Tutorial Article

An evidence-based approach to equine parasite control: It ain't the 60s anymore

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Summary

Most veterinarians continue to recommend anthelmintic treatment programmes for horses that derive from knowledge and concepts more than 40 years old. However, much has changed since these recommendations were first introduced and current approaches routinely fail to provide optimal or even adequate levels of parasite control. There are many reasons for this. Recent studies demonstrate that anthelmintic resistance in equine parasites is highly prevalent and multiple-drug resistance is common in some countries, but few veterinarians take this into account when making treatment decisions or when recommending rotation of anthelmintics. Furthermore, the current approach of treating all horses at frequent intervals was designed specifically to control the highly pathogenic large strongyle, *Strongylus vulgaris*. But this parasite is now quite uncommon in managed horses in most of the world. Presently, the cyathostomins (small strongyles) are the principal parasitic pathogens of mature horses. The biology and pathogenesis of cyathostomins and *S. vulgaris* are very different and therefore require an entirely different approach. Furthermore, it is known that parasites are highly over-dispersed in hosts, such that a small percentage of hosts harbour most of the parasites. The common practices of recommending the same treatment programme for all horses despite great differences in parasite burdens, recommending prophylactic treatment of all horses without indication of parasitic disease or knowing what species of parasites are infecting the horses, recommending use of drugs without knowledge of their efficacy and failing to perform diagnostic (faecal egg count) surveillance for estimating parasite burdens and determining treatment efficacy, are all incompatible with current standards of veterinary practice. Consequently, it is necessary that attitudes and approaches to parasite control in horses undergo a complete overhaul. This is best achieved by following an evidence-based approach that takes into account all of these issues and is based on science, not tradition.

Introduction

Parasites have been recognised as a cause of clinical disease in horses since the Roman Empire, and for centuries full control and treatment could not be achieved. The introduction of benzimidazole anthelmintics in the 1960s led to a revolution in equine parasite control. With these highly efficacious, safe and broad-spectrum drugs came new recommendations; horse owners were advised to deworm all horses every 8 weeks (Drudge and Lyons 1966). These recommendations were widely adopted, resulting in a dramatic reduction in morbidity and mortality from parasitic disease. For the first time ever it was possible to control equine parasites, leading to significant improvements in equine health and performance. By the 1970s and 80s new anthelmintic drug classes became available and rotation between drugs became a common practice. Unfortunately, parasitic nematodes have risen to the chemical challenge. Anthelmintic resistant cyathostomins (small strongyles) now are highly prevalent and even where drugs still are effective, the egg reappearance period (ERP) following treatment has become dramatically shorter (Tarigo-Martinie *et al*. 2001; Little *et al*. 2003; von Samson-Himmelstjerna *et al*. 2007; Lyons *et al*. 2008). Today, most horse owners continue to follow recommendations that are based on concepts and knowledge that are 40–50 years old and frequently use anthelmintics that have become largely ineffective due to the presence of drug-resistant parasites (Kaplan 2002; Kaplan *et al*. 2004). Therefore, it is imperative for veterinarians to become educated in the latest knowledge on parasite biology to modernise control practices and meet the new issues and challenges we now face.

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Evidence-based veterinary medicine (EBVM) is defined as the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients (Cockcroft and Holmes 2003; Holmes and Ramey 2007). In recent years, EBVM has gained increasing attention and recognition as a means to improve the quality of care in veterinary practice. Although many veterinarians are familiar with the term EBVM, most are still not familiar with many of the details regarding types and levels of evidence, nor how to evaluate the strength of different sources and types of evidence. Despite this, most veterinarians aspire to practice medicine at a high level of competence, and few will argue that the best available evidence should be used in making therapeutic decisions. Thus the practice of veterinary medicine evolves over time and the standard of care continues to improve. Almost nothing in equine veterinary medicine is done the same way it was done 40 years ago, and the equine patient is the beneficiary. However, the one area of veterinary practice that has failed to encompass this philosophy probably more than any other is parasite control. A recent article that evaluated equine parasitology from an evidence-based approach concluded that despite a large body of evidence, basic questions still have not been answered (Uhlinger 2007). Among other things, the author mentions that the role of cyathostomins as a cause of disease is not yet well illuminated and that a majority of horses are treated at fixed intervals throughout the year. Thus, equine veterinarians and their clients continue to follow a traditional approach to parasite control that is decades old, without questioning the biological logic or medical rationale of that approach.

As an example, if an equine veterinarian found a horse in a stable to be suffering from a bacterial infection, the veterinarian would perform a physical examination then would initiate a therapeutic plan based on that specific diagnosis and his/her clinical experience and knowledge of the recommendations of experts. The therapeutic plan might include use of an antibiotic, but because it is well known that unnecessary antibiotic treatment will promote drug resistance in bacteria, the veterinarian would never consider treating the remaining horses in the stable that all appeared clinically normal. However, that same veterinarian would probably not hesitate to treat every horse in the stable with an anthelmintic, even though not a single horse is showing any signs of parasitic disease. Furthermore, the veterinarian might very well choose an anthelmintic that is known from published research to have a high likelihood of failing due to the presence of drug-resistant worms. Why would a veterinarian make such a choice? It seems that an irrational fear of equine parasites has evolved over the years. Horse owners and veterinarians often similarly believe they must treat horses at frequent intervals to prevent parasitic disease. So the decision to treat is not based on any rational therapeutic consideration, but rather on fear of what might happen if they do not treat. Furthermore, horse owners and veterinarians ignore a large body of published literature on anthelmintic resistance by continuing to equate treatment with effective control.

A major goal of this article is to provide a framework by which equine veterinarians can think through the issues necessary to develop a sound medical approach to parasite control. Important questions that need to be addressed before appropriate treatment decisions can be made include: 1) Is there a clinical justification for treating this horse? 2) What parasite am I trying to eliminate? 3) What stages of that parasite are likely present? 4) Why did I pick this anthelmintic? 5) Will this drug kill the desired parasite(s) and stage(s)? 6) How confident am I that this drug will work as expected? 7) Are there better options - is this the best choice for this horse at this time? 8) Are there any adjunct management techniques that might help to achieve the ultimate goal of decreased transmission?

A shift in emphasis: the downfall of *Strongylus vulgaris* and the rise of cyathostomins

Prior to the introduction and strategic use of benzimidazole anthelmintics, it was estimated that 90% of colics were due to migrating arterial stages of the large strongyle parasite *Strongylus vulgaris* (Drudge and Lyons 1977). However, this figure has never been scientifically validated and it is likely that the true percentage was far lower. Several surveys at that time reported *S. vulgaris* to be 90–100% prevalent in horses (Slocombe and McCraw 1973; Tolliver *et al*. 1987; Lyons *et al*. 1990, 1992), so virtually all horses with colic would have been infected with *S. vulgaris*. But this does not necessarily mean that the parasite caused the disease in each case, as most horses without colic would also have been infected. Although experimental infections have shown that *S. vulgaris* is a parasite of high pathogenic potential (Duncan 1974; Duncan and Pirie 1975), we are not aware of any studies that have specifically evaluated the role of *S. vulgaris* in colic. Nevertheless, in the 1960s and 1970s *S. vulgaris* was recognised as an important cause of colic and was the primary target of parasite control programmes. A revolution in parasite control was introduced in the mid-60s in an approach that became known as the interval dose programme (Drudge and Lyons 1966). The basic framework of this approach was to prevent egg shedding of *S. vulgaris* by treating all horses at 2 month intervals year round. This control paradigm worked because *S. vulgaris* has a prepatent period of 6–7 months, but none of the anthelmintics available at that time had efficacy against the extraintestinal migrating or encysted stages. Since the anthelmintics could only eliminate the parasites once they entered the intestinal lumen, treatment every 8 weeks ensured that few *S. vulgaris* would mature to the adult egg laying stage before being eliminated by the next treatment. This approach became widely adopted and proved extremely successful in reducing morbidity and mortality due to S. *vulgaris* (Lyons *et al*. 1999). But by the

early 1980s it was recognised that cyathostomins frequently accounted for virtually 100% of the strongyle worm egg output of grazing horses (Herd *et al*. 1981). This major change in species prevalence has caused an important shift in the relative importance of these nematodes and cyathostomins are now recognised as the principal parasitic pathogen of horses (Love *et al*. 1999). Contributing to the pathogenic potential of cyathostomins is the problem of drug resistance, which is reaching alarming levels throughout much of the world. Disease symptoms in horses infected with cyathostomins range from a mild subclinical alteration in gastrointestinal function to a life-threatening disease known as larval cyathostominosis, characterised by severe weight loss, chronic diarrhoea and oedema (Love *et al*. 1999). Mucosal larval stages of cyathostomins induce an inflammatory enteropathy characterised by cellular infiltration and mucosal oedema with diffuse haemorrhagic foci resulting in a protein losing enteropathy (Love *et al*. 1999). The larval stages that emerge from the mucosa are the most pathogenic stage of the infection, whereas the adult worms have a much lower level of pathogenicity, which currently has not been well defined. In order to optimise horse health, it is necessary to prevent new infections. Although anthelmintic treatments are usually intended to kill adult worms, in actuality it is the prevention of egg shedding, thus preventing future infections, which has the greatest impact on horse health and overall worm control.

Anthelmintic resistance: a growing threat to parasite control and equine health

Modern control programmes have evolved to become almost completely dependent upon the intensive use of anthelmintics. Three major classes of anthelmintics are used to control nematode parasites in horses: benzimidazoles (fenbendazole, oxibendazole), tetrahydropyrimidines (pyrantel salts) and avermectin/milbemycins (ivermectin, moxidectin; also referred to as macrocyclic lactones). In addition, piperazine is sometimes used, although problems relating to spectrum, safety and efficacy have limited its use in recent decades. Currently, the only method available for determining if anthelmintics are effective on a farm is the faecal egg count reduction test (FECRT) in which faecal egg counts are measured both before and 14 days after treatment (see **Fig 1** for details). Failure of drugs to achieve high levels of egg reduction following treatment indicates the presence of anthelmintic resistant parasites on that farm.

Most equine anthelmintics only kill luminal stages of cyathostomins, but the majority of all the worms in a horse can exist as larval forms encysted within the intestinal mucosa. Following treatment with an effective anthelmintic, these mucosal larval forms appear to quickly repopulate the lumen, mature, mate, and begin to produce eggs. The amount of time required for eggs to reappear in the faeces following treatment is called the egg reappearance period (ERP) and this parameter differs for each drug. However, one cannot have egg reappearance if there never is egg disappearance. Thus, the existence of anthelmintic resistance on a farm will make the ERP parameter meaningless for a given drug.

In 2001–2002, a large multi-state study was performed to determine the prevalence of anthelmintic resistance on 44 horse farms in the southern USA (Kaplan *et al*. 2004). In this study the percentages of farms found to harbour resistant cyathostomins were: 97.7% for fenbendazole, 53.5% for oxibendazole, 40.5% for pyrantel pamoate and 0% for ivermectin. In terms of actual faecal egg count reductions (FECR), the mean percent reductions for all farms were 24.8% for fenbendazole, 73.8% for oxibendazole, 78.6% for pyrantel pamoate and 99.9% for ivermectin. With the exception of ivermectin, these values

Faecal egg count reduction test (FECRT)

The FECRT evaluates the efficacy of an anthelmintic drug based on its ability to reduce the faecal egg output after treatment. Faecal egg counts (FEC) are performed just before (or at the time of) and 14 days after treatment, and the egg reduction is calculated for each individual horse according to the formula:

$$\% \text{ FECR} = ([FEC_{pre}-FEC_{post}]/FEC_{pre}) \times 100$$

Any egg count technique can be employed for the FECRT, but it is recommended to use a technique with a detection limit of 25 eggs/g or less. Use always the same technique consistently.

The FECRT should be established on the farm level by calculating the FECR for a number of individual horses and then subsequently calculating the average FECR for the treated group. It is recommended to include at least 5–10 horses on each farm if possible.

Suggested cut-off values for resistance depend on the drug tested and the number of horses investigated, but for the range of 5–10 horses, the following cut-off values are recommended as general guidelines for strongyle nematodes:

Benzimidazoles:	90%
Pyrantel:	90%
Ivermectin:	95%
Moxidectin:	95%

If the farm average FECR falls below these values, anthelmintic resistance should be suspected. However, it is important to rule out other causes of decreased efficacy, such as misdosing, inadequate storage etc. One must also consider how many horses were tested and how high the starting FEC were. Due to inherent variability in the measurement of FEC when performing FECRT, interpretation of the data can sometimes be difficult when results fall into the borderline zones.

More detailed guidelines for performing a FECRT and making a diagnosis of anthelmintic resistance in horses are currently under development and will be published in the near future.

There are currently no available methods for diagnosis of anthelmintic resistance in equine tapeworms.

Fig 1: Recommended procedure for performing the faecal egg count reduction test (FECRT) in horses.

are far below the levels achieved when the products were first licensed, and are far below what is needed for effective treatment (i.e. ≥90%). The prevalence of resistance to fenbendazole, oxibendazole and pyrantel pamoate found in this study was far greater than in any previously published report (reviewed by Kaplan 2002). Furthermore, results from all 5 southern states were remarkably similar despite major differences in the types of farms and in physical geography. This demonstrated that drug resistance in cyathostomins is highly prevalent throughout the entire southern USA, and suggests that high levels of resistance are present throughout the US. Surveys for drug resistance performed in Italy (Traversa *et al*. 2007), Germany (Wirtherle *et al*. 2004; von Samson-Himmelstjerna *et al*. 2007), Sweden (Osterman Lind *et al*. 2007), Australia (Pook *et al*. 2002), and a recent study performed in Italy, Germany and the UK, confirmed high levels of benzimidazole resistance (38–85%), and low to moderate levels of pyrantel resistance (0–30%), but no compelling evidence of ivermectin resistance. It is interesting to note that the high prevalence of resistance to pyrantel pamoate found in the US study has not been detected in studies performed outside the USA. Many parasitologists have suspected that low-dose daily feeding of pyrantel tartrate may lead to resistance. Because the USA and Canada are the only countries in which daily feeding of low-dose pyrantel tartrate is practised, one must wonder whether this regimen of administration is having a major impact on the selection for resistance to other pyrantel compounds.

On almost half of all farms in the US study, only a single drug class (avermectin/milbemycins, also known as macrocyclic lactones) remained effective against cyathostomins. Avermectin/milbemycins, have been in use for more than 25 years and it is not known how long it will be before resistance to these drugs develops in cyathostomins but such resistance seems inevitable. Ruminants harbour strongylid nematodes closely related to cyathostomins, and here avermectin/milbemycin resistance is highly prevalent throughout much of the world (Kaplan 2004). Furthermore, numerous reports strongly suggest that avermectin/milbemycin resistance is fairly common in *Parascaris equorum* of horses (Boersema *et al*. 2002; Hearn and Peregrine 2003; Craig *et al*. 2007; Schougaard and Nielsen 2007; Slocombe *et al*. 2007; von Samson-Himmelstjerna *et al*. 2007; Lindgren *et al*. 2008; Veronesi *et al*. 2009). This demonstrates that avermectin/milbemycin resistance is already becoming a significant concern in an important nematode parasite of horses. Altogether, there is no biological rationale to believe that cyathostomins will not develop avermectin/milbemycin resistance. This has most recently been underlined by reports of greatly shortened ERP of cyathostomins after treatment with ivermectin (von Samson-Himmelstjerna *et al*. 2007; Lyons *et al*. 2008; Molento *et al*. 2008). All of these reports indicate that the ERP of ivermectin has decreased to 4 weeks, whereas in earlier studies the ERP was 8 weeks or longer (Borgsteede *et al*. 1993; Boersema *et al*. 1996). It has been suggested that shortened ERP represents the first sign of developing anthelmintic resistance (Sangster 1999). This was recently confirmed in a study demonstrating that the reduced ERP for ivermectin was due to a lack of efficacy against L4 larval stages within the intestinal lumen (Lyons *et al*. 2009). Thus, cyathostomin resistance to avermectin/milbemycin drugs is certainly developing and could reach levels producing therapeutic failures at any time. In fact, there are recent unpublished reports from both Brazil and the UK that strongly suggest that avermectin/milbemycin resistance in cyathostomins has already occurred. Given the published evidence that avermectin/milbemycin resistance in *P. equorum* is already an important problem, that resistance to benzimidazoles and pyrantel in cyathostomins is quite common and that resistance to avermectin/milbemycin drugs in cyathostomins is emerging, it is clear that no single drug class can be regarded as a safe choice for controlling equine nematode infections any longer. Horses are always co-infected with several nematode species at a time, thus faecal egg count surveillance and testing for drug resistance should be a routine component of equine health programmes.

The problem of drug resistance could theoretically be mitigated by the introduction of new classes of anthelmintic drugs with novel modes of action. However, the pharmaceutical industry has not introduced any new broad spectrum anthelmintic drug classes to the equine market since ivermectin in 1983 and there is very little evidence that it will happen in the near future. Moxidectin, which was first sold as an equine anthelmintic in 1995, is a closely related analogue of ivermectin belonging to the same drug class. In 2005, emodepside was approved as a new anthelmintic drug class (Harder *et al*. 2003) for use in cats (and later in dogs) only, and it remains unclear when, if ever, this drug will be introduced for usage in large animal species. Also, very recently, another novel class of anthelmintic, the amino-acetonitrile derivatives (AAD), have been developed for ruminant use (Kaminsky *et al*. 2008), and a product containing the drug monepantel was introduced in New Zealand in early 2009. However, no data are yet available on the potential of monepantel as an equine anthelmintic. Also in 2009, announcement of a new anthelmintic intended for use in sheep was made, which contains a combination of abamectin and the novel spiroindole drug, derquantel (World Association for the Advancement of Veterinary Parasitology, 22nd International Conference, Calgary, Canada, August 8–13, 2009). However, indications are that this drug will not be sold for use in horses. Thus, the discovery of new anthelmintic compounds does not guarantee that these drugs will ever be developed for use in horses.

In general, the great cost associated with the discovery and development of new drugs and the modest size of the equine anthelmintic market will greatly limit the future development and marketing of new anthelmintic

compounds for equine use. Additionally, it can be expected that any new drugs will be much more expensive than currently marketed products. Accordingly, it is highly unlikely that a stream of new equine anthelmintic products will follow in the near term. Consequently, it is most likely that an expansion in the spectrum and prevalence of resistance will continue to outpace the development and marketing of new anthelmintics for horses. We strongly hope that when the pharmaceutical industry finally introduces new anthelmintic drug classes to the equine market, the lesson has been learned not to rely blindly on frequent treatments, but to continuously use these new drugs in a sustainable, evidence-based approach. Only by taking the view that anthelmintics are extremely valuable and limited resources, and by using these drugs in a responsible manner, can we protect the efficacy of these drugs into the future.

Rotation of dewormers

Rotation between anthelmintic drug classes is commonly used on horse properties. This practice was originally recommended (Drudge and Lyons 1966) because few of the drugs available at the time were broad spectrum. Thus, to achieve adequate control of all potentially relevant parasite species, rotation between drug classes was advocated. With the introduction of broad spectrum drugs such as benzimidazoles and ivermectin, rotation was no longer required to fully control nematode parasites. However, drug rotation was continuously recommended, but now with a different purpose: prevention of resistance (Kelly *et al*. 1981).

Theoretically, parasites possessing resistant alleles enabling them to survive treatment with a particular drug can be killed by treating them with another drug with a different mode of action. Such counter-selection should, in theory, cause a decrease in the frequency of resistant gene alleles to the first drug. Unfortunately, there is absolutely no evidence to support this hypothesis. This is a classic example of how medical practice is often unduly influenced by a hypothesis that seems logical, but without any scientific evidence to back it up. In fact, one equine study clearly showed that rotating drugs with each treatment did not appear to slow development of resistance (Uhlinger and Kristula 1992). Furthermore, a computer modelling study of sheep nematode data that examined important factors that influence the development of drug resistance concluded that rotating drugs does not prevent accumulation of resistant genetic alleles, and does not slow down the evolution of resistance (Barnes *et al*. 1995).

This begs the question, if rotation of anthelmintics does not prevent resistance, why do veterinarians continue to recommend rotation? Is rotation of therapeutics used in any other aspect of veterinary practice? Would a veterinarian randomly rotate antibiotics? In fact, there are a number of reasons why rotation should not be recommended. First, advocating rotation creates a false presumption among horse owners and veterinarians that they have a bona-fide resistance prevention programme, when in fact they do not. Second, as mentioned previously, there are only 3 drug classes of broad spectrum anthelmintics and high prevalences of resistance exist for 2 of them. Thus, on many farms a rational rotation between drugs becomes impossible; rotating from an effective drug to a drug rendered ineffective due to parasite drug resistance simply is medically illogical and potentially dangerous. In such cases, rotation of drugs only serves to mask resistance, while at the same time potentially threatens the success of the control programme and the health of horses on that property (Reinemeyer and Henton 1987). Importantly, drug rotation cannot substitute for routine testing for anthelmintic resistance on the farm. Regardless of the treatment schedule used, all drugs must be routinely checked for resistance to ensure that efficacies are within the expected range. Despite these realities, some pharmaceutical companies continue to advocate recipe-type rotation strategies, and these most often include treatments with drugs known to have a high prevalence of resistance (http://www.getrotationright.com). Such marketing initiatives, which provide simplistic solutions to complex medical issues, make it all the more difficult to promote evidence-based approaches in a culture that is not eager to change.

How can we achieve optimal and sustainable worm control?

Strategies to decelerate further selection for drug resistance, thereby extending the lifetime of currently effective anthelmintics should be implemented whenever possible. Recipe-based treatment programmes based solely on the calendar without regard to the medical needs of individual horses, the biology of the parasites or whether the drug is actually effective against the target parasites can no longer be justified or recommended. An evidence-based approach must be adopted in which the biology of the target parasites and effectiveness of drugs are considered and each horse is viewed as an individual patient with individual medical needs. To develop such a programme we must: 1) follow epidemiological principles of nematode control; 2) determine which drugs are effective on each farm; 3) use the correct drug for the correct parasite developmental stage at the appropriate time of the year; 4) determine which horses require less or more frequent treatment by performing FEC; and 5) evaluate the overall success of the worm control programme by monitoring the FEC of all horses on the property at regular intervals.

In the course of recent studies investigating the prevalence of anthelmintic resistance we have met many horse owners who refuse to adjust their normal deworming routine even when shown results of FEC that are negative. This attitude commonly held by horse owners stems partly from the belief that all worms are bad and that no worms

should be tolerated in a horse. This attitude is also influenced by the widely held notion that all horses are highly susceptible to worms and, therefore, all horses should be treated the same. However, these notions are both completely false. Horses evolved with their intestinal worms and small numbers of most worms do not cause any significant health impairment, but rather help to stimulate immunity that serves to protect the horse from the establishment of a more serious worm burden (Monahan *et al*. 1997). Furthermore, small numbers of eggs shed by untreated horses are critical for slowing the development of anthelmintic resistance (details below). Finally, all horses are not the same. Parasite burdens are highly aggregated in hosts, meaning that about 20–30% of horses harbour about 80% of all the worms. On many farms this distribution is skewed even further. Thus, some horses consistently shed extremely high egg numbers even when treated frequently with anthelmintics (Nielsen *et al*. 2006a) while other horses have strong immunity and consistently shed very low numbers of eggs (**Fig 2**).

Parasite refugia

In recent years, parasitologists have come to view the most important factor affecting rates of selection for anthelmintic resistance as the proportion of selected to unselected parasites in a population (Sangster 1999; van Wyk 2001). The unselected portions of the population, called parasite refugia, provide a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistant genes. Parasites in refugia come from 3 sources: 1) eggs and larvae on pasture; 2) certain stages in the host not exposed to the drugs; and 3) worms in horses that are not treated with anthelmintic. As the relative size of the refugia increases, the rate of evolution towards resistance decreases (van Wyk 2001). Therefore, it is likely that, by serendipity, the lack of efficacy of ivermectin against encysted (mucosal) cyathostomin larvae may have helped to preserve its efficacy. These mucosal larvae, which are usually present in far greater numbers than the luminal adult stages (Chapman *et al*. 2003), provide a large refugia when ivermectin is administered to a horse. It has been suggested that the relatively good efficacy of moxidectin against these mucosal larval stages may increase the selection for resistance (Sangster 1999), but there still is no direct evidence to support this assertion. However, it has been demonstrated that larvicidal doses of fenbendazole may intensify the selection for resistance in cyathostomins (Reinemeyer *et al*. 2003), and available evidence from studies on sheep nematodes strongly suggests that control strategies that emphasise the maintenance of refugia will reduce the development of resistance (Waghorn *et al*. 2008).

Achieving successful nematode control while also maintaining adequate refugia is only possible through strategies utilising selective therapy, where routine FECs are performed to identify those horses that require treatment and those that do not (Duncan and Love 1991; Gomez and Georgi 1991; Krecek *et al*. 1994; Matthee and McGeoch 2004). Although this approach has been recommended for >15 years, it has not yet been widely implemented in equine establishments. In fact, several recent studies suggest that faecal analyses are minimally used, and instead total reliance is placed on frequent anthelmintic treatments (Anon 1998; Lloyd *et al*. 2000; Matthee *et al*. 2002; O'Meara and Mulcahy 2002). Although this treat-all-parasites-in-all-animals paradigm continues to be widely used, selective therapy is highly compatible with the host-parasite dynamics of cyathostomins. In a recent study on anthelmintic resistance (Kaplan *et al*. 2004), most farms deliberately delayed scheduled anthelmintic treatments (for purposes of the study), and farm data were only included if sufficient horses were passing adequate numbers of cyathostomin eggs. Nevertheless, in that study >33% of all horses on the 44 farms that met inclusion criteria had a FEC <20 eggs/gram (EPG), and on some farms the proportion exceeded 50%. This skewed distribution of FECs, combined with high degrees of anthelmintic resistance and frequent deworming, suggests that parasite control is being severely neglected in some horses, whereas the large majority of horses are being treated much more frequently than necessary. Leaving horses with low FECs untreated will have little impact on overall nematode control, but the small numbers of eggs shed may provide critical levels of refugia that will greatly dilute the contribution to pasture contamination made by treated horses. Such an approach will succeed in reducing selection pressure for resistance while improving overall parasite control (**Fig 2**).

Costs of performing FECs must be viewed as a necessary expense for maintaining optimal horse health. Owners must be warned against embracing the mistaken notion that since the price of a tube of dewormer is the same or less than the price of a FEC, it is cheaper to just go ahead and treat. Millions of tubes of anthelmintic are being administered to horses every year that are killing very few parasites either because there are very few worms in the horse to kill, or because the drug is ineffective as a result of resistance. Furthermore, there are future costs to over-treating in the form of worsening drug resistance. So, not only do current practices of over-treating horses waste money and promote drug resistance, but by not monitoring the success of the programme using FEC, there is no way to gauge how successful the programme actually is. Importantly, routine performance of FEC gets the veterinarian more involved in the health management of the stable, and promotes better equine health. In the early years of the modern age of anthelmintics (1960s and 1970s), passage of a nasogastric tube was required for administration of anthelmintics to horses. Consequently, deworming of horses was almost an exclusive activity of veterinarians. However, over the past few decades, the ready availability of safe, effective, inexpensive and easily

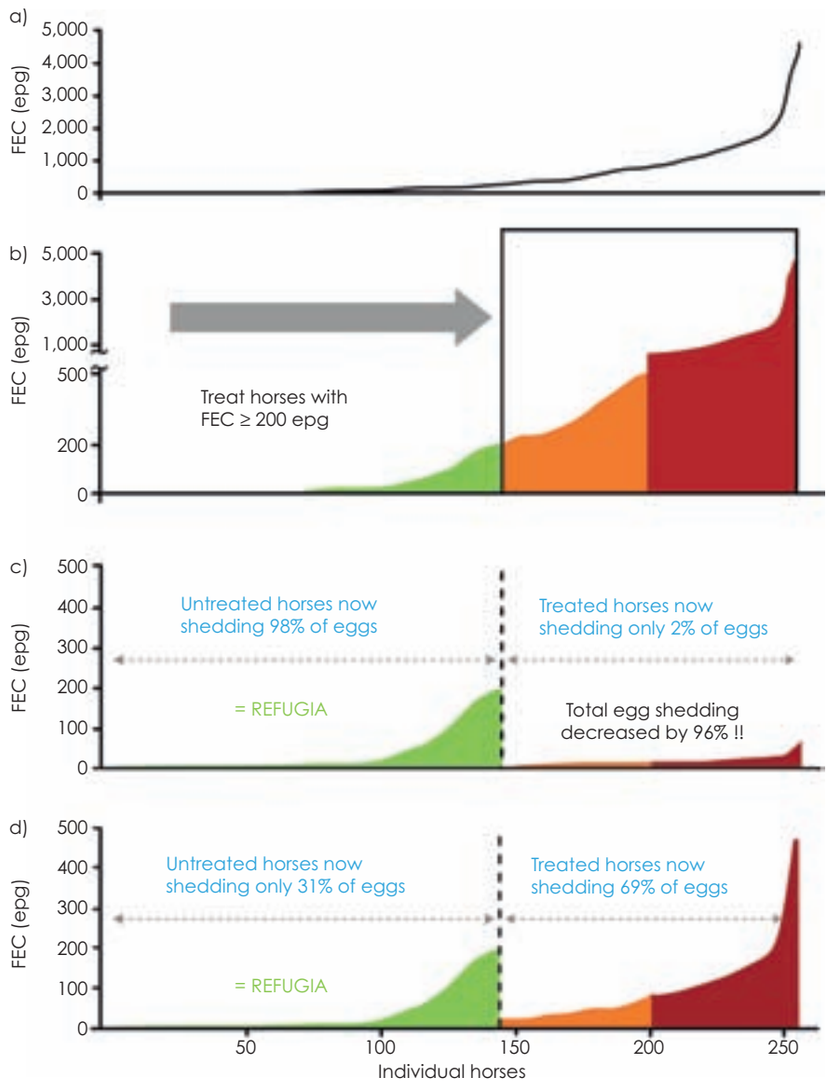

Fig 2: Distribution of faecal egg counts (FEC) for 261 horses on 12 horse farms and the predicted changes in that distribution in response to selective treatment. (a) The FEC of 261 horses from 12 horse farms are plotted left to right from lowest to highest, with magnitude of FEC on the Y-axis and individual horses on the X-axis. The line on the graph is formed by an overlapping of data points representing the FEC of the 261 individual horses. As can be seen, FEC are highly overdispersed in horse populations with the majority of horses shedding very low egg numbers and only a small percent having very high egg counts. (b) This graph shows the same data as in Figure 2a, but the Y-axis is broken to better visualise the data; this permits the data below 500 eggs/gram (epg) to be seen in more detail. These data demonstrate that horse populations can be divided into 3 categories of egg shedding; low egg shedders (0–200; green), moderate egg shedders (200–500; orange) and high egg shedders (>500; red). The high overdispersion of FEC among horses can be best understood by examining the relative egg output of horses in the different egg shedding categories. Low, moderate and high egg shedders represent 55, 18 and 27% of the horses, respectively. However, in terms of total egg output, low, moderate and high egg shedders are depositing 4, 13 and 83% of all the eggs shed onto pasture, respectively. (c) This graph illustrates the expected change in FEC distribution when using a drug with a 99.9% efficacy (e.g. ivermectin or moxidectin) in a selective therapy approach where only horses shedding 200 epg and above are treated. In this scenario, the total egg shedding is reduced by 96%, and yet more than half of the horses are left untreated. The horses with FEC<200 epg that are left untreated provide a large parasite refugia by shedding 98% of the all the eggs following treatment. This illustrates clearly that a selective treatment programme should achieve both major goals of cyathostomin control; a large reduction in the numbers of eggs being shed onto pasture (thereby reducing future infections), and the maintenance of refugia (thereby slowing the development of anthelmintic resistance). (d) This graph illustrates the expected change in FEC distribution when using a drug with a 90% efficacy. In contrast to the scenario in graph (c), if the same strategy is used but horses are treated with a drug that has a reduced efficacy of 90%, the egg shedding post treatment is dominated by eggs from worms that survived treatment (69%). Thus, the refugia are greatly diminished in this scenario and progression toward full-fledged anthelmintic resistance will occur much more rapidly. Consequently, utilising refugia to slow the development of resistance must be implemented while drugs are still highly effective, before resistance begins emerging. Once drug resistance starts to appear, there is little that can be done to prevent its further development other than to completely stop use of that drug.

administered anthelmintics has led to an important decrease in veterinary involvement in parasite control. This trend must change – veterinarians need to become more involved in developing and monitoring parasite control programmes, because the growing problem of anthelmintic resistance will only worsen in the future.

In Denmark, anthelmintic drug formulations have been available on a prescription only basis since 1999. This policy requires veterinary practitioners to establish a parasitological diagnosis prior to treatment, and disallows all prophylactic treatments. As a result, selective therapy based on routine FECs is implemented on a large scale basis and treatment intensity has been lowered considerably in this country (Nielsen *et al*. 2006b). In general, this legislation has led to very high degrees of veterinary involvement compared to other countries. Overall, most Danish veterinarians and horse owners appear positive to this change. In response to a European Union directive, in the past few years Sweden, the Netherlands and Finland implemented similar legislation, and it is likely that other countries in the European Union will follow. Thus, a change in legislation appears to be facilitating veterinary involvement, but it remains equally important to motivate both veterinarians and horse owners to commit to these modern sustainable approaches. In her recent review, Uhlinger (2007) expressed doubts as to whether such a change can be achieved worldwide, since the choice of treatment strategy has long been largely driven by marketing forces, and people have a strong belief in the necessity of an 8–12 week treatment interval for all horses. However, the only way to approach the goal of evidence-based parasite control is through continuing education of veterinary practitioners and dissemination of quality information to horse owners. Consequently, this should be given high priority by equine parasitologists and veterinary associations the world over.

Which parasites are important and which should be targeted in a control programme?

Cyathostomins (small strongyles) are considered the principal parasitic pathogens of adult horses (Love *et al*. 1999), but tapeworms (*Anoplocephala perfoliata*) are also recognised as potential pathogens of importance (see below). In addition, large strongyles (*Strongylus vulgaris*, *S. edentatus* and *S. equinus*) are significant pathogens and worthy of targeting in a worm control programme. As mentioned previously, the large strongyles, particularly *S. vulgaris*, are now quite rare in managed horses and require only once or twice yearly properly timed treatments to maintain these levels. In foals, the same parasites listed above for adult horses are also important, but added to this list is *Parascaris equorum*, which is considered the most important parasite of foals. Other less common and/or less important parasites such as bots (*Gasterophilus* spp.), stomach spirurid worms (*Draschia, Habronema*), pinworms (*Oxyuris equi*), *Onchocerca* spp., *Trichostrongylus axei, Dictyocaulus arnfeldi* and *Strongyloides westeri* are expected to be controlled by default in a properly designed programme that takes into account the main group of parasites targeted. If any of these less important parasites are diagnosed, they should be treated on a case-by-case basis, as it makes no medical sense to target parasites with frequent treatment without diagnostic evidence they are present and/or producing any clinical disease in the herd. It is important to note that in areas where frequent treatment of horses has not been practised over the past few decades, some of these parasites such as *Habronema* and *Draschia* (which cause 'summer sores') remain quite common and important.

The equine tapeworm *A. perfoliata* is prevalent in equine establishments worldwide (Gasser *et al*. 2005). In recent years, this parasite has received growing attention as a potential pathogen causing various types of colic. A few studies have been performed, but the evidence supporting tapeworms as an important cause of colic is still scant. Despite this, many pharmaceutical companies continue to promote frequent treatment for tapeworms. Tapeworms were first associated with ileocaecal intussusception and ileal rupture in several case reports (Barclay *et al*. 1982; Owen *et al*. 1989). This type of evidence is very frequent in equine parasitology, but is regarded as very low quality according to published evidence-based principles (Holmes and Ramey 2007). Subsequently, British scientists (Proudman and Edwards 1993) published a case control study that provided evidence for increased risk of ileocaecal colic in the presence of tapeworms. Proudman *et al*. (1998) then performed an epidemiological study in which tapeworm burdens measured by a serum antibody ELISA (Proudman and Trees 1996) were associated with an increased risk of both ileal impaction and spasmodic colic. This study has been regarded by some as providing definitive proof of *A. perfoliata*'s role as an important equine pathogen. More recently, a case-control study was performed which found higher tapeworm titres in horses with colic (Boswinkel and Sloet van Oldruitenborgh-Oosterbaan 2007). In addition, 2 studies associated pyrantel treatment with a lower colic incidence on horse farms with histories of frequent ivermectin treatment, suggesting that tapeworms played a role in the colics (Reeves *et al*. 1996; Little and Blikslager 2002).

However, more recent studies have questioned the validity of some of these findings. A validation of the serum ELISA was carried out in a Danish abattoir, and revealed much higher background antibody titre levels and a larger proportion of false-negative horses than in the earlier British study (Kjaer *et al*. 2007). This was followed up by a study documenting that horses can have high titres for up to 5 months after praziquantel treatment (Abbott *et al*. 2008). These studies illustrate that the serum antibody assay reflects exposure more than actual infection; thus it appears that further validation of this assay under different circumstances

is needed. In addition, a recent Canadian study (Trotz-Williams *et al*. 2008) found no association between tapeworm antibody titres and risk of colic. Interestingly, the authors of this study reported a significant correlation between tapeworm titres and access to pasture. Although it is not surprising that horses on pasture have greater exposure to tapeworm infections than stabled horses, this strongly suggests that access to pasture is a confounding factor in studies evaluating the pathological role of tapeworms. Thus, further studies evaluating the role of *A. perfoliata* in the equine colic complex are needed.

It is worth noting that studies utilising experimental infections to evaluate the causal relationship between *A. perfoliata* and intestinal disease have not been performed. Such studies could provide important insights. Abattoir surveys have related tapeworm burdens to the degree of local pathological damage (Williamson *et al*. 1997; Kjaer *et al*. 2007), but horses admitted for slaughter were not reported as showing clinical symptoms. It is clear that although *A. perfoliata* is prevalent in horse establishments, more evidence is needed to illuminate the circumstances under which this parasite causes disease. Nonetheless, treatment recommendations must be made based on available evidence. Given the strong seasonality of tapeworm transmission (Meana *et al*. 2005) and the potential for disease, it is likely that many horses will benefit from a properly timed single annual tapeworm treatment. But there is absolutely no evidence that frequent tapeworm treatments throughout the year provide any additional health benefit. Such evidence should be produced before veterinarians advise horse owners to treat for tapeworms repeatedly throughout the year.

Conclusion

The interval-dose programme, introduced more than 40 years ago provided great benefits to equine health for many years. However, much has changed during this time and there now exists a large body of evidence depicting the consequences of this approach. It is now clear that this approach places strong selection pressure for drug resistance in parasites of clinical importance and also selects for reduced ERPs in cyathostomins. Thus, large numbers of eggs are shed onto pastures despite frequent treatment, ensuring high levels of transmission. In addition, all but one of the commonly used anthelmintics only kill luminal stages of cyathostomins, whereas larval stages are responsible for most clinical disease (Love *et al*. 1999; Love 2003). Lastly, we now know that the relative susceptibility of horses to parasitic infection varies greatly, resulting in extreme differences in parasite burdens among horses. Given all of these issues, a programme that treats all horses the same, rather than as individual patients, will fail to provide optimal levels of parasite control.

The evidence supporting the effectiveness of the selective therapy approach for controlling equine parasites is still limited and most studies have only evaluated this approach over the short term. However, much evidence exists proving the inadequacy of traditional rotational approaches. Data simulations as presented in **Figure 2** support the selective approach, but more studies are needed to determine the long term benefits and risks. Perhaps the most central question to answer is: to what extent do equine parasites threaten equine health? The evidence is dominated by a large number of case reports describing various lesions and disease complexes associated with nematode parasites. But very few studies have verified parasites as being a risk factor for causing clinical disease, and it is well established that virtually all horses are infected with cyathostomin parasites no matter how often they are treated. Though there can be no disagreement that horses benefit from thoughtfully applied anthelmintic treatments, most equine parasites have limited pathogenicity and only seem to produce clinical disease when very high worm burdens result. When viewed in total, current evidence does not support a control strategy based on treating all horses at frequent intervals year round.

Clearly, the choice of parasite treatment strategy has become very complex. In addition to an unknown number of management-related factors, it depends on the species of parasites present on the premises, the relative prevalence and abundance of these species, time of the year and, most obviously, the level of anthelmintic resistance amongst them. The take home message must be that there is no such thing as a 'one size fits all programme' and achieving optimal parasite control has become a biological challenge that demands veterinary involvement. Furthermore, it remains a substantial challenge to get horse owners and their veterinarians to understand and implement new approaches based on current biological knowledge and current standards of veterinary care.

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