Horse and donkey parasitology: differences and analogies for a correct diagnostic and management of major helminth infections

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Abstract

In June 2022, a discussion took place during the XXXII Conference of the Italian Society of Parasitology (SoIPa), on the parallels of the main endoparasite infections of horses and donkeys. Although these two species are genetically different, they can be challenged by a similar range of parasites (i.e., small and large strongyles, and Parascaris spp.). Although equids can demonstrate some level of resilience to parasites, they have quite distinct helminth biodiversity, distribution, and intensity among different geographical locations and breeds. Heavily infected donkeys may show fewer clinical signs than horses. Although parasite control is primarily provided to horses, we consider that there may be a risk of drug-resistance parasite infection through passive infection in donkeys when sharing the same pasture areas. Knowing the possible lack of drug efficacy (< 90 or 80%), it is advocated the use of selective treatment for both species based on faecal egg counts. Adult horses should receive treatment when the threshold exceeds 200 to 500 eggs per gram (EPG) of small strongyles. Moreover, considering that there are no precise indications in donkeys, a value > 300 EPG may be a safe recommendation. We have highlighted the main points of the discussion covering the dynamics of helminth infections between the two species.

Keywords: Horse, donkey, endoparasite infection, anthelmintics, treatment protocols.
Introduction – Early data and similarities

Equids (horse, donkey, mule and hinny) originated about 55 million years ago in North America from a browsing species named *Hyracotherium* (Librado and Orlando, 2021), which had the size of a large dog. All living species of equids belong to the genus *Equus*, composed of two lineages, the caballine and the non-caballine animals, that are split into three phylogenetic clades. The domestic horse (*Equus ferus caballus*) and the Przewalski’s horse (*Equus ferus przewalskii*), belong to the first clade (caballine horses), while zebras and wild asses belong to the other two clades (non-caballine horses) (Cucchi et al. 2017). The modern horse has been intensely raised and selected (kinship) for their athletic potential focusing on morphological parameters of body weight, withers height, and also sports performance (Brown-Douglas et al. 2009; Schurs et al. 2022; Dall’Anese et al. 2023).

It is commonly believed that donkeys are short horses with long ears, however, these two animal species are different not only in their physical features and behavior but also in their genetic and physiological characteristics (Lizzaraga et al. 2004). The chromosome number of horses and donkeys is 64 and 62, respectively, making their hybrids (mules, and hinnies/asses) infertile animals. There are approximately 175 different breeds of donkeys worldwide (DAD-IS, 2017 - https://www.fao.org/dad-is), characterized by their ability to survive in mountainous and semi-arid environments with scarce water availability (Burden and Thiemann, 2015). Donkeys can survive even having a water loss of 20-30% of their weight (Matthews and van Loon, 2019), whereas horses are less tolerant of water deprivation (Matthews et al. 1997). Furthermore, even with the availability of water, the urine output of donkeys is lower than horses (Groserbaugh et al. 2011). Contrary to what happens in horses, donkeys have a greater ability to digest fibres of low nutritional value. These animals are characterized by their lower energy requirement (about 50-75%) than that needed by horses of the same size (Smith and Burden, 2013).
The different responses to pain and fear by the donkeys, compared to horses, led to the belief that donkeys could have superior tolerance to distress. For this reason, they are considered stoic animals that do not need regular veterinary care, vaccinations, or anthelmintic treatments (Molento and Vilela, 2021). However, donkeys may respond to discomfort and pain more subtly than horses. As an example, sick donkeys (i.e., parasites and bacterial infections) often show dullness and depression but the clinical diagnosis of the disease is performed only at an advanced stage (Burden and Thiemann, 2015).

Parasitic infections are the most important limiting factors for equids' health and performance, as all common parasites of horses infect donkeys (Matthews and Burden, 2013). In comparison, scientific publications on parasites in horses are 20 times higher than on donkeys (Molento and Vilela, 2021). Figure 1 shows a map of the main parasite studies only in donkeys with their geographical location. In this review, the differences between the main helminthic diseases affecting donkeys and horses, and the different treatment and management strategies will be examined. Some recommendations will be also highlighted.

**Helminth infections in horses and donkeys: head to head!**

Horses and donkeys not only share similar parasites but also hold high helminth biodiversity (Gianfaldoni *et al.* 2020; Sousa *et al.* 2021). Both species can act as reservoirs for each other, however, in donkeys parasitized with a high helminth burden, clinical signs such as diarrhoea, and poor body condition are less common than in horses (Matthews and Burden, 2013). Therefore, donkeys appear to be healthy even in the presence of a high parasitic load (Maestrini *et al.* 2020). The prevalence of major helminth infections in donkeys is reported in Table 1.

**Intestinal strongyles: epidemiology, diagnostic, innovative research**

As in horses and also in donkeys, the most common nematode parasites are intestinal strongyles
In both species, parasite infections are carried out mainly (> 90%) by small strongyles (Buono et al. 2021; Jota Baptista et al. 2021; Nielsen et al. 2021). A recent meta-analysis reported that *Cylicocyclus nassatus*, *Cylicostephanus longibursatus*, and *Cyathostomum catinatum* represent about 55% of the specimens in horses (Bellaw and Nielsen, 2020). The most common genera for donkeys were *Cylicostephanus* spp. and *Cylicocyclus* spp. (Maestrini et al. 2020; Perrucci et al. 2021).

In horses (Nielsen et al. 2021) and donkeys (Perrucci et al. 2021) small strongyles infections (cyathostominosis) are often asymptomatic. However, cyathostomins can cause colic, reduced nutrient absorption, diarrhoea, and weight loss, and in some cases intestinal infarction and death in horses (Molento, 2005; Steuer et al. 2018; Walshe et al. 2021). In donkeys, clinical signs due to parasite infections are somewhat rare (Getachew, 2006; Burden et al. 2010). It is known that a high parasite faecal egg count (FEC) (>1000 eggs per gram - EPG) may cause quantitative and qualitative milk reduction in asymptomatic lactating jennies (Perrucci et al. 2021). Small strongyles can be responsible for a clinical manifestation known as larval cyathostominosis in horses. This demonstration is caused by the synchronous emergence of the encysted larvae from the mucosa of the colon and caecum causing severe typhlocolitis. Although it is quite uncommon in both animal species, in the horse, the fatality rate of this syndrome can reach 50% (Love et al. 1999). Even though larval cyathostominosis has been reported in working donkeys (Oryan et al. 2015), the fatality rate of this syndrome is not known for the species. Matthews and Burden (2013) consider that the fatality would be lower than for horses. Although horse foals (< 1 year), yearlings (1-2 years), and young horses (3-5 years) are responsible for the majority of intestinal strongyle egg excretion (Lester et al. 2018; Scala et al. 2020), in donkeys this phenomenon still needs to be determined. Up to recently, no differences in parasite FEC have been observed among age categories (da Costa et al. 2018; Maestrini et al. 2020; Buono et al. 2021). Moreover, it has been reported that...
intestinal strongyles FEC is higher in donkeys than in horses (Mezgebu et al. 2013). This trend is not quite implicit but perhaps it could be due to different reasons, such as the lower frequency of anthelmintic treatment in donkeys than in horses (Buono et al. 2021). Another interesting observation is the smaller amount of faeces produced by donkeys when compared to an average size horse. Assuming a similar infection density, horses that produce a higher amount of faeces (15-20 kg/day), than donkeys (6-10 kg/day) would have a dilution of eggs on EPG, showing a lower FEC than donkeys (M. Molento, personal observation). More data needs to be gathered (performance, EPG, necropsy, i.e.) to demonstrate this biological condition.

Large strongyles encompass Strongylus spp., Triodontophorus spp., Craterostomum acuticaudatum, Oesophagodontus robustus, and Bidentostomum ivaschkini (Lichtenfels et al. 2008). Of these, the most pathogenic are those belonging to genus Strongylus (Cav et al. 2013). Three species of Strongylus spp. infect horses and donkeys (Strongylus vulgaris, S. equinus, and S. edentatus). In donkeys, S. asini has also been reported, whereas horses are less susceptible to this nematode (Malan et al. 1982). Strongylus asini is morphologically more similar to S. vulgaris than S. equinus and S. edentatus, however, the ITS-2 sequence of S. asini showed to be more similar to S. equinus and S. edentatus (Hung et al. 1996). In donkeys and zebras, S. asini develops in the lumen of the portal vein, having a comparable life cycle to S. vulgaris (Malan et al. 1982). Generally, large strongyles, are less abundant than small strongyles in horses and donkeys and these parasites are less common in farms that make constant use of macrocyclic lactones (i.e., ivermectin, abamectin, moxidectin). It has been reported that the prevalence of S. vulgaris may increase if selective therapy is adopted in horses (Tydén et al. 2019), and in donkeys (Sousa et al. 2021).

In horses, the overwhelming majority of intestinal strongyles egg excretion is concentrated in certain animals. In general, 15 to 30% of adult horses shed approximately 80% of eggs (80:20 distribution rule) (Tzelos and Matthews, 2016; Lester et al. 2018), and this
pattern is known as overdispersion. In donkeys, this behaviour has been less investigated and the levels of egg excretion are quite different, as about 40% of adult donkeys can shed approximately 80% of the eggs, suggesting an 80:40 distribution rule (Buono et al. 2021). These differences in the overdispersion of intestinal strongyle eggs between horses and donkeys have important practical implications. In horses, the anthelmintic treatment of 20% of the animals is adequate to limit pasture contamination, whereas in donkeys the number of treated animals, to obtain the same result would be considerably higher (Buono et al. 2021).

As selective therapy and other on-farm management (i.e. reproduction) focuses on individual animal performance, it has been shown that invasion of the intestinal mucosa by parasites activates a defensive mechanism involving the solute-like carrier family 11a1 (SLC11a1) gene, also known as NRAMP1 (Pires et al. 2021). The authors were looking to determine the DNA methylation profile of this gene in cyathostomin-infected horses correlating to FEC. First, they have shown that in the core of this gene, there were two cytosines adjacent to guanine (CpG) islands. The data presented a positive epigenetic correlation between the hypermethylatation of the island 2 of CpG of the gene and FEC. This information can help explain the differences in FEC detected among animals raised under similar conditions. Further research is been undertaken, looking to elucidate the host-specific aspects, and the involvement of certain genes across different horse categories (foals, yearlings, and adult horses) that may be related to host resilience to parasite infections. In the future, epigenetic processes shall be used as biomarkers to identify and target animals for anthelmintic treatments, as well as other breeding purposes (Pires et al. 2021). Epigenetic studies are still rare for horses and no such data has been produced for donkeys. As seen above, cyathostomin infections may be measured by individual FEC to be used in selective anthelmintic therapy. The difference in FEC is a phenotypic condition that might be explained by the genetic effects of horses. A new research approach was used by Dias de Castro et al. (2022) that looked into the genomic-wide
association studies (GWAS) using the Illumina Equine 70 K BeadChip to correlate genomic variants and FEC of 90 Thoroughbred horses. The GWAS used a panel containing 65,157 single nucleotide polymorphism (SNP) markers. The analysis revealed 33, 21, 30, 21, and 19 genes related to FEC, packed cell volume, eosinophils, neutrophils, and lymphocyte count, respectively. The data demonstrate a good correlation between important phenotypic health traits and the potential specific SNP markers.

Molento and Vilela (2021) have proposed a susceptible-infected-recovered (SIR) predicted model for cyathostomins under limited (low host infection rate), moderate, and severe (high host infection rate) infectivity scenarios for donkeys. The process data confirmed that once the infection level is low, disease recovery would be much faster than at the high-risk level. The larval numbers on pasture, parasite challenge and development in the host, parasite lifespan, and the return of host susceptibility shall be considered when interpreting the complexity of the host-parasite model. The SIR model simulations should be taken into consideration when proposing herd management and health control programs for donkeys and horses in distinct climatic zones (Molento and Vilela, 2021).

Considering the widespread anthelmintic resistance (AR), the use of selective therapy has been advocated to control parasite infections, avoiding parasite selection. In horses, a cut-off of 200-500 EPG has been adopted (Nielsen et al. 2014), whereas in donkeys there are no specific indications, and a value of 300 EPG has been suggested (Matthews and Burden, 2013). However, considering that donkeys with > 1000 EPG are often asymptomatic this safe FEC limit could be increased. As drug treatment is a human-made perturbation, the problem is that the lack of efficacy maintains the parasite infection, increasing the risk of heavy parasite infections of equids.

The diagnosis of intestinal strongyles is routinely based on copromicroscopic examination (Dias de Castro et al. 2017) and faecal culture for larval identification (Bevilaqua
et al. 1993; Lichtenfels et al. 2008; Madeira de Carvalho et al. 2008; Santos et al. 2016, 2018) to differentiate between large and small strongyles. However, larval cultures can result in false negative for S. vulgaris but real-time PCR (Nielsen et al. 2008), conventional PCR, and other PCR-based methods (Gasser et al. 1996; Hung et al. 1999) are available for S. vulgaris diagnosis in horses and donkeys (AbouLaila et al. 2020).

*Parascaris* spp.

Generally, equine ascarids refer to only one species: *Parascaris equorum*. However, in the literature other two species have been described: *P. univalens* and *P. trivalens*. These parasite species differ in having one (*P. univalens*), two (*P. bivalens* also named *P. equorum*) (Goday and Pimpinelli, 1986), or three (*P. trivalens*) pairs of chromosomes (Li, 1937). Hybrids between *P. univalens* and *P. equorum* have been described, however, they are sterile (Goday and Pimpinelli, 1986). *Parascaris univalens* and *P. equorum* are quite similar morphologically and they differ only in their spicula, which appear distally truncated in *P. univalens* and rounded in *P. equorum* respectively (Biocca et al. 1978). Different ascarid populations were karyotyped and identified as *P. univalens* suggesting that this ascarid species and not *P. equorum* is the predominant one in horses (Martin et al. 2018, 2021a). There are few phylogenetic analyses in donkeys, however, a recent study on mitochondrial genes COX1 and NADH1 showed that *Parascaris* spp. isolated from donkeys formed a distinct clade compared to those collected from mountain zebra and domestic horses (Peng et al. 2019). Furthermore, a recent whole-genome analysis performed in horses, donkeys, and zebras showed that *P. univalens* found in horses belong to distinct clades than those reported in donkeys and zebras (Han et al. 2022).

*Parascaris* spp. in horses represents the most important parasite infecting young animals, causing coughing, nasal discharge, lethargy, poor appetite, diarrhoea, and colic.
In working equids, poor body condition has been associated with ascarid infection (Getachew et al. 2010; Seyoum et al. 2015). However, horse foals and donkeys bred under optimal farm management programs may not show this pattern (Bellaw et al. 2016, Buono et al. 2021; Nielsen et al. 2021). In horses, the most important ongoing complication of this parasitosis is small intestine impaction and intussusception, which often requires surgery with a poor prognosis (Tatz et al. 2012), but there is no evidence of clinical complications in donkeys.

In horses, ascarid eggs are excreted mainly by foals and yearlings (< 1.4 years old) (Hautala et al. 2019; Scala et al. 2021), whereas in donkeys a high prevalence of Parascaris spp. can be seen regardless of the age of the animals (Getachew et al. 2008, 2010). These differences could be justified by the poor farming conditions of the donkeys that may not have developed an acceptable degree of immunity, associated with the lack of suitable nutrition (Getachew et al. 2010). A recent paper showed that even if ascarid eggs were reported in all age groups, a significantly higher prevalence was found in younger donkeys confirming that, as in horses, the main contaminators of roundworm eggs are juvenile animals (Buono et al. 2021).

The most common diagnostic method in horses and donkeys is by FEC. However, it is not possible to find eggs during the prepatent period and FEC may not correlate well with the worm burden (Nielsen et al. 2010). No statistical association has been seen between FEC and adult worms in horses (Fabiani et al. 2016). Transabdominal ultrasound may be used in routine diagnostics, but veterinarians must have sufficient practice to identify adult Parascaris spp. worms in foals (Nielsen et al. 2016).

The control of Parascaris spp. represent a key point in breeding farms and all foals under the age of six months should be considered potentially infected and at risk of developing acute clinical signs. Therefore, selective therapy is not recommended for juvenile animals if...
the stud has a history of *Parascaris* spp. infection. For this reason, anthelmintic treatments must be given to horses and donkeys younger than one year of age. Moreover, it is important to evaluate the presence of other intestinal parasites (i.e. strongyles, *Strongyloides westeri*, Anoplocephalidae) and the efficacy of the anthelmintic against *Parascaris* spp. (Nielsen, 2016a). The widespread resistance of *Parascaris* spp. and small strongyles toward macrocyclic lactones and tetrahydropyrimidines/benzimidazoles, respectively, has complicated the pharmacological control of these helminths considering that in case of mixed parasitic infections, the efficacy of any actives could be reduced (Molento et al. 2008; Morris et al. 2019).

*Dictyocaulus arnfieldi*

*Dictyocaulus arnfieldi* is the lungworm parasite of equids, that infects the respiratory tract. Animals became infected by ingesting the infective larvae during grazing. The donkey represents the competent host, and they are permissive of the entire life cycle of this nematode whereas, in horses, *D. arnfieldi* rarely develops into an adult, although the transmission between horses has been reported (Matthews, 2002).

Donkeys can be infected by a high number of adult helminths without showing clinical signs (Matthews and Burden, 2013) or only slight hyperpnoea and harsh lung sounds (Matthews, 2002). In donkeys, persistent infections are very common and patent infections can persist for at least five years. In this regard, donkeys can act as reservoirs and main pasture contaminators, representing an important risk factor for co-grazing horses (Beelitz et al. 1996). Horses may show signs of persistent cough, tachypnoea, chronic pneumonia, and pulmonary oedema. Infections can easily develop secondary bacterial infections. In horses, patency is shorter than in donkeys which can range from six weeks to eight months, in foals and older horses, respectively (Matthews, 2002). Furthermore, young horses are at a major risk of
infection than adult horses and are also characterized by a higher larval output (Jenkins et al. 2020).

Considering the clinical signs that can occur in horses (light coughing), it is advisable to pay attention to those animals who share the same pasture with donkeys. It has been reported that donkeys co-grazing with horses are less infected than those who do not co-graze. Thus, the diagnosis of donkeys that share pasture with horses is essential for controlling this parasite and for reducing the risk of infection in horses (Buono et al. 2021). In infected donkeys, the diagnosis is performed through the finding of first-stage larvae (L1), whether free or inside the eggs, in the faeces by modified Baermann technique (Rode and Jorgensen, 1989). Considering that temperature fluctuations during the first 48 h following faecal collection could adversely affect the recovery of L1, it is mandatory to perform the parasitological examination on fresh samples (Rode and Jorgensen, 1989).

Horse lungworm infections do not often reach patency and faecal diagnosis is more difficult than in donkeys. Trans-tracheal aspirates can be useful for demonstrating the increase in eosinophil numbers and endoscopic examination may reveal the presence of larvae in the airways, lymphoid follicular hyperplasia, and exudate in the trachea and bronchioles (Dixon et al. 1995). Furthermore, the enzyme-linked immune sorbent assay (ELISA) test can demonstrate the presence of antibodies from five weeks after infection, and it could be useful during high-risk seasonal (late winter) infections (Tagesu, 2018). Resistance to macrocyclic lactones was determined in D. viviparus of cattle (Molento et al. 2006) but no reports have confirmed the expected high efficacy in donkeys and horses.

*Anoplocephala* spp.

Tapeworm infection represents a serious worldwide parasitic disease of equids caused by the species *Anoplocephala perfoliata*, *A. magna* that infect horses and donkeys, and
Paranaplocephala mammillana that occurs only in horses. These tapeworm species differ from each other in size, location, and pathogenicity (Nielsen, 2016b). Anoplocephala magna and P. mammillana, are less frequent and also have an uncertain or marginal pathogenic role (Gasser et al. 2005). Some biological behaviour of A. perfoliata includes the preferential adhesion sites, consisting of the cecum wall and the ileo-caeco-colic ostium. The parasite has the tendency to cluster with numerous specimens in this region causing serious clinical intestinal disorders (Edwards, 1986; Fogarty, 1994; Trotz-Williams et al. 2008). The significant association between heavy parasitic burdens (greater than 100 specimens) of A. perfoliata and both medical (i.e. spasmodic) and surgical colics of the ileo-caecal-colic tract (i.e. ileocecal, caecal-caecal and caecal-colic intussusceptions, ileal impaction) has been demonstrated (Proudman et al. 1993, 1998; Reinemeyer and Nielsen, 2009; Veronesi et al. 2009; Pavone et al. 2011) in horses. The pathogenesis and the clinical impact of this infection in donkey is still limited. However, colic might be considered an occasional and exceptional onset of infection in both hosts. Animals in good health can tolerate a high parasitic load, and tapeworm infections are usually suspected due to vague clinical signs – as weight loss, the opacity of the coat, generic digestive disorders, such as constipation alternating with moderate diarrhoea.

Anoplocephalidae infections are considered a typical parasitosis of equids on pasture, although infections can occur in stabled animals, through the feeding of forage contaminated with oribatid mites, the intermediate hosts of the life cycle. In most of the developed countries, the prevalence of infection has been increasing over time, due to the absence of efficacy of the most used modern anthelmintics (i.e., ivermectin and moxidectin). The parasite also reduce the competitive pressure of further parasites of the digestive tract as strongyles (Bello and Abell, 1999; Gasser et al. 2005). The worldwide prevalence of infection in horses ranges from 18 and 82% with the highest positivity rates observed in humid and rainy areas that favours the development of the intermediate hosts (i.e., Sweden, United Kingdom, Germany, etc.)
Infection occurs in animals of all ages and patent infections can be described starting between the 16th and 20th weeks of life (Gasser et al. 2005). However, there were some reports showing the highest prevalence and intensity of infection in animals younger than 3 years of age (Campigli et al. 2009). In donkeys, epidemiological studies have reported high prevalences in Africa (> 80%) (Matthews and Burden, 2013), and low in Europe (< 10%) (Buono et al. 2021).

Tapeworm infection in equids can be detected by direct parasitological methods based on qualitative tools. Differently from the other Cyclophillidea, the search for proglottids in faeces is of scant diagnostic value. The proglottids are rarely detectable since before they are released with faeces they are broken down directly in the intestine (Nielsen, 2016b). The traditional techniques of concentration by flotation show an overall poor sensitivity (between 11% and 40%) for A. perfoliata infection. This is due to the inconstant egg output even in massive infestations (>100 specimens), and cannot be considered predictive of colic risk (Williamson et al. 1998; Abbott and Barret 2008). To improve the sensibility of detection, specific techniques have been developed in horses that can be used also in donkeys i.e. Proudman’s test (flotation concentration test) (Proudman and Edwards, 1992) and the Cornell-Wisconsin test (sediment concentration test) (Egwang and Slocombe, 1982). These techniques can reach sensitivities between 61 and 92% for parasitic loads greater than 20 specimens (Williamson et al, 1998). Immuno-diagnostic assays have also been developed and validated in horses for the detection of antibodies (IgG) stimulated by somatic or excretory/secretory antigens of A. perfoliata with a mean sensitivity of 68% and a specificity of 95% (Proudman and Trees, 1996a). A semi-quantitative CA-ELISA test (capture antigen enzyme-linked immunosorbent assay), using a purified 12/13 kDa antigen of A. perfoliata, is available in the UK and USA and can be used both for large-scale epidemiological screening and in the clinic as an early diagnostic test to prevent colic episodes (Proudman and Trees, 1996b). In addition,
a commercially available ELISA test has also been validated for the detection of antibodies in saliva with a sensitivity of 83% and a specificity of 85% (Lightbody et al. 2016, 2018). Such assay seems to be more useful than those conducted on sera to evaluate the efficacy of drug treatment, since post-treatment antibody levels in saliva decrease faster than in the blood. A coproantigen test in ELISA was also validated to detect the excreted/secreted proteins of *A. perfoliata*, showing a sensitivity of 74% and specificity of 92% (Kania and Reinemeyer, 2005) but is not currently available. Neither of these immunological tests has been validated in donkeys but several experiences have been conducted showing good sensibility (Getachew et al. 2012).

**Anthelmintics in horses and donkeys**

Donkeys are characterized by the greater activity of some cytochromes p450 isoenzymes than horses, giving them a greater ability to metabolize certain drugs (Peck et al. 1997). For this reason, there may be differences in the drugs’ disposition and availability, which may require higher concentrations or shorter dosing intervals than those used in horses to obtain effective drug concentrations for optimum parasite control (Horspool et al. 1994; Mealey et al. 1997; Grosenbaugh et al. 2011).

The most common anthelmintic drugs used in equids are benzimidazoles (BZDs), tetrahydropyrimidines (THP), macrocyclic lactones (MLs), and praziquantel (PZQ) (Gokbulut and McKellar, 2018). Only a few drugs are registered for use in donkeys (none exclusive). Thus, extra-label administration of products registered for horses or ruminants is the norm. Although there is less than a hand-full data on the pharmacokinetics and pharmacodynamics of anthelmintic drugs in donkeys and mules (Gokbulut et al. 2014, 2016a), anthelmintic treatment is performed using the same doses and regimens suggested for horses without considering species, breed, nutritional status, or individual (height and weight) differences.
(Lizzaraga et al. 2004; Veneziano et al. 2011, 2013) leading to a reduction in effectiveness (Molento et al. 2008), and an increase risk of toxic signs due to overdosing (Grosenbaugh et al. 2011). Therefore, there is a great need for more data on the donkey as well as new horse anthelmintic drugs and treatment strategies to support welfare (Senior, 2013).

**Tetrahydropyrimidines**

Pyrantel (PYR) is the only molecule of its class, licensed for horses and is available as salt PYR pamoate (syn. Embonate), insoluble in water and as PYR tartrate (soluble in water). PYR pamoate is available as paste or granule formulations, and it is poorly absorbed in the gastrointestinal tract, which increases its persistence in the intestine (Bjorn et al. 1996). The mechanism of action of THP is by binding to nicotinic acetylcholine receptors of the nematode muscle cells causing spastic paralysis and subsequent elimination from the host (Martin and Robertson, 2007).

A pharmacokinetic study showed that PYR pamoate administered to horses at 13.2 mg/kg body weight (BW) was poorly absorbed and the plasma concentration of the parent drug was very low (C\text{max} 0.09 ± 0.02). Moreover, its persistence in faeces was 48 h and the highest dry faecal concentration (1.034 mg/g) was detected at 24 h (Gokbulut et al. 2001a). In donkeys, PYR pamoate paste formulation at 6.94 mg/kg BW, showed a lower C\text{max} and a smaller area under the curve (AUC) than the granule formulation administered at the same dose (Gokbulut et al. 2014) (Table 2). This difference in plasma levels can be attributed to lower intestinal absorption of the paste rather than granule formulation. The pharmacokinetic parameters of PYR in donkeys are quite different from those reported in horses, showing in this latter a lower concentration and a short mean residence time (MRT) than in donkeys and, consequently a lower bioavailability (Gokbulut et al. 2014). These differences were attributed to a different diet as donkeys were fed with hay while horses were kept in grass pastures. The process
promoted a decrease in the gut transit time resulting in a lower bioavailability of PYR in horses (Gokbulut et al. 2001a). Moreover, residues of PYR were found in the faeces of donkeys and horses for up to 120 h (Gokbulut et al. 2014) and 48 h (Gokbulut et al. 2001a), respectively.

In equids, PYR is licensed at 6.6 mg/kg/BW (Gokbulut and McKellar, 2018) and it is highly effective against adults of small strongyles, S. vulgaris, and *Parascaris* spp. but shows moderate activity against *S. edentatus* and *O. equi* (Mirk, 1985). Moreover, a high dose, twice the nematocidal dose of PYR (13.2 mg/kg/BW) was effective in controlling *A. perfoliata* infection (Slocombe, 1979; Höglund et al. 1998). In donkeys, PYR showed high efficacy against cyathostominns and *S. vulgaris* (Napoli et al. 2013; Gokbulut et al. 2014; Buono et al. 2018). Although it has been reported that PYR administered high dose used for intestinal strongyles was effective against tapeworms in horses (Höglund et al. 1998), there are still no studies on the effectiveness of PYR pamoate against cestodes of donkeys.

*Benzimidazoles and Pro-benzimidazoles*

The first anthelmintic drug belonging to the BZDs class licensed in 1961 for horses was thiabendazole (TBZ) (Drudge et al. 1981). BZDs are characterized by poor water solubility and are administered as paste or drench formulations in horses (Gokbulut and McKellar, 2018). BZDs bind to the β-tubulin of microtubules, preventing their polymerization, destroying the cellular structure causing the death of the parasite (Martin, 1997).

Fenbendazole (FBZ) represents the most common BZD used for horses that belongs to the methylcarbamate group. The pharmacokinetics of FBZ is different in donkeys and horses and influencing its efficacy. FBZ is poorly absorbed from the GI tract of horses, and this would explain why higher concentrations are needed to be effective against migrating larvae and encysted larval stages of cyathostominns (McKellar et al. 2002). Following oral administration in donkeys, FBZ and its metabolite, FBZ sulphoxide (Oxfendazole – FBZSO) and FBZ
sulphone (FBZSO₂) were not detected in plasma probably due to the lower absorption and greater faecal excretion when compared to horses (Gokbulut et al. 2006). Furthermore, FBZ showed a longer gut transit time in donkeys than in horses (Gokbulut et al. 2006) (Table 2).

In horses, FBZ is licensed at a dosage of 7.5 mg/kg/BW and it is effective against adult large and small strongyles, *Oxyuris equi*. FBZ appears to be the best option for controlling *P. equorum* in foals, characterized by large ascarid burdens (Reinemeyer and Nielsen, 2017). Moreover, in horses, a five-day regimen of FBZ at 10 mg/kg/BW was effective for controlling the larval stage of small strongyles in enteric mucosa (Duncan et al. 1998). However, a reduced efficacy against early third-stage larvae (EL3), late L3 (LL3), and L4 were reported probably due to the presence of BZD-resistant cyathostomin populations (Reinemeyer et al. 2015; Bellaw et al. 2018). Fenbendazole is registered for use in donkeys, and it seems to have the same spectra of action as in the horse (Gokbulut and McKellar, 2018).

In donkeys, following oral administration FBZ of 10 mg/kg/BW, was not detected in plasma probably due to the lower absorption and greater faecal excretion of the drug faster than in horses (Gokbulut et al. 2006). The lack of absorption of FBZ supports its ineffectiveness against *D. arnfieldi* even when administered at high doses (50 mg/kg/BW) (Taylor and Craig, 1993).

Mebendazole (MBZ) is an anthelmintic drug belonging to the methylcarbamate group and pharmacokinetic studies have shown that the peak plasma concentration and AUC were lower than those of albendazole however T½ and MRT were longer than FBZSO and ABZ when administered at 10 mg/kg/BW (Gokbulut et al. 2006, 2016a) (Table 2).

The suggested dose of MBZ is 5-10 mg/kg/BW for horses (McKellar and Scott, 1990), and when administered at 8.8 mg/kg/BW it was effective against large and small strongyle (Colglazier et al. 1977). In donkeys, MBZ oral paste administered at 10 mg/kg/BW, and at 20 mg/kg/BW was effective against cyathostomins. Moreover, at 10 mg/kg/BW, there was no
residue in the milk of donkeys, different from what happened when administered at 20 mg/kg/BW. The data suggests that MBZ at 10 mg/kg/BW results effective for controlling cyathostomins in donkeys and its milk-withdrawal period is zero (Gokbulut et al. 2016a). Furthermore, MBZ administered at 20 mg/kg/BW for 5 consecutive days was effective in treating D. arnfieldi infection in donkeys (McKellar and Scott, 1990).

Albendazole (ABZ) belongs to the methylcarbamate group, and it is recommended orally in horses at a dosage of 5 mg/kg/BW. The pharmacokinetics parameters of ABZ and its metabolites (albendazole sulphoxide – ABZSO and albendazole sulphone – ABZSO₂) are shown in Table 2. In ponies experimentally infected, ABZ administered at 50 mg/kg/BW twice a day for two days was effective in controlling S. vulgaris larvae in the cranial mesenteric artery showing few toxic signs in 3 of 11 ponies (Georgi et al. 1980). Furthermore, when administered at 50 mg/kg/BW twice a day for four days and at 25 mg/kg/BW three times a day for 5 days resulted in a faster larval kill but more toxic symptoms and death occurred in 3 of 6 ponies (Georgi et al. 1980). An extra-label pellet formulation of ABZ licensed for ruminants and administered to horses at a dose of 7.5 mg/kg/BW showed a reduced efficacy against small strongyle. However, considering that there are no precise indications on the evaluation of the formulation used, it is not possible to state the certain presence of AR (Salas-Romero et al. 2017). ABZ suspension (25 mg/ml) was administered in a single oral dose at 10 mg/kg/BW and two oral doses 14 days apart at 10 mg/kg/BW in donkeys and both doses showed high efficacy against adult stages of large and small strongyles until the end of the study period (Imam et al. 2010).

**Macrocyclic lactones**

Macrocyclic Lactones (avermectins and milbemycins) are a class of natural and semisynthetic drugs of which ivermectin, (IVM), moxidectin (MOX), doramectin (DRM), and eprinomectin...
Macrocyclic Lactones are characterized by a high activity against endo (i.e., nematodes) and ectoparasites (i.e. mites, flies, lice) in humans and animals and thus are also defined as endectocides (Gokbulut and McKellar, 2018). Apart from that, although IVM and MOX have a similar mechanism of action by binding to glutamate and gamma-butyric acid-gated chloride channels, these drugs have profound pharmacological differences (Dent et al. 1997; Feng et al. 2002) and must be further studies in donkeys.

In horses, the kinetic of IVM was evaluated in several studies showing significant differences probably due to the distinct methods of application. A larger AUC and a longer MRT in donkeys than in horses were reported (Gokbulut et al., 2005). This data suggests that in the gastrointestinal tract of donkeys, IVM had a longer persistence and greater absorption. However, Marriner et al. (1987) reported a larger AUC and a higher $C_{\text{max}}$ in horses than in donkeys and these differences could be due also to diet, breed, and anatomical differences between horses and donkeys (Table 3). No pharmacokinetic data of MOX are available in donkeys.

In horses, IVM and MOX are registered at 200 μg/kg/BW and 400 μg/kg/BW, respectively. Both IVM and MOX, only when used orally in combination with praziquantel are active against tapeworms (Gokbulut and McKellar, 2018). Although MLs are highly effective in controlling intestinal strongyles they are not effective to control roundworms (Veronesi et al. 2010). In donkeys, off-label IVM administered at 200 μg/kg/BW was highly effective for controlling small strongyles (Papini et al. 2020). Even though IVM (200 μg/kg/BW) and MOX (400 μg/kg/BW) were effective for controlling intestinal strongyle infection 14 days post-treatment, a shorter egg reappearance period (ERP) was reported for both active drugs in Italy (Buono et al. 2018).

Ivermectin and moxidectin administered at 200 μg/kg/BW and 400 μg/kg/BW,
respectively, are the drugs of choice for the treatment of *D. arnfieldi* in horses and donkeys (Lyons *et al.* 1985; Coles *et al.* 1998; Matthews and Burden, 2013).

Doramectin (DRM) following oral administration at 200 µg/kg/BW showed a high persistence and bioavailability than IVM (Gokbulut *et al.* 2005) in donkeys, and it also showed a larger AUC and a longer MRT than in horses (Table 3). Furthermore, in horses, DRM administered orally at 200 µg/kg/BW showed a faster absorption than the injectable 1% formulation administered at the same dose by intramuscular route (Pérez *et al.* 2010).

In horses, DRM administered both orally and intramuscularly at 200 µg/kg/BW was effective for controlling intestinal strongyles (Pérez *et al.* 2010). In naturally infected horses, DRM following oral administration at 200 µg/kg/BW was effective against small strongyles with an egg reappearance period of 10 weeks (Cirak *et al.* 2007). In donkeys, DRM administered at 1 ml/50 kg by subcutaneous injection was effective for controlling small strongyles until day 28 post-treatment (Elmeligy *et al.* 2021).

Eprinomectin (EPM) is the last licensed drug belonging to the avermectins (Gokbulut and McKellar, 2018) that is 2 or 3 times more effective than the IVM and gives zero milk-withdrawal time. Therefore, EPM can be used safely in lactating animals (Shoop *et al.* 1996). The pharmacokinetic parameters of EPM in horses and donkeys are shown in Table 3 and the low disposition rate of EPM in the milk of animals allows the use of the drug in milk-producing horses (Gokbulut *et al.* 2016b) and donkeys (Gokbulut *et al.* 2011). In donkeys, EPM following pour-on administration (bovine dose - 500 µg/kg/BW) was effective in eliminating *D. arnfieldi* larvae for 28 days (Veneziano *et al.* 2011). Moreover, following topical administration, EPM showed high efficacy against large and small strongyles (Gokbulut *et al.* 2011).
**Praziquantel**

Praziquantel (PZQ) is an isoquinoline and it is licensed both in human and animal medicine for controlling cestodes and trematodes (Gokbulut and McKellar, 2018). PZQ acts by binding to the parasites' glutathione S-transferase (McTigue et al. 1995), altering the concentration of intracellular calcium, causing muscle contractions and tegument rupture (Harnett, 1988). There are no data on the pharmacokinetics of PZQ in horses and donkeys but, it is quickly and widely absorbed following administration in humans (Leopold et al. 1978).

In horses, PZQ is registered at 1.0 mg/kg/BW and a PZQ paste of 9% was effective for controlling *A. perfoliata, A. magna,* and *A. mammilana* (Slocombe et al. 2007). Moreover, following PZQ administration, the prevalence of cestodes was reduced by 96% until 10 weeks post-treatment (Lyons et al. 2017). Similarly, PZQ paste administered orally at 1 mg/kg/BW was effective for controlling *A. perfoliata* in donkeys (Getachew et al. 2013). In equids PZQ is licensed in association with the MLs (IVM and MOX) however, anecdotal data suggest that PZQ should be poorly tolerated in donkeys (Matthews and Burden, 2013). Pyrantel pamoate paste administered at a dose of 13.2 mg/kg/BW was safe and highly efficacious for controlling *Anoplocephala* spp. infection in horses (Marchiondo et al. 2006) and, although there are no safety studies in donkeys, it would be safer to administer PYR (at a double dose of 13.2 mg/kg/BW) than PZQ for controlling *Anoplocephala* spp.

**Anthelmintic resistance in equids: horses versus donkeys**

Resistance is the ability of a worm population to survive treatments generally effective against the same species and stage of infection (Sangster, 1999). Drug resistance was first reported in horses in the 1960s against phenothiazine in small strongyles (Gibson, 1960). Resistance to anthelmintics persists for many years and is transmitted to parasite populations being a genetic-based trait. In horses, the overuse of anthelmintics has led to the development of resistance,
especially against small strongyles and Parascaris spp. (Molento, 2005; Peregrine et al. 2014).

The faecal egg count reduction test is the in vivo test for determining the effectiveness of anthelmintic treatment against intestinal strongyles and Parascaris spp. in horses and donkeys and it is based on the percentage of reduction of eggs in the faces after 14 days post-treatment (Nielsen et al. 2019). The first report of cyathostomin resistance to PYR in horses was in 1996 (Chapman et al. 1996) and nowadays, resistance to this drug class is very common (Zanet et al. 2021; Nielsen, 2022). In horses, resistance to THP was evaluated since 2000 in 37 studies and reported in 34 (92%) (Nielsen, 2022).

Resistance to the BZD shas been commonly reported in the equine industry worldwide (Matthews, 2014) and in wild equids (Kuzmina et al. 2020), showing that resistance against this anthelmintic drug class is not always associated with the intensity of anthelmintic treatments. In horse strongyle infection, resistance to the BZDs has been associated with the polymorphisms of codons 167, 168, and 200 of isotype 1 β tubulin (tbb-1) (Ishii et al. 2017; Özben et al. 2022). In horses, since 2000, anthelmintic resistance against BZDs has been evaluated in 58 studies and it was reported in all of them (Nielsen, 2022). Moreover, in horses, multiple resistance to different anthelmintic drug classes has been reported (Flores et al. 2020) and it is quite common to find a population of small strongyles resistant both to BZ and THP (Canever et al. 2013). Another minor mutation was described by Ishii et al. (2018) at codon 172 that deserves further research.

Although MLs are the most commonly administered anthelmintic drug in horses (Tzelos et al. 2019) as in donkeys (Buono et al. 2021), drug resistance is not so common and it may develop in a more complex way – as more genes are involved. However, in the last year, several studies have reported a reduced efficacy of MLs against small strongyles in horses, both as a reduced efficacy at 14 days post-treatment and, as a shortened egg reappearance period (ERP) (Molento et al. 2008, 2012; Tzelos et al. 2017; Nielsen et al. 2020; Abbas et al. 2022).
that it was postulated representing the first sign of emerging resistance (Sangster, 1999). For this reason, in the next few years, an increased numbers of reports of AR to MLs are expected worldwide. A recent study showed that a shortened ERP cannot be explained only by the survival of fourth-stage larvae but probably could be associated also with other factors such as the selection of species or strains that accelerate their life cycle. Thus, a shortened ERP could not indicate the development of drug resistance (Nielsen et al. 2022).

Since 2000, resistance against MLs in horses has been evaluated in 57 studies and reported in 13 (23%) (Nielsen, 2022). In several nematode species, MLs resistance is associated with a group of genes that encode ATP-binding cassette transporters (Tydén et al. 2014; Raza et al. 2015).

In donkeys, drug resistance has not been reported as commonly as in horses and few clinical trials have been performed for evaluating the efficacy of the most common anthelmintic drugs (FBZ, PYR, and MLs) (Matthews and Burden, 2013). Resistance to PYR was reported in two donkeys farm in the UK (Lawson et al. 2015), furthermore, in one of these farms, a suspected resistance to MOX was reported 10 years earlier after continuous use of the cattle formulation (Trawford et al. 2005). However, considering that donkeys were treated orally using an injectable formulation licensed for cattle, the data reported for MOX probably did not confirm the presence of anthelmintic resistance. Recently, a population of small strongyles resistant to FBZ and PYR was reported in an Italian donkey farm, also associated with a reduction of ERP for IVM and MOX (Buono et al. 2018).

In horses, the first report of MLs resistance in Parascaris spp. was described by Boersema et al. (2002) in the Netherlands. Nowadays, anthelmintic resistance to MLs have been reported in 29 out of 32 studies worldwide, while resistance against THP and BZDs was reported in 4 out of 16 and 3 out of 13 studies, respectively (Nielsen, 2022). The sporadic resistance of Parascaris spp. against BZDs and THP should be due to the limited studies on
the effectiveness of these anthelmintic drug classes. Thus, drug resistance should be more common than those reported in the literature, as also suggested in some studies (Hautala et al, 2019; Martin et al. 2018, 2021b).

Anthelmintic resistance of *P. univalens* against BZs is not associated with single nucleotide polymorphism suggesting that the mechanism of anthelmintic resistance in this parasite is different from those reported for intestinal strongyles (Martin et al. 2021b). The lack of efficacy of IVM, MOX, and PYR has been reported also in donkeys (Matthews and Burden, 2013). Studies on anthelmintic efficacy in donkeys are reported in Table 4.

**Conclusions**

The host-parasite relationship is a complex process in equids that still needs much attention. Although donkeys and horses are closely related species and share practically the same parasite fauna, they are divergent in their physiological, and pharmacological (absorption, and distribution of drugs) characteristics. Some features such as breed, geographic location/climate, parasite challenge and intensity, immune response, and control methods including chemical use shall be regarded as a priority to help solve important parasite infections in both species. Target selective treatment can also be adopted, looking mainly for clinical signs, performance (body growth and withers height), and to FEC. Once adopted, the selective strategy may help to preserve drug effectiveness and the welfare both horses and donkeys. Horses and donkeys are “different cousins”, for this reason, precise farm management and parasite control program must take these differences into account.

**Author’s contributions.**

FB conceived and designed the study and wrote the first draft of the manuscript. VV, FV, and MBM conceived and designed the study and wrote and reviewed the manuscript.
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Competing interests.

The authors declare there are no conflicts of interest.

Ethical standards.

Not applicable.
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Figure 1. Choropleth map on the main epidemiological studies on major helminth infection in donkeys. N° in square brackets [*] represent the references reported in Table 1. **Africa**: Egypt [1-2], Ethiopia [3-38], Kenya [39-40], Morocco [41], Nigeria [42-43], Sudan [44-45], South Africa [46-47], Uganda [48-49]; **America**: Mexico [50-52]; **Asia**: India [53-57], Iran [58-62], Iraq [63], Mongolia [64]; **Europe**: Denmark [65], Germany [66-68], Italy [69-73], Macedonia and Thessalia-Greece [74], Portugal [75-76], Serbia [77], Turkey [78-82], Ukraine [83-84].
Table 1. Epidemiological studies of major helminth infections in donkeys.

<table>
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<tr>
<th>Country</th>
<th>Intestinal strongyles</th>
<th>Parascaris spp.</th>
<th>Dictyocaulus arnfieldi</th>
<th>Anoplocephala spp.</th>
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<td>Study</td>
<td>Yield (%)</td>
<td>Nitrate (%)</td>
<td>Phosphate (%)</td>
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<tr>
<td>Morocco</td>
<td>47.0%</td>
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<td>Nigeria</td>
<td>57.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudan</td>
<td>29.0%</td>
<td>4.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>+</td>
<td>96.0</td>
<td>9.6</td>
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<tr>
<td>Uganda</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>AMERICA</td>
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<td>Mexico</td>
<td>80%</td>
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References:
- Mathewos et al. 2021b [35]
- Negash et al. 2021 [36]
- Adeba et al. 2022 [37]
- Fesseha et al. 2022 [38]
- Lewa et al. 1999 [39]
- Mulwa et al. 2020 [40]
- Pandey 1980 [41]
- Ahmed et al. 2008 [42]
- Jajere et al. 2016 [43]
- Kheir and Kheir, 1981 [44]
- Seri et al. 2004a [45]
- Mushi et al. 2003 [46]
- Wells et al. 1998 [47]
- Saul et al. 1997 [48]
- Nakayima et al. 2017 [49]
- Burden et al. 2010 [50]

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<tr>
<th>Country</th>
<th>Percentage</th>
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<td><strong>ASIA</strong></td>
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<tr>
<td>India</td>
<td>93.6%</td>
<td>Valdés-Cruz et al. 2013 [51]</td>
</tr>
<tr>
<td>India</td>
<td>78.9%</td>
<td>Villa-Mancera et al. 2021 [52]</td>
</tr>
<tr>
<td>India</td>
<td>76.1%</td>
<td>Shrikhande et al. 2009 [54]</td>
</tr>
<tr>
<td>India</td>
<td>55.3%</td>
<td>Parsani et al. 2013 [56]</td>
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<tr>
<td>India</td>
<td>40.7%</td>
<td>Sathiyamoorthy et al. 2016 [57]</td>
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<td>Iran</td>
<td>46.7%</td>
<td>Hosseini et al. 2009 [58]</td>
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<td>Iran</td>
<td>67.3%</td>
<td>Karimi-Ghafrarrokh et al. 2014 [59]</td>
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<td>Iran</td>
<td>100%</td>
<td>Tavassoli et al. 2016 [60]</td>
</tr>
<tr>
<td>Iran</td>
<td>96.4%</td>
<td>Saadi et al. 2018 [61]</td>
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<tr>
<td>Iraq</td>
<td>57.1%</td>
<td>Wannas et al. 2012 [63]</td>
</tr>
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<td>Mongolia</td>
<td>6.4%</td>
<td>Painer et al. 2011 [64]</td>
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<td><strong>EUROPE</strong></td>
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</tr>
<tr>
<td>Denmark</td>
<td>91.7%</td>
<td>Beelitz et al. 1996 [68]</td>
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<td>Germany</td>
<td>48.0%</td>
<td>Gothe and Heil, 1984 [66]</td>
</tr>
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<td>Germany</td>
<td>93.6%</td>
<td>+</td>
</tr>
<tr>
<td>Germany</td>
<td>2.8%</td>
<td>+</td>
</tr>
<tr>
<td>Germany</td>
<td>2.2%</td>
<td>+</td>
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<tr>
<td>Germany</td>
<td>16.2%</td>
<td>Beelitz et al. 1996 [68]</td>
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<td>Germany</td>
<td>+</td>
<td>Beelitz et al. 1996 [68]</td>
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<tr>
<td>Country</td>
<td>Strongyle Type</td>
<td>Prevalence (%), Species</td>
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<td>------------------------------</td>
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<td>-------------------------</td>
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<tr>
<td>Italy</td>
<td></td>
<td>77.0%</td>
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<tr>
<td></td>
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<td>93.8%</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>84.9%</td>
</tr>
<tr>
<td>Macedonia and Thessalia-Greece</td>
<td>73.0% large strongyles</td>
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<td></td>
<td>37.8% small strongyles</td>
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<tr>
<td>Portugal</td>
<td>+</td>
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<tr>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Serbia</td>
<td>33.3% S. vulgaris</td>
<td>27.7%</td>
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<tr>
<td>Turkey</td>
<td>94.7%</td>
<td>2.6%</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>72.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td>96.7%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Ukraine</td>
<td>100%</td>
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</tr>
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<td>100%</td>
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</tbody>
</table>

+: positive animals. [*]: see figure 1.
Table 2. Comparative studies on pharmacokinetic parameters of Tetrahydropyrimidines and Benzimidazoles in horses and donkeys (adapted from Gokbulut and McKellar, 2018)

<table>
<thead>
<tr>
<th>Species</th>
<th>Anthelmintic drug</th>
<th>Abbreviation</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;last&lt;/sub&gt; (µg h/ml)</th>
<th>AUMC&lt;sub&gt;last&lt;/sub&gt; (µg h&lt;sup&gt;2&lt;/sup&gt;/ml)</th>
<th>MRT (h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;λ (h)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Horse</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pyrantel paste</td>
<td>PYR</td>
<td>0.09 ± 0.03</td>
<td>7.50 ± 1.41</td>
<td>1.06 ± 0.24</td>
<td>-</td>
<td>11.99 ± 1.30</td>
<td>13.43 ± 1.38</td>
<td>Gokbulut et al. 2001a</td>
<td></td>
</tr>
<tr>
<td>(13.3 mg/kg)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenbendazole</td>
<td>FBZ</td>
<td>0.04 ± 0.01</td>
<td>8.00 ± 2.70</td>
<td>0.61 ± 0.11</td>
<td>9.33 ± 2.89</td>
<td>14.21 ± 1.74</td>
<td>-</td>
<td>McKellar et al. 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FBZSO</td>
<td>0.01 ± 0.00</td>
<td>9.50 ± 3.52</td>
<td>0.17 ± 0.02</td>
<td>2.26 ± 0.46</td>
<td>12.90 ± 1.33</td>
<td>-</td>
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<tr>
<td></td>
<td>FBZSO₂</td>
<td>0.06 ± 0.01</td>
<td>10.50 ± 3.20</td>
<td>1.12 ± 0.19</td>
<td>12.54 ± 2.43</td>
<td>16.50 ± 1.00</td>
<td>-</td>
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<tr>
<td></td>
<td>FBZ</td>
<td>0.11 ± 0.05</td>
<td>10.00 ± 7.38</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Marriner and Bogan, 1985</td>
<td></td>
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<tr>
<td></td>
<td>FBZSO₂</td>
<td>0.16 ± 0.08</td>
<td>12.00 ± 6.20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Netobimin</td>
<td>ABZSO</td>
<td>0.53 ± 0.14</td>
<td>10.50 ± 3.66</td>
<td>8.63 ± 1.01</td>
<td>129.12 ± 20.10</td>
<td>15.08 ± 2.50</td>
<td>5.97 ± 1.59</td>
<td>Gokbulut et al. 2009</td>
<td></td>
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<tr>
<td></td>
<td>ABZSO₂</td>
<td>0.36 ± 0.09</td>
<td>19.50 ± 3.96</td>
<td>8.21 ± 2.87</td>
<td>177.55 ± 74.17</td>
<td>21.33 ± 2.31</td>
<td>7.44 ± 1.06</td>
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<tr>
<td><strong>Donkey</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pyrantel paste</td>
<td>PYR</td>
<td>0.09 ± 0.02</td>
<td>14.86 ± 5.52</td>
<td>2.65 ± 0.81</td>
<td>-</td>
<td>24.80 ± 5.54</td>
<td>12.39 ± 5.35</td>
<td>Gokbulut et al. 2014</td>
<td></td>
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<tr>
<td>(6.94 mg/kg)</td>
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<td></td>
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<tr>
<td>Pyrantel granule</td>
<td>PYR</td>
<td>0.21 ± 0.07</td>
<td>14.00 ± 9.45</td>
<td>5.60 ± 0.59</td>
<td>-</td>
<td>25.44 ±</td>
<td>14.86 ± 5.59</td>
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<tr>
<td>Drug</td>
<td>Compound</td>
<td>$C_{\text{max}}$</td>
<td>$T_{\text{max}}$</td>
<td>$AUC_{\text{last}}$</td>
<td>$AUMC_{\text{last}}$</td>
<td>MRT</td>
<td>$T_{1/2,\lambda_z}$</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Albenazine</td>
<td>ABZSO</td>
<td>10.95 ± 1.92</td>
<td>5.67 ± 2.89</td>
<td>58.12 ± 14.18</td>
<td>4.49 ± 0.74</td>
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<tr>
<td></td>
<td>ABZSO$_2$</td>
<td>15.38 ± 1.50</td>
<td>8.00 ± 2.53</td>
<td>161.00 ± 22.99</td>
<td>7.53 ± 0.35</td>
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<tr>
<td>Albendazole</td>
<td>ABZSO</td>
<td>6.65 ± 3.22</td>
<td>0.84 ± 0.14</td>
<td>9.15 ± 1.20</td>
<td>6.65 ± 3.22</td>
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<tr>
<td></td>
<td>ABZSO$_2$</td>
<td>7.44 ± 1.19</td>
<td>0.05 ± 0.11</td>
<td>9.98 ± 1.58</td>
<td>7.44 ± 1.19</td>
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<tr>
<td>Mebendazole</td>
<td>MBZ</td>
<td>11.97 ± 4.38</td>
<td>7.33 ± 3.93</td>
<td>19.49 ± 7.86</td>
<td>20.34 ± 7.59</td>
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</tr>
<tr>
<td>(10 mg/kg/BW)</td>
<td>MBZ</td>
<td>13.13 ± 3.85</td>
<td>8.00 ± 0.00</td>
<td>33.78 ± 10.38</td>
<td>23.43 ± 5.55</td>
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<tr>
<td>Mebendazole</td>
<td>MBZ</td>
<td>15.38 ± 1.50</td>
<td>1.42 ± 0.20</td>
<td>20.34 ± 7.59</td>
<td>11.97 ± 4.38</td>
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<tr>
<td>(20 mg/kg/BW)</td>
<td>MBZ</td>
<td>10.95 ± 1.92</td>
<td>8.00 ± 2.53</td>
<td>58.12 ± 14.18</td>
<td>4.49 ± 0.74</td>
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</table>

$C_{\text{max}}$: peak plasma concentration, $T_{\text{max}}$: time to reach peak plasma concentration, $AUC_{\text{last}}$: area under the (zero moment), $AUMC_{\text{last}}$: area under the first moment curve, MRT: mean residence time, $T_{1/2,\lambda_z}$: terminal half-life, PYR: pyrantel, FBZ: fenbendazole, FBZSO: fenbendazole sulphone, FBZSO$_2$: fenbendazole sulphone, ABZSO: albendazole sulphone, ABZSO$_2$: albendazole sulphone, MBZ: mebendazole.

FBZSO administered

Gokbulut et al. 2006

Gokbulut et al. 2016a

https://doi.org/10.1017/S0031182023000525 Published online by Cambridge University Press
Table 3. Comparative studies on pharmacokinetic parameters of Macrocyclic Lactones in horses and donkeys (adapted from Gokbulut and McKellar, 2018)

<table>
<thead>
<tr>
<th>Species</th>
<th>Anthelmintic drug</th>
<th>Route</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;last&lt;/sub&gt; (ng h/ml)</th>
<th>MRT (h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; λ&lt;sub&gt;z&lt;/sub&gt; (h)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Ivermectin (200 µg/kg)</td>
<td>P.O.</td>
<td>82.3</td>
<td>3.1</td>
<td>4821.6</td>
<td>-</td>
<td>66.3</td>
<td>Marriner et al. 1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P.O.</td>
<td>46.3</td>
<td>7.0</td>
<td>2646</td>
<td>-</td>
<td>-</td>
<td>Scott, 1997</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>44.0</td>
<td>2.2</td>
<td>3184</td>
<td>114.7</td>
<td>102</td>
<td>Pérez et al. 1999</td>
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<td></td>
<td></td>
<td></td>
<td>21.4</td>
<td>7.9</td>
<td>1106.4</td>
<td>55.2</td>
<td>51.6</td>
<td>Gokbulut et al. 2001b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P.O.</td>
<td>51.3</td>
<td>3.6</td>
<td>3290.4</td>
<td>100.8</td>
<td>69.4</td>
<td>Pérez et al. 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61.3</td>
<td>4.1</td>
<td>3959</td>
<td>176.2</td>
<td>156.7</td>
<td>Gokbulut et al. 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P.O.</td>
<td>25.8</td>
<td>5.5</td>
<td>1941.8</td>
<td>117.6</td>
<td>88.1</td>
<td>Gokbulut et al. 2016b</td>
</tr>
<tr>
<td></td>
<td>P.O. paste</td>
<td></td>
<td>30.1</td>
<td>7.92</td>
<td>2736</td>
<td>122.4</td>
<td>131.52</td>
<td>Saumell et al. 2017</td>
</tr>
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<td></td>
<td>P.O. sol.</td>
<td></td>
<td>33.7</td>
<td>12</td>
<td>3312</td>
<td>124.8</td>
<td>151.68</td>
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<tr>
<td></td>
<td>Doramectin (200 µg/kg)</td>
<td>P.O.</td>
<td>21.3</td>
<td>8.0</td>
<td>1279.2</td>
<td>72.0</td>
<td>93.8</td>
<td>Gokbulut et al. 2001b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51.6</td>
<td>4.8</td>
<td>4286.4</td>
<td>185.3</td>
<td>124.3</td>
<td>Pérez et al. 2010</td>
</tr>
<tr>
<td></td>
<td>Eprinomectin (500 µg/kg)</td>
<td>T.</td>
<td>17.7</td>
<td>43.2</td>
<td>424.6</td>
<td>70.3</td>
<td>32.9</td>
<td>Gokbulut et al. 2016b</td>
</tr>
<tr>
<td>Donkey</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ivermectin (200 µg/kg)</td>
<td>P.O.</td>
<td>23.6</td>
<td>24</td>
<td>2863.2</td>
<td>156.0</td>
<td>177.6</td>
<td>Gokbulut et al. 2005</td>
</tr>
<tr>
<td></td>
<td>Ivermectin (300 µg/kg)</td>
<td></td>
<td>43.2</td>
<td>8.0</td>
<td>1811</td>
<td>-</td>
<td>-</td>
<td>Scott, 1997</td>
</tr>
<tr>
<td></td>
<td>Doramectin (200 µg/kg)</td>
<td>P.O.</td>
<td>33.9</td>
<td>24.0</td>
<td>5493.6</td>
<td>218.4</td>
<td>266.4</td>
<td>Gokbulut et al. 2005</td>
</tr>
<tr>
<td>Eprinomectin (500 µg/kg)</td>
<td>T.</td>
<td>6.1</td>
<td>113.0</td>
<td>1761.4</td>
<td>215.5</td>
<td>113.44</td>
<td>Gokbulut et al. 2011</td>
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<td>------------------------</td>
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</tr>
<tr>
<td></td>
<td>14.2</td>
<td>81.1</td>
<td>3106.4</td>
<td>214.8</td>
<td>151.9</td>
<td></td>
<td>Gokbulut et al. 2013</td>
<td></td>
</tr>
</tbody>
</table>

$C_{\text{max}}$: peak plasma concentration, $T_{\text{max}}$: time to reach peak plasma concentration, $\text{AUC}_{\text{last}}$: area under the (zero moment) curve from time 0 to the last detectable concentration, MRT: mean residence time, $T_{1/2\lambda z}$: terminal half-life. P.O.: oral route/Per Os, T.: topical.
<table>
<thead>
<tr>
<th>Country</th>
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PYR: pyrantel pamoate; ABZ: abendazole; MBZ: mebendazole; FBZ: fenbendazole; IVM: ivermectin; MOX: moxidectin; EPM: eprinomectin; DRM: doramectin; PZQ: praziquantel; SC: subcutaneous administration; IM: intramuscular administration; Inj. for.: injectable formulation; PO: per os. According to American Association of Equine Practitioners Parasite Control Guidelines cut-off (Nielsen et al. 2019), the cut-off values used to interpret the results of FECRT were the following: PYR susceptible (S) > 90%, suspected resistance (SR) 85%-90%, resistant (R) < 85%; FBZ susceptible (S) > 95%, suspected resistance (SR) 90%-95%, resistant (R) < 90%; IVM/MOX susceptible (S) > 98%, suspected resistance (SR) 95%-98%, resistant (R) < 95%. §: for these anthelmintic drugs are not suggested cut-off values in AAEP Guidelines.