to the owner of the operation. The latter study, and a study by Reeves et al. (1996) also did not find any association between colic and use of the horse.

Horses used for eventing, showing, or horses in training, particularly flat-trained racehorses, have been shown to be at increased risk in some studies (Kaneene et al., 1997; Tinker et al., 1997a: Hillyer et al., 2001). However, in these studies confounding factors such as age, breed and type of horse, nutrition, exercise and transport were not all taken into account when considering use of horse as a risk-factor for colic. Use of horse may be significant when specific types of colic are considered e.g., strangulating obstructions of the large colon in brood mares (Reeves et al., 1996). Mild episodes of colic may also be missed on premises where horses spend most of their time at pasture and are not used for any activities (Kaneene et al., 1997).

In addition to recent change of pasture, recent change of premises is associated with increased risk of EGS (Gilmour and Jolly, 1974; Doxey et al., 1991). Horses on premises where EGS has previously occurred are also at increased risk (Wood et al., 1998; McCarthy et al., 2004b). Newton et al. (2004) reported that recurrence of EGS was associated with establishments with larger numbers of horses, the presence of younger animals, stud farms and livery/riding establishments and rearing of domestic birds. Some of these findings may be explained by age and pasture associated risk-factors whereas others, such as rearing of domestic birds, require further investigation.

7. Conclusions

Several risk factors for colic have long been recognised: "the effects of water are but transitory and insignificant unless in co-operation with other agents, such as an improper quantity of deteriorated food, or overfeeding of an animal whose vital powers have been exhausted by overwork...farmers cannot understand why they should be so much troubled with this disease; but wherever I have been, much of it has existed..." (Gamgee, 1857). Epidemiological studies have illustrated the role that management-level and horse-level factors play in the development of colic and have identified previously unknown risk-factors. The significance of individual risk-factors varies between studies. This may be explained by the variation in numbers and geographical locations of the populations, including selection of cases and controls, and even the definition of colic used (Reeves, 1997; Goncalves et al., 2002).

Given that the equine gastrointestinal tract evolved to cope with trickle-feeding it is perhaps not surprising to discover the role that current management practices play. Horse owners should be made aware of the significance of these practices, particularly in horses affected by colic, and advised of measures that may be implemented to prevent recurrence. Further research is required to more precisely define the role of factors such as nutrition and exercise in this disease and the effect of preventative measures.

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Is equine colic seasonal? Novel application of a model based approach

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Abstract

Background: Colic is an important cause of mortality and morbidity in domesticated horses yet many questions about this condition remain to be answered. One such question is: does season have an effect on the occurrence of colic? Time-series analysis provides a rigorous statistical approach to this question but until now, to our knowledge, it has not been used in this context. Traditional time-series modelling approaches have limited applicability in the case of relatively rare diseases, such as specific types of equine colic. In this paper we present a modelling approach that respects the discrete nature of the count data and, using a regression model with a correlated latent variable and one with a linear trend, we explored the seasonality of specific types of colic occurring at a UK referral hospital between January 1995–December 2004.

Results: Six- and twelve-month cyclical patterns were identified for all colics, all medical colics, epiploic foramen entrapment (EFE), equine grass sickness (EGS), surgically treated and large colon displacement/torsion colic groups. A twelve-month cyclical pattern only was seen in the large colon impaction colic group. There was no evidence of any cyclical pattern in the pedunculated lipoma group. These results were consistent irrespective of whether we were using a model including latent correlation or trend. Problems were encountered in attempting to include both trend and latent serial dependence in models simultaneously; this is likely to be a consequence of a lack of power to separate these two effects in the presence of small counts, yet in reality the underlying physical effect is likely to be a combination of both.

Conclusion: The use of a regression model with either an autocorrelated latent variable or a linear trend has allowed us to establish formally a seasonal component to certain types of colic presented to a UK referral hospital over a 10 year period. These patterns appeared to coincide with either times of managemental change or periods when horses are more likely to be intensively managed. Further studies are required to identify the determinants of the observed seasonality. Importantly, this type of regression model has applications beyond the study of equine colic and it may be useful in the investigation of seasonal patterns in other, relatively rare, conditions in all species.

Background

Analysis of temporal patterns in data (i.e. data that arises over time) constitutes an important area of statistics, with applications in a wide range of fields from economics to engineering [1]. Consistent seasonal patterns in disease suggest the possibility of predictable behaviour, and in human medicine these have assisted rational planning of hospital resources in addition to providing clues regarding disease aetiology. The latter aspect is important in stimulating research to further the understanding of disease causality. Time-series analysis has been used in the human medical field to investigate a number of non-infectious conditions including asthma and aortic aneurysms [2] and in veterinary epidemiology to investigate patterns in infectious diseases [3-6]. However these statistical methods have received relatively little attention in the field of non-infectious veterinary diseases and, to our knowledge, have not previously been reported in the investigation of colic in the horse.

Colic is an important cause of mortality and morbidity in domesticated horses and has a complex, multifactorial nature [7-10]. Many questions about this condition remain to be answered including the effect of season on the occurrence of colic. Knowledge of a seasonal pattern (or indeed lack of evidence of a seasonal pattern) in the incidence of colic within a population could assist identification of risk-factors for this disease. Such information could be used to devise preventative strategies, such as altered management practices, to potentially reduce its occurrence. Increased incidence of colic has been identified in certain months of the year in several different equine populations [8,11-14] but the association between season and colic is unclear. This may, in part, be attributable to limitations in the statistical approaches that have previously been used to address this issue [15].

Many standard statistical approaches are built upon the assumption that observations are mutually independent. This assumption is likely to be inappropriate in the case of colic since many factors may be interdependent; observations in adjacent months might be more similar than those which occur months apart due to, for example, similarities in feed types and duration of stabling. Time-series methods provide a valid means of investigating seasonal patterns in colic. Traditional approaches, such as the Auto-regressive Integrated Moving Average (ARIMA) of Box and Jenkins [16] offer a number of possibilities. However, this approach requires the number of observations at each time of interest to be large for the Normal distribution-based assumptions upon which it is based to remain valid. This method would not be suitable for diseases, such as admissions of colic cases to a hospital, in which the counts per month are relatively small (i.e. typically less than 30). In the latter situation, it is necessary to use a modelling approach that respects the discrete nature of the count data. One possibility lies in the use of a Poisson distribution to model count data within a framework broadly analogous to that of generalised linear modelling [17].

The aim of this study was to determine if there was any evidence of seasonality in horses presented to a UK referral hospital with particular types of colic. Using a Bayesian approach, we fitted a regression model which incorporated autocorrelation as a latent variable, to reflect the fact that, having taken account of seasonality and trend, any remaining serial dependence may operate over a shorter temporal scale and is likely to represent unmeasured influential covariates which themselves vary over time. In addition we fitted a model without latent correlation but with a linear trend. Based on current evidence in the literature, our *a priori* hypotheses were that equine grass sickness (EGS) and epiploic foramen entrapments (EFE) would demonstrate seasonality but that intestinal obstruction by pedunculated lipomas would be a random event without any evidence of seasonality. It was unclear if a seasonal effect would be seen in the other colic groups.

Results

Exploratory data analysis

The total numbers of colic cases for each diagnostic category are shown in Table 1 and boxplots of detrended colic admissions by month for each colic group are presented in Figure 1. Total admissions of all colic cases to the hospital appeared to peak in the months of April/May and again in October/November/December. A similar pattern was also evident in the medically and surgically treated colic groups. There was a clear seasonal effect for EGS, with a pronounced peak in May and a suggestion of a secondary peak in October. Cases of EFE appeared to peak in the months of December/January. There did appear to be a possible seasonal component to cases of large colon displacements and torsions, with peaks in the spring and autumn months, whereas primary large colon impaction colics appeared to peak over the autumn and winter months. There was no graphical evidence of a seasonal effect in cases of pedunculated lipoma.

Regression model with seasonal components, trend and an autocorrelated latent variable

The posterior distribution summaries for each colic type are presented in Table 2. With the exception of lipoma for which our preliminary assessment of no evidence of a seasonal pattern was confirmed, the only colic for which a model with twelve-monthly cycles only appeared superior to a model with 12 and 6-month cycles was large colon displacement/torsion. Twelve and 6-monthly cyclical components were identified for EGS, large colon impaction and EFE colics. Weaker 12 and 6-monthly cycles were

Table 1: Colic categories, case definitions and number of cases in each category admitted to the PLEH between January 1st 1995 and 31st December 2004

Colic category	Case definition	Total number
All Colics	All confirmed cases of colic admitted to the hospital	2580
All Surgical Colics	Colic cases with surgical lesions confirmed at exploratory laparotomy or post-mortem examination	1612
All Medical Colics	All colic cases that resolved with medical treatment only	968
Pedunculated Lipoma	Obstruction of small intestine by a pedunculated lipoma diagnosed at exploratory laparotomy or post-mortem examination	231
Epiploic Foramen Entrapment	Entrapment of the small intestine in the epiploic foramen diagnosed at exploratory laparotomy or post-mortem examination	92
Equine Grass Sickness	Equine grass sickeness cases confirmed by histological examination of the ileum	109
Large colon displacements or torsions	Displacement or torsion of the large colon diagnosed by rectal examination, clinical signs and response to treatment; treated either surgically or medically or diagnosed at post-mortem examination	435
Large colon impactions	Primary large colon impactions confirmed by rectal examination and response to treatment (medically treated group) or at exploratory laparotomy	214

evident in the all colics, all medically treated colics and all surgical colics groups. The weaker signal in the latter three is justified by the fact that these represent combinations of colics of different types, each of which has their own distinct seasonal profile. Despite this level of aggregation a small seasonal profile emerges. Note that although the credible intervals for sine and cosine terms representing 12-month cyclical components for all colics, surgical colics and medical colics do not strictly exclude 0, in each case their extremity is very close to 0 and so we retained these terms. Unsurprisingly, more convincing segregation between models upon the basis of the DIC statistic was possible in the cases where larger data sets were available for analysis (all colics, all surgical colics, all medical colics and large colon displacements), and we should interpret the findings in the cases where counts per month are small more cautiously. Estimates of the seasonal component for the "best" model and its relationship to the month of the year for each colic type are shown in Figure 2.

The inclusion of trend and serial correlation together in models of this nature where the number of cases observed at a particular time point is small is potentially problematic, as it may prove difficult to separate positive serial dependence and trend. Indeed, if positive trend exists and there may be positive serial correlation, parameters in the model are potentially highly correlated and the MCMC algorithm struggles in the presence of low counts. As expected there were problems with convergence for many of the models including both terms; we therefore do not include the DICs from models incorporating latent serial correlation together with a linear trend in Table 3 because they are likely to be unreliable.

Models either without trend/with latent serial correlation or with trend/without latent serial correlation, provided better convergence of the MCMC algorithm. For the same data set we find situations where a model with latent serial correlation and 12- and 6-month cycles but no trend term is selected as optimal by DIC comparison (Table 3), whereas in the case where serial dependence is excluded, a model with those same seasonal components and a positive trend is selected (Table 4). With the exception of EFE for which no evidence of trend emerges, for each of these latter models the trend term is of the order of 0.005 (standard deviation of the order of 0.002). More compelling evidence of an increasing trend over time occurs in the cases where sample sizes are larger.

In the model incorporating latent serial correlation but no trend, it is interesting that although the parameter which controls the dependence (α) does not have a marked effect on the model (as judged by the fact that the credible interval contains 0) the posterior mean for α in all cases, though small, is positive. Whilst we must be cautious concerning over-interpretation of this finding in the presence of large uncertainty, a small but positive effect may represent positive serial correlation, or it could in part be measuring the increasing trend which we were unable to include simultaneously for statistical reasons. (Note that, whilst comparisons within Tables are valid, comparisons between DICs presented in Table 3 and Table 4 cannot be drawn, as they represent different classes of models, one with and one without a latent correlation structure).

For our purposes, given that our primary interest concerns seasonality, whether we included latent serial correlation or trend, the estimates of the seasonal components were broadly similar across models and this renders our findings regarding seasonality robust in the presence of these largely statistical effects.

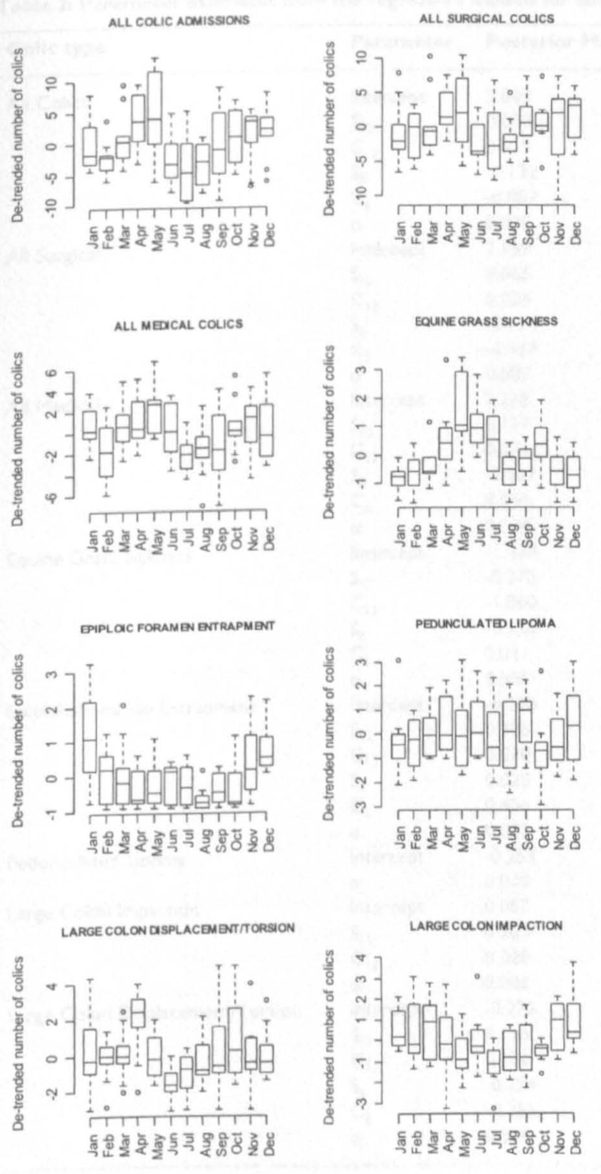

Figure 1
Boxplots of de-trended (annual average subtracted) colic admissions by month for each colic admitted to a UK referral hospital between January 1995 – December 2004.

Discussion

The aim of the present study was to investigate the seasonality of different types of colic presented at a UK equine referral hospital. Cohen [15] stated the need for new statistical or epidemiological models that could address deficiencies in our knowledge regarding equine colic. This model provides a useful means of investigating temporal patterns in equine colic, and to our knowledge, this is the first report that uses time-series methods of analysis to explore seasonal patterns in equine colic.

Two studies in the UK have described an apparent peak in cases of colic of any cause in spring and autumn months [11,13]. In the present study, similar patterns were evident in the all colic and all medically or surgically treated colic groups with small peaks evident around the months of March/April and October/November. Hillyer et al. [13] suggested that the seasonal pattern of colic in the racehorse population under investigation in their study may have been associated with stage of training or level of activity. Increased risk of colic has been identified following change in diet and stabling in the preceding 2 weeks [18,19] and following decreased exposure to pasture [20]. Therefore, these patterns of colic may not be surprising given that, at these times of the year in the UK, changes in management practices such as turnout, stabling and exercise are more likely to occur.

This modelling approach confirmed our hypothesis that EGS would exhibit seasonality, as demonstrated by other workers using different approaches. Although EGS may occur at any time of the year, the peak incidence of this condition in the UK is reported in the months of spring and summer, and the month of May in particular [21,22]. In the present study, EGS exhibited significant 12- and 6-month cyclical components, cases peaking in the month of May with a secondary less pronounced peak in the month of October. Risk factors for EGS that have been identified in epidemiological studies previously include increased risk associated with change of field in the previous 2 weeks [22], non-feeding of hay or haylage and change of feed type or quantity 14 days prior to disease [23]. The seasonal pattern of EGS identified in the present study coincides with months of the year that may be associated with change in grazing practices and feed types in the UK.

Use of this model also confirmed our hypothesis that EFE would exhibit seasonality. Using data arising over a 10 year period at the same hospital (1991–2001), multivariable modelling confirmed that EFE was consistently more prevalent in the months of December, January and February [24]. There was a suggestion of a seasonal pattern of distribution for each year studied but, using traditional methods of analysis, we were unable to confirm this statistically. The results from the present study revealed 6- and 12- month cyclical components to cases of EFE presented at this hospital; the main peak occurred in the months of November, December and January with a secondary, less pronounced peak in the months of April, May and June. In Germany, Scheideman [25] reported that although EFE cases were seen throughout the year, a marked increase in cases was evident during the period

Table 2: Parameter estimates from the regression models for each colic type.

Colic type	Parameter	Posterior Mean	Posterior Standard Deviation	95% Credible Interval
All Colics	Intercept	2.849	0.966	1.059, 4.737
	S_{12}	0.082	0.043	-0.002, 0.167
	C_{12}	0.029	0.043	-0.055, 0.113
	S_6	-0.132	0.033	-0.196, -0.067
	C_6	-0.007	0.033	-0.071, 0.058
	α	0.005	0.012	-0.018, 0.029
All Surgical	Intercept	2.159	1.089	-0.017, 4.156
	S_{12}	0.065	0.054	-0.042, 0.173
	C_{12}	0.034	0.055	-0.073, 0.142
	S_6	-0.114	0.042	-0.196, -0.032
	C_6	-0.037	0.041	-0.119, 0.044
	α	0.007	0.015	-0.024, 0.037
All Medical	Intercept	2.218	1.035	0.271, 4.225
	S_{12}	0.117	0.061	-0.001, 0.237
	C_{12}	0.021	0.059	-0.095, 0.136
	S_6	-0.167	0.051	-0.267, -0.067
	C_6	0.044	0.049	-0.054, 0.140
	α	0.004	0.014	-0.023, 0.031
Equine Grass Sickness	Intercept	-1.430	1.278	-3.750, 1.244
	S_{12}	-0.275	0.190	-0.655, 0.093
	C_{12}	-1.060	0.206	-1.481, -0.673
	S_6	-0.638	0.172	-0.980, -0.306
	C_6	0.041	0.163	-0.277, 0.357
	α	0.006	0.024	-0.042, 0.054
Epiploic Foramen Entrapment	Intercept	-0.698	1.029	-2.710, 1.456
	S_{12}	0.396	0.199	0.013, 0.794
	C_{12}	0.590	0.168	0.271, 0.929
	S_6	0.028	0.167	-0.302, 0.356
	C_6	0.404	0.169	0.077, 0.736
	α	0.002	0.020	-0.038, 0.041
Pedunculated Lipoma	Intercept	-0.253	1.123	-2.489, 1.872
	α	0.010	0.019	-0.028, 0.049
Large Colon Impaction	Intercept	0.057	0.957	-1.643, 1.999
	S_{12}	0.265	0.118	0.033, 0.497
	C_{12}	0.389	0.118	0.162, 0.622
	α	0.005	0.021	-0.038, 0.046
Large Colon Displacement/Torsion	Intercept	-0.275	1.112	-2.388, 2.065
	S_{12}	0.116	0.101	-0.084, 0.315
	C_{12}	0.166	0.110	-0.049, 0.383
	S_6	-0.234	0.090	-0.410, -0.058
	C_6	-0.256	0.090	-0.433, -0.080
	α	0.005	0.022	-0.039, 0.049

For compactness, $S_{12} = \sin\left(\frac{2\pi t}{12}\right)$, $C_{12} = \cos\left(\frac{2\pi t}{12}\right)$, $S_6 = \sin\left(\frac{2\pi t}{6}\right)$ and $C_6 = \cos\left(\frac{2\pi t}{6}\right)$

between December and April. The seasonality of EFE may reflect changes in stabling, turnout, exercise and feeding practices common to these times of the year; these are currently under investigation in a prospective study.

The large colon impaction colic group exhibited 12 month cyclicity, with an increasing number of cases identified in the autumn and winter months (peak December/January) decreasing over the spring months with the lowest incidence over the months of July and August. A slightly different cyclical pattern was identified in the large colon displacement/torsion colic group with peak incidence in the months of Spring and Autumn, similar to that seen in the all colic and all medically or surgically treated colic groups. Hillyer et al. [26] identified a number of factors associated with increased risk of simple colonic obstruction and distension colic (defined as primary large colon impactions and simple large colon displacements). These included an increasing number of hours spent in a stable, recent change in a regular exercise programme and

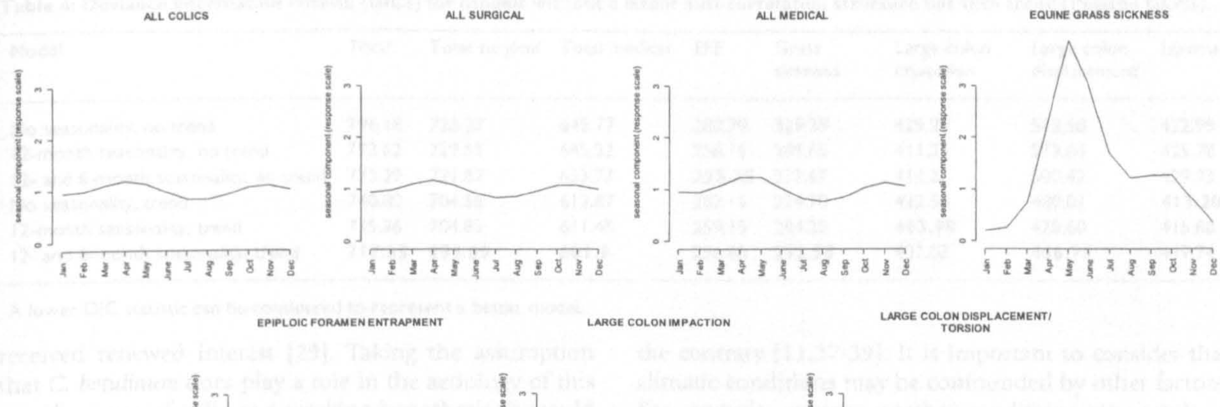

Figure 2
Estimate of model's seasonal component for each colic type. For each colic type an estimate of the model's seasonal component was extracted using the posterior mean of the parameter associated with each of the sine and cosine terms based on the frequencies detected for each group in Table 2. With the exception of the large colon impaction group (12 month cycles only) all models incorporated 12- and 6-monthly cycles.

stabling for 24 hours per day. These factors may explain the reduced incidence of colic of either type evident in the months of June, July and August when horses, in general, are less likely to be stabled for prolonged periods in the UK. Many factors have been associated with large colon impactions including acute decrease in exercise or cessation of daily turnout [27] and feeding of coarse roughage [28]. These factors may, in part, account for the increased incidence of this colic type coinciding with months of the year when cold, wet weather is more likely to occur in the UK. Under these conditions horses are more likely to be housed and to be given more supplementary roughage (i.e. hay/haylage in addition to grass). Large colon torsion has been associated with mares in the periparturient period [28] which might explain the increased prevalence of this colic type between the months of January and May; however brood mares comprise a relatively small component of this hospital's caseload.

Obstruction of intestine by pedunculated lipomas in theory should be a random event, and this model confirmed our *a priori* hypothesis that no seasonal component to this condition would be identified.

We have alluded to the difficulties in detecting serial dependence in the presence of trend when samples are small. With larger samples it might be possible to separate more conclusively trend and latent serial dependence and further research using larger samples sizes is warranted.

Considering first the possible interpretation of latent serial correlation in the context of colic, we take EGS as an example. The role of *Clostridium botulinum* in EGS has

Table 3: Deviance information criteria (DICs) for models with a latent autocorrelation structure.

Model	Total	Total surgical	Total medical	EFE	Grass sickness	Large colon impaction	Large colon displacement	Lipoma
No seasonality, no trend	756.83	718.59	607.42	282.14	339.02	414.80	483.27	**419.58**
12-month seasonality, no trend	754.20	720.39	604.86	261.33	280.39	**391.20**	481.77	421.54
12- and 6-month seasonality, no trend	**732.29**	**708.46**	**592.65**	**258.93**	**267.09**	394.47	**459.30**	425.44

A lower DIC statistic can be considered to represent a better model

Table 4: Deviance information criteria (DICs) for models without a latent autocorrelation structure but with trend (Poisson GLMs).

Model	Total	Total surgical	Total medical	EFE	Grass sickness	Large colon impaction	Large colon displacement	Lipoma
No seasonality, no trend	796.18	728.37	645.77	280.79	329.39	429.29	513.58	422.95
12-month seasonality, no trend	793.62	729.59	645.22	258.15	289.65	411.25	513.64	425.78
12- and 6-month seasonality, no trend	773.29	721.87	633.73	**255.35**	277.67	414.21	500.42	429.93
No seasonality, trend	740.80	704.58	613.87	282.11	324.70	422.58	480.01	**413.20**
12-month seasonality, trend	735.36	704.83	611.45	259.15	284.20	**403.98**	478.60	415.88
12- and 6-month seasonality, trend	**717.63**	**698.06**	**601.9**	256.60	**272.58**	407.02	**466.76**	419.74

A lower DIC statistic can be considered to represent a better model.

received renewed interest [29]. Taking the assumption that *C. botulinum* does play a role in the aetiology of this specific cause of colic as a working hypothesis, it would seem plausible that the levels of the pathogen in the environment will be temporally structured so that they are similar in proximate months and less similar in months which are far apart, irrespective of the seasonal effect. Using space-time K-function analysis, French et al. [30] demonstrated strong evidence of space-time clustering of this disease, particularly within the first 10 km and 20 days of a case, which would support the latter idea. Similarly, feed types and amounts, periods of stabling and turnout are more likely to be similar in proximate months.

Considering now the interpretation of a positive linear trend which was evident in all models excepting that for EFE not including latent correlation, knowledge of continued improvements in the medical and surgical management of colic and resultant increased success rates following treatment [31] may have positively influenced referring vets and owners making them more willing to undertake referral. This trend may also reflect increased levels of insurance in the hospital referral population, making surgical correction or intensive medical treatment an option when previously it may not have been affordable. In the case of colic due to intestinal obstruction by a pedunculated lipoma, which most frequently occurs in older ponies and horses [32-34], a combination of affordability and knowledge that surgical success rates following treatment of this condition are comparable to, or in some cases better than, other surgical lesions in younger horses [35] may account for this annual trend. Alternatively, there may simply be a greater number of older ponies or horses in the general equine population [36]. It was also interesting to note that an annual trend was not evident in cases of EFE admitted to the hospital. This finding may be due to insufficient power to detect a marked effect based on the relatively small numbers of EFE in this series.

Weather-related factors have not been shown to be statistically significant in relation to colic using traditional methods of analysis, despite many anecdotal reports to the contrary [11,37-39]. It is important to consider that climatic conditions may be confounded by other factors. For example, extreme weather conditions may result in altered management practices such as reduced level of horse activity [40]. Nevertheless, identification of any weather-related patterns associated with colic may assist identification of causal factors. Time-series analysis provides a more elegant and valid means of studying seasonal patterns to colic and may also provide a more appropriate means of investigating associations between weather patterns and disease [5].

A number of approaches may be used to investigate temporal patterns in data and, when choosing the most suitable method, it is important to recognise that different types of dependence which are context-specific may occur. First, the number of events in month t might explicitly depend upon the number of events in month t-1 e.g. if one is considering the evolution of an infectious disease which propagates by direct contact between infected individuals. This type of dependence is described as "observation driven" [41]. Secondly, the counts in month t and month t-1 might be independent, conditional upon some latent process which is temporally structured and contains serial correlation. For example, the number of individuals suffering from hypothermia might be influenced by climatic conditions, which themselves vary with time, and are likely to be autocorrelated i.e. the weather in month t is likely to be in some way similar to the weather in month t-1. Here, dependence (and subsequent models) is described as "parameter driven" [42]. The two dependence assumptions are qualitatively different and require different modelling approaches. There is little reason to suppose that the number of colic cases admitted to a hospital facility in month t is directly influenced by the number in the previous month (t-1). Instead, it seems more plausible that there may be some underlying, unmeasured (or indeed immeasurable) process which has a direct influence on the monthly counts. It is our belief that the parameter driven approach is likely to be most relevant to data pertaining to colic in the horse and is the basis upon which the model was chosen.

An important issue in Markov Chain Monte Carlo (MCMC) based analysis is that of convergence of the Markov Chains and whether the samples being generated are from the true posterior distribution under the model framework. In order to test this, we ran two chains simultaneously using differing starting values, and found that in each case the posterior summaries obtained were analogous. In addition, we examined the $\hat{R}$ statistic (the "potential scale reduction factor") provided by WinBUGS and found that in all cases barring the models which attempted to incorporate both trend and latent correlation this was very close to 1.

A further issue in Bayesian analysis concerns the sensitivity of the resultant posterior distribution to the choice of prior distribution. Given that, for all parameters, we have selected vague priors we do not believe this to be an issue here; in addition, although the counts at each time point were relatively small, the length of each series was large ($n = 120$ in all but one case where $n = 119$) so we would expect the data to dominate.

The issue of determining a suitable autocorrelation structure for the error term in these models is also important. There exists only a single series of data, in contrast with a longitudinal data set for which we can gain knowledge about the autocorrelation structure by exploiting the replication in the data [43]. Our selection of a latent variable including only first-order correlation (correlation with the previous time point) is rather arbitrary, but seems reasonable on scientific grounds in that there may be environmental factors which are very similar in proximate months. It would be possible within this modelling framework to incorporate more complex error structures, for example, allowing dependence on even earlier time points. It is likely, however, that with the small counts available longer-term effects of this nature could not be detected.

The exact gastrointestinal dysfunction or lesion is unknown in many cases of colic that occur within the general equine population [10,11,20]. It is important to recognise that data based on colic cases presented to a referral hospital represent only a small proportion of all colic cases occurring within a geographical location: such a population is biased towards horses with lesions requiring surgical correction or more intensive medical treatment, and whose owners are willing to undertake referral. In addition, studies investigating specifically diagnosed cases of colic would include only a minority of cases seen in the general population [8]. However such studies are necessary due to the fact that risk-factors and patterns of disease may be different for various types of colic, and investigation of colic of any cause may miss some of these [44]. The colic types investigated in the present study also represent the more severe forms of the disease i.e. those which do not resolve spontaneously or following simple medical treatment, making the investigation of causality and potential prevention of relatively greater importance. It is unlikely that there would be any effect of season on the referral of colic cases to the clinic.

The models produced in this paper are biologically plausible and provide useful information on the temporal patterns of different colic types. This work demonstrates in principle how standard and non-standard Poisson regression-based approaches can be used in other veterinary applications where disease incidence is relatively rare. These results also provide an insight into the aetiology of different colic types admitted to a UK referral hospital. There is a suggestion of increased admissions of certain colic types at times of managemental change (surgically and/or medically treated colics, large colon displacements/torsions and EGS) and during periods of intensive management (months of the year when horses are more likely to be stabled or stabled for longer periods of time) e.g. EFE and large colon impaction. These results are based on the findings from a single UK referral equine hospital; further studies are required to determine the relationship between season and colic incidence in other geographical locations using hospital and non-hospital based populations.

Conclusion

We have used a regression model which has the flexibility to incorporate latent serial correlation to explore the seasonal prevalence of different colic types presented at a UK equine referral hospital. This is a novel statistical approach in the field of equine colic research and it has enabled us to confirm a seasonal pattern for equine grass sickness, as demonstrated by other workers using different methods of analysis, and to formally establish the existence of a marked seasonal effect in cases of epiploic foramen entrapment. In addition, a seasonal pattern was evident to admissions of all colic types, all surgical and medical colics and in cases of large colon impaction and large colon displacement/volvulus. Use of this model confirmed that intestinal obstruction by pedunculated lipomas showed no seasonal effect. Knowledge of the seasonal associations with certain types of colic is consistent with an aetiological role for managemental change and periods of intense management such as prolonged stabling. Further studies are required to identify the determinants of the observed seasonality. This type of regression model has applications beyond the study of equine colic and it may be useful in the investigation of seasonal patterns in other, relatively rare, conditions in all species.

Methods
Colic data
All cases of colic admitted to the Philip Leverhulme Equine Hospital, University of Liverpool between 1st January 1995 and 31st December 2004 were reviewed retrospectively. The numbers of colic cases occurring in each of the 120 months under investigation were recorded and aggregated as counts per month in the groups defined in Table 1.

Exploratory data analysis
For each colic type, the effect of increasing yearly case numbers was removed (de-trended) by subtracting an annual average to create a residual [45]. A box plot of these residuals by month was then generated. This allowed us to search for preliminary descriptive evidence of seasonality without the data being complicated by the presence of an annual trend (defined as an increase/decrease in the number of colic cases admitted over time for each 12 month period).

Regression model
Our chosen model for incorporating latent correlation was similar to the generalised linear model with Poisson response and logarithmic link function, which is commonly used to model independent count data [17] but has an added level of complexity in that dependence between observations in the series is explicitly incorporated via a latent variable. This is an example of a Bayesian Hierarchical model (see, for example [46]). This approach allows us, having accounted for seasonality and trend, to determine whether any correlation between observations at successive time points, over a shorter scale than that indicated by cycles or trend, remains. Having accounted for these factors, we can then determine whether observations in two successive months are more (or less) similar than we might expect by chance.

The most general model incorporating cycles at both 6 and 12-month frequencies is as follows: Let N_t be the number of admissions in month t, and t indicate annual trend. The harmonic components at 6- and 12-month frequencies are used to represent the seasonal components, and α represent the dependence between latent variables in successive months. From an inferential point of view our interest concerns whether the 95% credible interval for α contains 0, which equates to no evidence of latent serial correlation.

$$N_t \sim \text{Poisson}(\mu_t)$$

$$\log(\mu_t) = \beta_0 + \beta_1 \sin\left(\frac{2\pi t}{12}\right) + \beta_2 \cos\left(\frac{2\pi t}{12}\right) + \beta_3 \sin\left(\frac{2\pi t}{6}\right) + \beta_4 \cos\left(\frac{2\pi t}{6}\right) + \beta_5 t + e_t$$

$$e_t \sim N(\mu_t, \sigma_\tau^2$$

$$\mu_t = \alpha + e_{t-1}$$

The model detailed above treats the unobserved variables as a latent, temporally varying process (here autoregressive of order 1 so that the latent variable in the current month is allowed to depend via a Normal distribution on the equivalent latent variable in the previous month; in principle in its most general form the structure could be of order q where $q \geq 1$).

The model was fitted within a Bayesian framework as described in [47] using Markov Chain Monte Carlo (MCMC) methods within the software package WinBugs [48] in combination with the R library "R2WinBUGS" [49]. A 'burn-in' of 20,000 iterations was used and a sample of 100,000 realisations from the posterior distribution for each parameter was produced. The output chain for each parameter was thinned to every 10th observation to reduce correlation between samples in the posterior distribution. Vague prior distributions were adopted for each of the β parameters (reflecting a lack of prior belief concerning parameter values), and the prior distribution for α was Uniform on [-1, 1] (although we believe *a priori* that any latent dependence in models for data of this kind is likely to be positive, bounding the parameter in this way allows us to examine the evidence in favour of serial dependence being present via a 95% credible interval for α which excludes 0). Markov chain convergence was assessed by comparing two chains from divergent starting values and comparing traces, and in addition examining the $\hat{R}$ statistic provided by WinBUGS which is the "potential scale reduction factor" and for a convergent chain approaches the value 1. Final inference was therefore based upon 16,000 draws (from the two chains judged to be in equilibrium) from the posterior distribution for each parameter. In the case where the 95% credible interval for the sine component at a given frequency excluded 0 but the cosine component did not, or vice versa, both terms were retained due to the fact that the sine and cosine terms together uniquely determine the location and scale of the cycle. Analogous models were compared using the Deviance Information Criterion (DIC) [50] which we present in Tables 3 and 4. The DIC penalises models which are over-complex so that a "good" model represents a balance between plausible explanation of the data and model parsimony; in broad terms, the smaller the DIC, the better the model. In each case, we select as optimal the model which both carries the smallest DIC value and is the simplest.

Within each selected "best" model for each colic, the posterior mean, posterior standard deviation and 95% credible interval for each parameter are given in Table 2. We only report in full parameter estimates for the model with serial dependence and without trend; as we have discussed the estimates of seasonal components in the models with trend but no serial dependence are identical save for sampling variation induced by the MCMC algorithm. Within a Bayesian framework we cannot make statements about the "statistical significance" of parameter estimates as the common concept of a *p*-value and associated concepts of statistical significance are founded upon frequentist, rather than Bayesian, arguments. Instead, as an initial screen, we judged those parameters for which the standard deviation was smaller than half of the mean to have a marked effect on the outcome of interest (mean number of colic cases observed). We also reported the posterior 95% credible interval: an equivalent approach in this case involves identifying parameters for which this interval does not contain the value 0.

For each colic type, an estimate of the model's seasonal component was calculated by exponentiating from the chosen "best" model the sum of the posterior means of the seasonal components on the log scale, thus representing a multiplicative term in a model for the original observations. This enabled us to produce a graphical representation of the cyclical patterns in each group in relation to months of the year (Figure 2).

Authors' contributions

DA designed the study, acquired the data and drafted the manuscript. HC participated in design of the study, performed the statistical modelling and drafted the manuscript. GP conceived the study, participated in its design and critically reviewed the manuscript. CP compiled the data, participated in the design of the study and critically reviewed the manuscript. All authors have read and approved the final manuscript.

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EPIDEMIOLOGY OF COLIC PROJECT

THE UNIVERSITY of LIVERPOOL

CASE QUESTIONNAIRE

CLINIC NO. ☐ UK ☐ USA ☐ IRELAND STUDY NUMBER

☐ EFE

☐ EOSINOPHILIC ENTERITIS/COLITIS

LESION TYPE:

SURGERY DATE DAY MONTH YEAR

CASE HORSE / PONY NAME

OWNER / CARER NAME

STREET / ROAD

VILLAGE

TOWN / CITY

COUNTY

POSTCODE

TELEPHONE NUMBERS

PREMISES ADDRESS

PREMISES POSTCODE

QUESTIONNAIRE DATE / /

QUESTIONNAIRE TIME
Use 24 hour clock GMT DURATION mins

DATE OF DEATH (if applicable) / / *Enter 00/00/0000 if still alive*

14838

EPIDEMIOLOGY OF COLIC PROJECT

THE UNIVERSITY of LIVERPOOL

HBLB

CONTROL QUESTIONNAIRE

CLINIC NO. ☐☐ ☐ UK ☐ USA ☐ IRELAND STUDY NUMBER ☐☐☐☐

☐ UNMATCHED MATCHED TO: MONTH ☐☐ YEAR ☐☐☐☐

☐ MATCHED MATCHED TO CASE NO: ☐☐☐

CONTOL HORSE / PONY NAME

OWNER / CARER NAME

STREET / ROAD

VILLAGE

TOWN / CITY

COUNTY

POSTCODE

TELEPHONE NUMBERS

PREMISES ADDRESS

PREMISES POSTCODE

QUESTIONNAIRE DATE ☐☐ / ☐☐ / ☐☐☐☐

QUESTIONNAIRE TIME ☐☐ : ☐☐ GMT DURATION ☐☐ mins

Use 24 hour clock

DAYS BETWEEN QUESTIONNAIRE ADMINISTRATION AND TIME OF INTEREST ☐☐☐

23027

SECTION A GENERAL HORSE AND MANAGEMENT DETAILS

A1. Are you the owner / carer / trainer of (horses' name)?

Owner	☐ YES	☐ NO
Primary carer	☐ YES	☐ NO
Trainer	☐ YES	☐ NO

A2. What is (horse's name) age, breed and sex?

Breed: ______ CODE ☐☐

Age: ☐☐.☐ years

Sex: ☐ gelding ☐ mare / filly ☐ colt / stallion

A3. What is (horse's name) height and weight?

Height ☐☐.☐ hh Approximate / actual

Weight ☐☐☐☐ KG Approximate / actual

A4. What is (horse's name) principally used as?
N.B. state competition level / if actively breeding or not

Use: ______ CODE ☐☐

Competition type: ______ CODE ☐☐

SECTION B MEDICAL DETAILS

B1. Has (horse's name) suffered from any medical problems (including injury / illness / surgery) within the last 12 months requiring veterinary advice or attention?

☐ YES ☐ NO ☐ DON'T KNOW

Orthopaedic / lameness	☐ YES	☐ NO	☐ DON'T KNOW
Respiratory	☐ YES	☐ NO	☐ DON'T KNOW
Dental / gastrointestinal	☐ YES	☐ NO	☐ DON'T KNOW
Weight loss	☐ YES	☐ NO	☐ DON'T KNOW
Reproductive / urinary	☐ YES	☐ NO	☐ DON'T KNOW
Ears / eyes	☐ YES	☐ NO	☐ DON'T KNOW
Skin / hair	☐ YES	☐ NO	☐ DON'T KNOW
Neurological	☐ YES	☐ NO	☐ DON'T KNOW
Lethargy / fever	☐ YES	☐ NO	☐ DON'T KNOW
Other:	☐ YES	☐ NO	☐ DON'T KNOW

B2. Has (horse's name) received any medication in the last 12 months (excluding wormers or vaccinations)?

☐ YES ☐ NO ☐ DON'T KNOW

MEDICATION BRAND / TYPE	DURATION ADMINISTERED	WHEN LAST GIVEN

MEDICATION TYPE: **CODE** ☐☐

CURRENTLY RECEIVING MEDICATION? ☐ YES ☐ NO ☐ DON'TKNOW

B3. Has (horse's name) ever had abdominal surgery? ☐ YES ☐ NO ☐ DON'T KNOW

Duration since abdominal surgery ☐☐☐☐ months

Was this surgery to correct a problem related to colic? ☐ YES ☐ NO ☐ DON'T KNOW

Details of surgery if known:

CODE: ☐☐

B4. To your knowledge has (horse's name) ever received any NSAID'S such as phenylbutazone (bute) or flunixin (finadyne / banamine)?

☐ YES ☐ NO ☐ DON'T KNOW

When was this last administered? **CODE** ☐☐

Duration of NSAID's: ☐☐☐ days

Type of NSAID's:

B5. Has (horse's name) suffered any episodes of colic previously)?

☐ YES ☐ NO ☐ DON'T KNOW

How long ago did the last episode occur? ☐☐☐ **months**

How many episodes have occurred within the last 12 months? ☐☐

No of episodes requiring veterinary intervention: ☐

No. of episodes that resolved without veterinary attention ☐

Type of colic:
- ☐ Not applicable
- ☐ Didn't need medical treatment (vet called / not called)
- ☐ Resolved following medical treatment
- ☐ Combination of treatment and no treatment (multiple episodes)
- ☐ Required surgical intervention (with or without previous medical treatment)

Do you know what may have caused these episodes? If so specify:

Have the episodes changed in frequency over the past 12 months?

☐ Not applicable ☐ More frequent ☐ Less frequent ☐ Same frequency

Have the episodes changed in severity over the past 12 months ?

☐ Not applicable ☐ Increased severity ☐ Reduced severity ☐ About the same severity

SECTION C PREMISES

C1. What type of premises is (horse's name) currently kept at?

- ☐ Professional working / competition yard
- ☐ Livery yard
- ☐ Private yard
- ☐ Field / pasture only
- ☐ Stud farm
- ☐ Riding school / equestrian college
- ☐ Other

C2. How many horses / ponies are on the premises in total? ☐☐☐

C3. How many people feed (horse's name) on a daily basis? ☐☐

C4. Who is the principle carer of (horse's name)?

CODE ☐☐

C5. Has (horse's name) changed premises (i.e. involving an overnight stay) within the last 12 months?

☐ YES ☐ NO ☐ DON'T KNOW

How many premises in total has (horse's name) been on in the last 12 months? ☐☐

How many times has a change of premises occurred? ☐☐

When did the last change in premises take place? ☐☐☐.☐ **weeks ago**

SECTION D HOUSING AND GRAZING

D1. What is (horse's name) current management ?

- ☐ Stabled all the time with no exercise & no turnout
- ☐ Stabled all the time apart from when exercised - no turnout
- ☐ Stabled at night with <2hrs turnout every day
- ☐ Stabled at night with 2 or >2hrs turnout every day
- ☐ Stabled in day, out overnight
- ☐ Turned out all the time
- ☐ Stabled with irregular turnout e.g. weather dependent / every other day
- ☐ Other (specify)

D2. Has this routine changed within the last 4 weeks? ☐ YES ☐ NO ☐ DON'T KNOW

If YES,
how long ago did this happen? ☐☐ days ago

What type of change was this? ________ CODE ☐☐

D3. What type of stable is (horse's name) kept in?

- ☐ Not stabled
- ☐ Indoor american barn
- ☐ Traditional open stable block
- ☐ Single stable
- ☐ Communal barn / stable
- ☐ Converted building
- ☐ Other (specify)

D4. What type of bedding is (horse's name) currently on?

- ☐ not applicable, not stabled
- ☐ straw - unknown type
- ☐ straw - oat
- ☐ straw - barley
- ☐ straw - wheat
- ☐ woodshavings / chips
- ☐ cardboard / paper
- ☐ rubber matting only
- ☐ hemp
- ☐ flax
- ☐ Other (specify)

D5. Has the type or batch of bedding changed within the last 4 weeks?

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

If YES, when did this change occur? ☐☐ days ago

What type of change was this?

☐ different type of bedding ☐ different batch of bedding (but same type) ☐ other

If the type of bedding has changed, what was used previously? ______ CODE ☐☐

D6. Has (horse's name) ever been known to eat bedding?

- ☐ No
- ☐ Yes, different type to bedding currently on
- ☐ Yes, type of bedding currently on
- ☐ Don't know
- ☐ Not applicable

D7. What is (horse's name) water source in the stable?

- ☐ manually filled container / bucket
- ☐ automatic drinker
- ☐ both
- ☐ other
- ☐ not applicable

PASTURE

D8. What sort of area is (horse's name) turned out onto?

- ☐ not relevant, not turned out
- ☐ grass field
- ☐ sand / dirt arena or school
- ☐ yard
- ☐ circular pen in field
- ☐ other (state:)
- ☐ combination of field and arena / yard

D9. What type of pasture is (horse's name) turned out onto?

- ☐ not applicable
- ☐ reseeded, new pasture
- ☐ mature pasture, not reseeded
- ☐ mature pasture, part reseeded
- ☐ don't know

D10. How many hours a day on average has (horse's name) been turned out at pasture over the last 4 weeks?

No of hours per week: [ ][ ][ ].[ ]

D11. Has (horse's name) moved onto a different pasture within the last 4 weeks?

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

Number of pastures grazed in last 4 weeks: [ ][ ]

D12. How long has (horse's name) been on the current pasture?

[ ][ ][ ].[ ] months

D13. How big is the current pasture? [ ][ ].[ ][ ] acres

D14. In total, how many horses / ponies currently share grazing or have access to this pasture? [ ][ ]

D15. Is (horse's name) most frequently turned out on his / her own?

☐ YES, turned out on own ☐ NO, turned out with others ☐ DON'T KNOW ☐ N/A

D16. Have any other domestic species (defined as non wild animals) grazed or had access to the current pasture(s) (those grazed in the last 4 weeks) in the last 12 months?
this includes: donkeys, poultry, sheep, cattle, pigs, llamas / alpacas or other farmed / pet animals

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

species of animal(s) CODE [ ][ ]

duration of time since last on the pasture: CODE [ ]

D17. Do any of the following apply to the pastures (horse's name) has been on in the last 4 weeks?

Do other domestic species share pasture all the time? ☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

CODE [ ][ ]

Are other domestic species in adjacent fields? ☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

CODE [ ][ ]

Are other domestic species rotated onto the pastures? ☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

CODE [ ][ ]

Is manure used to fertilise the pasture? ☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

D18. Has the pasture been treated in the last 4 weeks? ☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

when was this done? [ ] date / days ago

what was performed? [ ] **CODE** [ ]

fertiliser type (if used) [ ] **CODE** [ ]

D19. What is (horse's name) water source at pasture?

Trough / bucket filled manually	YES	NO
Automatic filling tank	YES	NO
Natural running water e.g. stream	YES	NO
Stagnant water source	YES	NO

CODE [ ][ ]

D20. Have any species of wildlife been seen regularly (i.e. at least once a week) on the current premises ?

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

SPECIES 1 [ ] **CODE** [ ][ ]

SPECIES 2 [ ] **CODE** [ ][ ]

SPECIES 3 [ ] **CODE** [ ][ ]

D21. Do any of the pastures grazed in the last 12 months have a problem with weeds or plants known to be harmful to horses (e.g. ragwort)?

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

Type of plant(s) [ ] **CODE** [ ]

Pasture treatment for these ☐ none ☐ physically removed ☐ weedkillers ☐ physically removed & weedkillers

D22. Are there any mining works / industrial plants on or adjacent to any pastures (horse's name) has grazed in the last 12 months?

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

DETAILS:

D23. Are you aware of any specific mineral deficiencies in the local soil that (horse's name) has grazed on in the last 12 months?

☐ **no, soil tested** ☐ **yes, soil tested** ☐ **local area deficient, soil not tested** ☐ **no idea**

Details including any supplementation given:

SECTION E NUTRITION

E1. How many people (maximum) currently prepare (horse's name) feed on a daily basis? ☐☐ people

E2. Do the same people feed (horse's name) every day?

☐ YES ☐ NO ☐ DON'T KNOW ☐ N/A

E3. Currently, how many times a day is (horse's name) fed?

FORAGE - Hay / haylage

- ☐ none
- ☐ once daily
- ☐ twice daily
- ☐ three times daily
- ☐ four times daily
- ☐ fed ad lib, always forage avaliable
- ☐ fed every other day or less
- ☐ Other (state)

BUCKET FEED - straights/concentrate / chaff

- ☐ none
- ☐ once daily
- ☐ twice daily
- ☐ three times daily
- ☐ four times daily
- ☐ more than 4 times daily
- ☐ fed irregularly every other day or less
- ☐ Other (state)

E4. What time(s) of day are these fed? (use 24hour clock)

Feed 1	☐☐ : ☐☐ hrs	CODE ☐	Feed 4	☐☐ : ☐☐ hrs CODE ☐
Feed 2	☐☐ : ☐☐ hrs	CODE ☐	Feed 5	☐☐ : ☐☐ hrs CODE ☐
Feed 3	☐☐ : ☐☐ hrs	CODE ☐	Feed 6	☐☐ : ☐☐ hrs CODE ☐

E5. Is (horse's name) fed at the same time as the other horses in that group / part of the yard?

- ☐ not applicable
- ☐ same frequency & time
- ☐ same frequency, different times
- ☐ more frequently
- ☐ less frequently
- ☐ don't know

E6&7. Is (horse's name) fed at the same time i.e. to within an hour:

Monday - Friday	Saturdays & Sundays
☐ Never varies	☐ Never varies
☐ occasionally varies	☐ occasionally varies
☐ regularly varies	☐ regularly varies
☐ don't know	☐ don't know
☐ N/A	☐ N/A

E8. What type of roughage is (horse's name) currently fed?

- ☐ none - grass only
- ☐ silage
- ☐ dry hay
- ☐ dry hay & haylage
- ☐ soaked hay
- ☐ soaked hay & haylage
- ☐ haylage
- ☐ other (state)
- ☐ horsehage

If fed on HAY is this: ☐ Bought in ☐ made on farm ☐ both ☐ don't know

Type of hay: ______ CODE ☐☐

E9. How much roughage is (horse's name) currently fed per day? ______

ACTUAL WEIGHT ☐☐.☐☐ **Kg** **ESTIMATED WEIGHT** ☐☐.☐☐ **Kg**

E10. How is this fed to (horse's name)?

☐ loose off floor / ground ☐ hayrack ☐ haynet ☐ other container ☐ combination floor & haynet / hayrack

E11. Has the FREQUENCY of roughage feeding changed within the last 4 weeks? ☐ **NO** ☐ **YES** ☐ **DON'T KNOW** ☐ **N/A**

If YES, type of change:

- ☐ increased frequency
- ☐ decreased frequency
- ☐ varies on a regular basis
- ☐ altered frequency for a few days only

When did this change start? ☐☐ days ago

E12. Has the QUANTITY of roughage fed changed within the last 4 weeks? ☐ **NO** ☐ **YES** ☐ **DON'T KNOW** ☐ **N/A**

If YES, type of change:

- ☐ gradual increase (over several weeks)
- ☐ sudden increase (over a few days)
- ☐ gradual decrease(over several weeks)
- ☐ sudden decrease (over a few days)
- ☐ varies on a regular basis

When did this change start? ☐☐ days ago

E13. Has the TYPE of roughage fed changed within the last 4 weeks? ☐ **NO** ☐ **YES** ☐ **DON'T KNOW** ☐ **N/A**

If YES, type of change: ______ **CODE** ☐ Days since change: ☐☐

E14. Has the BATCH of roughage changed in the last 4 weeks?

☐ **NO** ☐ **YES** ☐ **DON'T KNOW** ☐ **N/A**

If YES, days since change: ☐☐

E15. Could you list the types and quantities of concentrates / chaff that (horse's name) is currently receiving? *(include type of processing e.g. flaked, molassed / unmolassed)*

TYPE & BRAND NAME	QUANTITY PER FEED / DAY (specify)

FEED WEIGHTS: ☐ Exact ☐ estimated ☐ not applicable ☐ impossible to estimate

PROPRIETARY CONCENTRATE DIET ☐ NO ☐ YES ☐ DON'T KNOW

WEIGHT ☐☐.☐☐ Kg / day **BRAND NAME (CODE)** ☐☐☐ % PROTEIN ☐☐.☐ % FAT ☐☐.☐

LOCAL FEED MILL CONCENTRATE DIET ☐ NO ☐ YES ☐ DON'T KNOW

WEIGHT ☐☐.☐☐ Kg / day DESCRIPTION (including FIRM NAME & protein / fat if known)

GRAIN ☐ NO ☐ YES ☐ DON'T KNOW

WEIGHT ☐☐.☐☐ Kg / day TYPE OF GRAIN FED **CODE** ☐☐

SUGAR BEET PULP ☐ NO ☐ YES ☐ DON'T KNOW

DRY WEIGHT ☐☐.☐☐ Kg / day ☐ flaked ☐ pelleted ☐ don't know ☐ molassed ☐ unmolassed ☐ don't know

FORAGE / OTHER FIBRE SOURCE ☐ NO ☐ YES ☐ DON'T KNOW

TOTAL WEIGHT ☐☐.☐☐ Kg / day TYPE **CODE:** ☐☐

E16. **Has the FREQUENCY of concentrate feeding changed within the last 4 weeks?**

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

If YES, type of change:
- ☐ increased frequency
- ☐ decreased frequency
- ☐ varies on a regular basis
- ☐ altered frequency for a few days only

days since change: ☐☐

E17. **Has the QUANTITY of concentrate fed changed within the last 4 weeks?**

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

If YES, type of change:
- ☐ gradual increase (over several weeks)
- ☐ sudden increase (over a few days)
- ☐ gradual decrease(over several weeks)
- ☐ sudden decrease (over a few days)
- ☐ varies on a regular basis

days since change ☐☐

E18. **Has the TYPE of concentrate (including brand / manufacturer) changed in the last 4 weeks?**

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

If yes describe change ______ **CODE** ☐☐

E19. **Has the batch of concentrate feed changed within the last 4 weeks?**

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

How often do you buy / have a delivery of concentrate / chaff feed ? Every ☐☐ days

When did you last open a new bag of feed that (horse's name) is currently receiving? ☐☐ days ago

23027

DIETARY SUPPLEMENTS

E20. Does (horse's name) receive any dietary supplements such as vegetables or fruit, herbal remedies, pro-biotics, oil, mineral / salt licks?

☐ NO ☐ YES ☐ DON'T KNOW

Type of supplement, brand name and quantity:

VEGETABLES / FRUIT	☐ NO	☐ YES	☐ DON'T KNOW
GARLIC / OTHER HERBAL	☐ NO	☐ YES	☐ DON'T KNOW
ORTHOPAEDIC SUPPLEMENT	☐ NO	☐ YES	☐ DON'T KNOW
PROBIOTICS	☐ NO	☐ YES	☐ DON'T KNOW
SALT / MINERAL LICK OR SUPPLEMENT	☐ NO	☐ YES	☐ DON'T KNOW
OIL	☐ NO	☐ YES	☐ DON'T KNOW

OTHER CODE ☐☐

E21. Have any of these been added in the last 4 weeks?

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

If YES:

Which one? ________ **CODE** ☐☐

How many days ago was this added? ☐☐ days

SECTION F EXERCISE AND TRANSPORT

F1. How many days per week is (horse's name) currently being exercised? ☐ days / week

F2. Currently, how many hours exercise (including horse walker) is (horse's name) doing per week?

☐☐.☐ hours / week

F3. Have any recent changes in exercise intensity or duration taken place within the last 4 weeks?

☐ NO ☐ YES - gradual ☐ YES - sudden ☐ DON'TKNOW

If YES: **Type of exercise change**

☐ increased duration ☐ decreased intensity

☐ increased intensity ☐ decreased intensity & duration

☐ increased duration & intensity ☐ other

☐ decreased duration

Reason: **CODE** ☐☐

F4. What sort of exercise is performed most of the time?

CODE ☐☐

F5. Where does exercise normally take place?

CODE ☐☐

F6. Has (horse's name) been transported within the last 4 weeks?

☐ NO ☐ YES ☐ DON'T KNOW

If YES: **Number of journeys in last 4 weeks (there & back = 2):** ☐☐

Total duration of transport: ☐☐.☐ hrs

Days since last transported: ☐☐ days

23027

SECTION G BEHAVIOUR

GENERAL BEHAVIOUR

G1. Is (horse's name) easily frightened (e.g flapping bag)? ☐ NO ☐ YES ☐ DON'T KNOW

G2. If (horse's name) is startled, how quickly does he / she settle down?

- ☐ very quickly, then continues to behave as normal
- ☐ will settle down after a few minutes, then behaves as normal
- ☐ remaines unsettled for longer than a few minutes

G3. How does (horse's name) respond to an unknown object e.g. football?

- ☐ very interested, becomes excited (will snort, defacate or vocalise)
- ☐ interested but soon ignores it
- ☐ not bothered, shows little interest

G4. Does (horse's name) ever sweat up when excited (as opposed to after travelling / exercise)?

- ☐ very easily & does this every time
- ☐ occasionally will sweat up when excited
- ☐ never sweats up when excited

G5. Does (horse's name) ever tremble or shake when frightened / startled?

☐ NO ☐ YES ☐ DON'T KNOW

G6. How does (horse's name) react to what is going on around in either the stable (stall) or field?

- ☐ very curious, will go and investigate or become very excited
- ☐ curious, will watch but doesn't investigate or become excited
- ☐ not interested, continues grazing or resting

G7. How does (horse's name) react to meeting other horses? (e.g. on a hack / at competitions)

- ☐ very excited, will sweat up, defacate or snort
- ☐ shows interest but does not become overly excited
- ☐ not bothered, remains calm

BEHAVIOUR AND STABLING

G8. Does (horse's name) show signs of restlessness when stabled (stalled) or would you describe he / she as being settled?

☐ YES, is not settled ☐ NO, is settled ☐ don't know ☐ Not applicable, never stabled

G9. Does (horse's name) become distressed when left alone in the stable / stall?

☐ YES, becomes distressed ☐ NO, not bothered ☐ don't know ☐ Not applicable, never stabled on own

G10. How does (horse's name) react just before being fed?

- ☐ becomes very agitated (paces, bangs at door)
- ☐ shows interest, looks over door but doesn't become overly excited
- ☐ shows little or no interest

G11. How quickly does (horse's name) eat concentrate / bucket feeds?

- ☐ very quickly - will bolt food
- ☐ eats all feed immediately at normal speed
- ☐ eats all the feed but not all at once
- ☐ does not eat all concentrate feed, picks at feed

G12. How quickly does (horse's name) eat forage?

- ☐ eats all forage quickly without stopping for long periods
- ☐ eats all forage but not at once, will go back to it
- ☐ doesn't eat all forage, tends to pick at feed
- ☐ don't know

G13. If (horse's name) is stressed (e.g. move to new premises or following transport / competition) do you see any change in feeding patterns?

- ☐ YES, will completely go off one or more feeds
- ☐ YES, eats some of one or more feeds
- ☐ NO, eats as normal

G14. Is (horse's name) fed regularly with other horses sharing the same field / yard?

☐ NO ☐ YES ☐ DON'T KNOW

If YES, is (horse's name) agressive towards other horses at these times? ☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

G15. Is (horse's name) aggressive towards humans during feeding? ☐ NO ☐ YES ☐ DON'T KNOW

G16.Can (horse's name) see other horses from his / her stable (stall)?

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

Has this changed within the last 4 weeks?

☐ YES, can now see others when previously couldn't ☐ YES, cannot see others, could previously ☐ No change

G17. Can (horse's name) touch other horses whilst in the stable / stall?

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

Has this changed within the last 4 weeks?

☐ YES, can now touch others when previously couldn't ☐ YES, cannot touch others, could previously ☐ No change

G18. Does (horse's name) become irritated when handled?

- ☐ YES - Regularly, irritated by one or more type of handling
- ☐ YES - Occasionally or only in response to a specific type situtation e,g, girth tightening
- ☐ NO - Never

G19. Is (horse's name) able to have direct physical contact with another horse / pony on a regular basis (e.g. turned out together or able to groom each other over a fence)?

- ☐ NO / RARE physical contact with other horses / ponies
- ☐ OCCASIONAL contact (not every day)
- ☐ REGULAR physical contact every day

G20. If stabled (stalled) what is the main source of light in the stable (stall) in the middle of the day?

☐ natural daylight only ☐ daylight and artificial ighting ☐ artificial lighting only

Is the stable lit by artificial lighting at night?

☐ YES, lights on at night most / all nights ☐ Occasionally left on overnight ☐ NO, always switched off at night

STEREOTYPIC BEHAVIOUR

G21. Does (horse's name) exhibit any stereotypic behaviour (often referred to as vices)?

☐ NO ☐ YES ☐ DON'T KNOW

IF NO GO TO SECTION H

CRIB-BITING / WINDSUCKING	☐ YES	☐ NO
WOODCHEWING	☐ YES	☐ NO
WEAVING	☐ YES	☐ NO
BOX WALKING	☐ YES	☐ NO
OTHER LOCOMOTOR (state)	☐ YES	☐ NO
OTHER ORAL (state)	☐ YES	☐ NO

G22. When is this behaviour seen / are these behaviours seen ?

- ☐ Only when stabled
- ☐ Only when turned out
- ☐ Both stabled and when turned out
- ☐ Other (state)

G23. How often is this behaviour seen and how would you describe it in terms of severity?

Severity of behaviour

- ☐ Mild
- ☐ Moderate
- ☐ Severe

Frequency of behaviour

- ☐ seen every day for prolonged periods
- ☐ seen every day but for short periods of time
- ☐ seen at least once a week, not every day
- ☐ seen on rare / specific occasions
- ☐ not currently seen e.g. wearing collar, kept turned out

G24. In relation to being fed when do you see this behaviour?

- ☐ seen before feeding but not during / after
- ☐ not seen before but observed during / after feeding
- ☐ behaviour observed before during and after feeding
- ☐ not seen before, during or after feeding

G25. Does this behaviour / do these behaviours change at feeding time?

- ☐ YES, increased - exhibited more often / for longer periods
- ☐ YES, decreased - exhibited less often / for shorter time periods
- ☐ NO change - behaviour remains at same intensity / frequency

G26. Do you take any measures to try to stop these behaviours from occurring?

☐ NO ☐ YES ☐ DON'T KNOW ☐ N/A

If YES, what measures are taken?

CODE ☐☐

Do these measures work?

CODE ☐☐

G27. Do you know if this behaviour / these behaviours are seen in any of (horse's name's) relatives?

Sire:

Dam:

Siblings:

Offspring:

- ☐ YES, known to be seen in one or more relatives
- ☐ NO, not seen in relatives known to owner / carer
- ☐ DON'T KNOW

SECTION H - PREVENTATIVE MEDICINE

DENTISTRY

H1. How often does (horse's name) have his / her teeth checked?

- ☐ not done
- ☐ more than every 6 months
- ☐ every 12 months
- ☐ every 1-2 years
- ☐ every 7-12 months
- ☐ infrequent / only done if required
- ☐ every 6 months

H2. When were they last examined? CODE ☐☐.☐ months

H3. Who is this done by?

☐ Veterinary surgeon ☐ equine dentist ☐ other (e.g. owner) ☐ both vet & dentist

VACCINATION

H4. Is horse's name vaccinated regularly based on your vet's recommendations? ☐ NO ☐ YES ☐ DON'T KNOW

H5. When was (horse's name) last vaccinated? ☐☐.☐ months ago

H6. Do you know what vaccine was administered? CODE ☐☐

ANTHELMINTICS & OTHER WORM PROPHYLAXIS

H7. How often is (horse's name) wormed?

- ☐ Never / rarely
- ☐ wormed only if FEC / ELISA high
- ☐ Every 6-13 weeks
- ☐ daily wormer
- ☐ 14 weeks - 6 monthly
- ☐ monthly wormer
- ☐ less than 6 monthly
- ☐ other (state)

H8 & 9. When was (horse's name) last wormed and what product was used?

☐☐.☐ weeks ago

CODE ☐☐

H10 & 11. When was (horse's name) last wormed before that and what product was used?

☐☐.☐ weeks ago

CODE ☐☐

H12. Has (horse's name) received a double dose of pyrantel (Strongid P / Pyratape P / Equitape) or a dose of praziquantel (Equimax) to treat specifically for tapeworms in the last 12 months?

☐ NO ☐ YES ☐ DON'T KNOW

H13. Are all the other horses sharing the pasture wormed?

☐ NO ☐ YES ☐ DON'T KNOW ☐ NOT APPLICABLE

H14. Are all the horses wormed at the same time?

☐ NO ☐ YES ☐ DON'T KNOW ☐ NOT APPLICABLE

H15. Is (horse's name) wormed:

☐ more often than other horses
☐ less often than other horses
☐ about the same
☐ don't know
☐ not applicable

H16. Has (horse's name) shared or grazed on a field that any new horses have been turned out onto in the last 4 weeks?

☐ NO ☐ YES ☐ DON'T KNOW ☐ NOT APPLICABLE

H17. What sort of pasture management is undertaken to reduce any parasite burden?
Tick the options that apply:

removal of droppings (specify if hand / machine)
rotation with other species
harrowing
rotation of fields
other
none taken

CODE ☐☐

H18. Has (horse's name) had faecal analysis and / or blood samples to test for parasite burden performed within the last 12 months?

☐ NO ☐ YES ☐ DON'T KNOW

WEC result (epg): ☐☐☐☐

Thank you very much for your participation with this project. The results will be forwarded to you at the end of this study.

COMMENTS / NOTES TO BE ADDED TO DATABASE: