



Manipulating small ruminant parasite epidemiology through the combination of nutritional strategies

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ABSTRACT

It is increasingly being recognized that non-chemical parasite control strategies may need to be combined to control more effectively gastrointestinal parasitism, result in resilient production systems and reduce reliance on anthelmintics. Here, we consider if and how metabolizable protein (MP) supplementation and anti-parasitic plant secondary metabolites (PSM) may modulate parasite epidemiology through intervention in pasture contamination, development of infection on pasture and larval challenge as target processes. We then propose that combining two or more non-chemical parasite control strategies may have additive effects on host resistance, especially if the individual strategies target different drivers of parasite epidemiology, different processes in the parasite life cycle or different phases of acquired immunity to parasites. This epidemiological framework is used to review recent findings on combining maternal MP supplementation and grazing the PSM-rich bioactive forage chicory as an example of combining nutritional treatments to manipulate parasite epidemiology in a temperate production system. In the absence of available data for combined nutritional strategies in tropical production systems, we make predictions on the consequences of combining such strategies in these systems. We conclude that currently published studies on combining nutritional strategies under temperate conditions show potential to improve additively host resilience and reduce reliance on anthelmintics; however, effects on epidemiology have to date not shown the additive results hypothesized. The framework developed may assist further in evaluating combined (nutritional) strategies to manipulate parasite epidemiology.

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1. Introduction

It has long been known, or at least suspected, that improved host nutrition may detrimentally affect gastrointestinal nematodes (Clunies-Ross and Gordon, 1933; Taylor, 1935; Gibson, 1963). Such anti-parasitic activity has been considered to arise from indirect nutritional effects, i.e. those mediated through nutritional modulation of host immune responses, or direct nutritional effects, i.e. those

arising from ingestion of anti-parasitic plant secondary metabolites, PSM (Coop and Kyriazakis, 2001; Houdijk and Athanasiadou, 2003). For other possibilities of how host nutrition may affect parasites, including the modulation of gut environment and allowing for a reduction in the nutrients available to parasites, we refer to Houdijk and Athanasiadou (2003). The above indirect and direct effects of host nutrition on gastrointestinal nematodes form the basis for the use of immunonutrition and bioactive forage consumption, respectively, as potential non-chemical parasite control strategies. Although these strategies have largely been developed independently and their underlying mechanisms are usually considered in isolation, it is

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increasingly being concluded that such indirect and direct nutritional effects may need to be combined to achieve the most effective, sustainable parasite control (Coop and Kyriazakis, 2001; Houdijk and Athanasiadou, 2003; Torres-Acosta and Hoste, 2008; Athanasiadou et al., 2008).

This review focuses on the possibility of using metabolizable protein (MP) supplementation and PSM-rich bioactive plants to modulate the epidemiology of gastrointestinal nematode infections in sheep, although we will occasionally refer to other host–parasite systems where appropriate. We focus on MP because it is often scarce for growing and reproducing sheep, for example, due to consumption of low-quality forages or restricted feeding, at times of high MP requirements for growth and periparturient reproductive functions (AFRC, 1993). Parasitism further increases MP requirements for maintenance, arising from parasite-induced repair of damaged host tissue (Coop and Kyriazakis, 1999), and for production of the proteinaceous immune response components involved in regulating worm establishment, fecundity and survival (Balic et al., 2000; Coop and Holmes, 1996). MP supplementation may improve resistance to parasites, observed as reduced worm burdens and FEC, because in its absence, the allocation of scarce MP would be prioritized to maintenance and productive functions rather than expression of immune functions (Coop and Kyriazakis, 1999).

Plants with anti-parasitic properties indigenous to many parts of the world have regularly been reported in the literature, including the anti-parasitic efficacy of their extracts and/or purified PSM (Hammond et al., 1997; Schlage et al., 2000; Houdijk and Athanasiadou, 2003; Sori et al., 2004; Githiori et al., 2006; Hoste et al., 2006). Recent studies have confirmed and extended these reports, demonstrating anti-parasitic activity from bioactive forages such as chicory (*Cichorium intybus*), birdsfoot trefoil (*Lotus corniculatus*), sainfoin (*Onobrychis viciifolia*) (Heckendorn et al., 2007) and sericea lespedeza (*Lespedeza cuneata*) (Lange et al., 2006), but also from tropical plants such as acacia (*Acacia cyanophylla*) foliage (Akkari et al., 2008), *Ziziphus nummularia* bark and *Acacia nilotica* fruit (Bachaya et al., 2009), *Chenopodium album* and *Caesalpinia crista* (Jabbar et al., 2007), falcon's claw acacia (*Acacia polacantha*) (Max et al., 2007), *Coriandrum sativum* (Egualo et al., 2007) and ginger (*Zingiber officinale*) (Iqbal et al., 2006). Although more than 100,000 PSM have been described (Acamovic and Brooker, 2005), anti-parasitic properties have so far been reported for a few PSM, including lactones (Molan et al., 2003a), alkaloids (Satou et al., 2002), glycosides (Akhtar and Ahmad, 1992) and tannins (Athanasiadou et al., 2001a; Molan et al., 2003b).

In this paper, we first describe the main facets of gastrointestinal nematode epidemiology and review evidence to identify whether MP nutrition and PSM can impact on selected processes in the parasite life cycle as drivers for parasite epidemiology. Whilst we do this for MP nutrition and PSM separately for the sake of clarity, PSM effects on parasitism may to some extent arise from improved MP supply; for example, the anti-parasitic PSM condensed tannins (CT) may bind to dietary protein, resulting in reduced protein degradation in the rumen and thus potentially providing increased intestinal MP supply (Barry and Manley,

1984). Likewise, protein feed ingredients like peas, beans and lupins contain a wide range of PSM (Jezierny et al., 2010), with known or unknown anti-parasitic activities. It should also be noted that additional MP supply may arise from improved fermentable energy intake, as the latter may limit rumen MP supply. Indeed, recent studies have demonstrated improved resistance and resilience to gastrointestinal parasites in goats browsing protein rich fodder trees following supplementation with fermentable energy sources (Knox et al., 2006; Hoste et al., 2008).

The second part of the review considers the combination of nutritional strategies to affect parasite epidemiology. We first develop a framework to assess the potential benefits of combining nutritional strategies on parasite epidemiology. We then describe our recent experience with combining maternal MP supplementation and chicory grazing as an example of combining indirect and direct nutritional parasite control strategies in temperate sheep production systems. We then extend these principles to tropical production systems, although to our knowledge, combining (MP) supplementation with bioactive forage feeding has not (yet) been experimentally tested under these conditions. Therefore, this part of the review is more speculative and, almost by necessity, centres on the dual consequences of supplementation with bioactive forages, i.e. additional nutrient supply and provision of anti-parasitic PSM. The review concludes with suggestions for further research and implications for non-chemical, nutritionally based parasite control strategies.

2. Epidemiology of gastrointestinal nematode infections

Adult parasites within the gastrointestinal tract produce eggs, which are excreted via the faeces onto the pasture (contamination), where over time eggs develop into infective larvae, L₃ (development). The infective larvae vertically migrate onto forage, and are ingested by sheep through grazing (challenge) to develop into adult parasites within the sheep gastrointestinal tract. Controlling (reducing) gastrointestinal nematode infections in grazing animals can be seen as disrupting this cycle, through controlling (1) the source of infection to reduce contamination of the pasture, (2) egg hatchability and L₃ appearance to reduce the development of infection on the pasture, and (3) L₃ uptake to reduce challenge from the pasture (Fig. 1).

The main sources of infectivity early in the season are overwintering larvae and infected periparturient ewes, whilst subsequent pasture infectivity also derives from patent lambs. At less than 0.5%, translation (i.e. number of worms as a percentage of number of eggs deposited) for winter deposition of *Teladorsagia circumcincta* eggs is low but significant (Bailey et al., 2009), and thus puts periparturient ewes at risk of infection (Waller et al., 2004; Makovcová et al., 2009). The elevated ewe FEC, which may also in part result from resumed development of inhibited larvae (Sargison et al., 2007; Waller et al., 2004), arises from periparturient relaxation of immunity (PPRI) to parasites (Barger, 1993; Beasley et al., 2010). The seasonal reproductive cycle further assist epidemiology especially under temperate conditions, as worm eggs excreted by

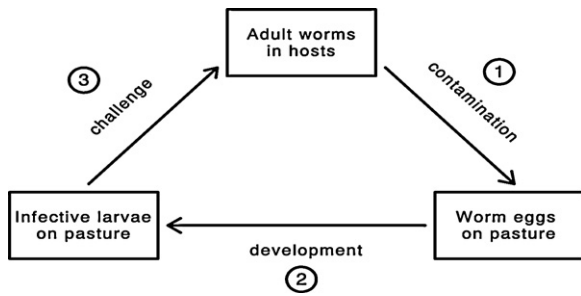


Fig. 1. Representation of the gastrointestinal nematode life cycle, which identifies contamination of, development on and challenge from pasture as target processes to modulate parasite epidemiology through (nutritional) intervention.

periparturient ewes are deposited during spring time, i.e. under appropriate climatic conditions that favour their development into L₃ and build-up of pasture infectivity for late spring and summer. Hence, ewes can be a main source of infection for their parasite-naïve offspring, as for example observed when *T. circumcincta*-infected ewes are turned out on parasitologically safe pastures (Kidane et al., 2010a).

Gastrointestinal nematodes are not equally distributed within a population, and consequently, not all animals within that population are equally infective to the pasture. A small proportion of the flock usually has the highest FEC, whilst conversely most animals have low to moderate FEC (Sreter et al., 1994; Stear et al., 1995). Whilst this variation may have a genetic basis (Stear et al., 1995), additional host factors such as age, sex and immune status also influence sheep FEC and thus their contribution to pasture infectivity (Houdijk and Athanasiadou, 2003; Torres-Acosta and Hoste, 2008).

We now consider whether nutritional strategies can modulate parasite epidemiology through reducing contamination, development and/or challenge (Fig. 1), and provide evidence whether and how these processes are affected by MP supplementation and by exploiting anti-parasitic PSM.

2.1. Controlling pasture contamination

The FEC can be seen as the link between sheep and pasture, and reducing FEC in general, and periparturient ewe FEC in particular, has the potential to greatly reduce pasture contamination to avoid initial and later build-up of pasture infectivity. In absolute terms, ewe FEC may not be high but due to their large faecal output, a single ewe could easily excrete more than 1 million eggs per day (Familton and McAnulty, 1997; Houdijk et al., 2003).

Accounting for faecal volume (Houdijk, 2008), the observed FEC can be seen as essentially the accumulated outcome of parasite establishment, fecundity and survival. Since each of these host resistance characteristics is at least to some degree under immunological control (Claerebout and Vercruyse, 2000; Seaton et al., 1989), MP supplementation at times of MP scarcity has the potential to reduce pasture contamination through increased immunity. In addition, ingestion of adequate levels of anti-parasitic PSM

may result in reduced parasite establishment, fecundity of existing parasites and/or reduced worm burdens. The latter would be associated with a reduction in FEC, although depending on the worm species involved, worm fecundity may actually increase as worm density reduces (Barger, 1987). Providing that adequate PSM intake is achieved, such effects would be expected to occur at low and high levels of MP nutrition (Athanasiadou and Kyriazakis, 2004) as well as during acquisition and expression of immunity (Athanasiadou et al., 2008). Thus, host nutrition has the potential to reduce pasture infectivity by reducing contamination through both MP supplementation and PSM ingestion (Fig. 1).

A large number of studies have demonstrated that MP supplementation results in reduced FEC and worm burdens, especially during the phase of expression of immunity. For earlier studies, we refer to previous reviews (Coop and Kyriazakis, 1999, 2001; Houdijk et al., 2001a; Kahn, 2003; Steel, 2003; Houdijk and Athanasiadou, 2003; Kyriazakis and Houdijk, 2006; Sykes and Kyriazakis, 2007). In addition, recent studies, including some not referred to previously, are also in agreement with these findings in both lambs (Bricarello et al., 2005; McClure, 2009; Greer et al., 2009; Louvandini et al., 2006) and ewes (Sykes et al., 2007; Zaralis et al., 2009; Kidane et al., 2009a, 2010b). Although it is not yet fully understood how MP nutrition affects resistance to nematodes, a large number of studies in small ruminants show correlations with directly measured immune responses (Athanasiadou et al., 2008), supported by similar recent observations in growing and lactating rodents (Tu et al., 2008; Jones et al., 2009). Thus, MP supplementation can reduce pasture contamination through controlling the source of infection (Fig. 1). Evidently, the magnitude of these effects would be dependent on the degree of MP scarcity (Houdijk and Athanasiadou, 2003) or MP pressure (Kahn et al., 2003a) in the absence of supplementation. This would be consistent with observations that the largest contribution to pasture infectivity comes from sheep with high production potential (Zaralis et al., 2009; Kidane et al., 2010b; Wallace et al., 1995, 1996), multiple rearing ewes (Houdijk et al., 2001b; Donaldson et al., 2001; Kahn et al., 2003b), ewes that lose maternal body weight (Kahn et al., 2003a) and ewes with low body (protein) reserves (Houdijk et al., 2001c). From an epidemiological point of view, nutritional intervention targeting these animals within a flock would result in the greatest benefit for the flock as a whole.

Many studies have shown that feeding PSM-rich forages or drenching with PSM-rich extracts is anti-parasitic towards incoming larvae and/or established adult nematodes (Athanasiadou et al., 2000a, 2001a; Paolini et al., 2005; Tzamaloukas et al., 2005a; Minho et al., 2008; Max et al., 2009). The latter is usually associated with reduced FEC, although several recent studies have demonstrated that PSM ingestion may only affect worm fecundity (Manolaraki et al., 2010; Rios-De-Alvarez et al., 2008; Heckendorn et al., 2006; Max et al., 2007; Paolini et al., 2003). Dietary inclusion of up to 6% of quebracho CT or grazing PSM-rich forages also reduced FEC (Athanasiadou et al., 2000b, 2007; Butter et al., 2000; Hoste et al., 2006; Kidane

et al., 2010a). Whilst the reduced FEC and worm burdens following PSM ingestion may arise from their direct anthelmintic properties, the improved host resistance may also be immunologically mediated (Tzamaloukas et al., 2006; Rios-De-Alvarez et al., 2008; Paolini et al., 2003). Although it cannot be excluded that these effects have a nutritional basis, arising from increased protein or mineral supply (Barry and Manley, 1984; Barry, 1998; Kidane et al., 2010a), it is evident that exploiting PSM has great potential to manipulate parasite epidemiology through reducing pasture contamination (Fig. 1).

2.2. Controlling development of parasite infection on the pasture

Under controlled conditions, developmental success from worm eggs to infective larvae can be as high as 90% (O'Connor et al., 2006). However, such levels are rarely reported under field conditions, where development is typically less than 20% (O'Connor et al., 2008; Familton and McAnulty, 1997; Niezen et al., 2002). O'Connor et al. (2006) concluded that faecal moisture is one of the most important factors affecting the success rate of larval development and subsequent survival. This suggests that dietary effects on faecal dry matter content may potentially impact on larval development and survival. However, MP supplementation does not seem to affect systematically faecal dry matter contents in pen studies (Greer et al., 2009; Houdijk et al., 2009). It is not known (yet) whether this would also be the case in field studies, but, from the limited information available, it can be suggested that the impact of protein supplementation on pasture infectivity through a reduction in the rate of development of infective stages is likely to be limited. In addition, any diet-induced variation in faecal moisture is likely to be diluted or masked by climatic influences (e.g. rain fall, drought etc.).

However, MP supplementation could affect egg hatchability and larval development, if these are sensitive to host immunity. *Haemonchus contortus* and *Trichostrongylus colubriformis* eggs tended to have a reduced hatchability when harvested from genetically resistant sheep compared to their susceptible counterparts (Kemper et al., 2010). However, Jørgensen et al. (1998) observed that combined egg hatchability and larval development of nematode eggs obtained from sheep selected for low FEC was significantly reduced by >60% compared to their high FEC counterparts, and observed the same for worm eggs derived from post-lactational ewes compared to recently weaned lambs. In agreement with these authors, we would argue that these observations indirectly suggest that larval development may be sensitive to host immunity. Therefore, MP nutrition may affect larval development, although this hypothesis remains to be addressed.

To a variable extent, ingested PSM are excreted intact or partly metabolized in the faeces (Acamovic and Brooker, 2005). This suggests that if an impact of PSM on egg hatching and larval development can be demonstrated, then PSM ingestion has the potential to reduce infection pressure through interference with development from egg to L₃, as this also takes place in the faeces. Indeed a large number of *in vitro* studies support the view that purified

PSM and extracts from PSM-rich forages can reduce egg hatchability and larval development. This has been shown for commercial CT extracts (Athanasiadou et al., 2001a; Butter et al., 2001; Max, 2010) and extracts from tanniferous forages (Molan et al., 2000; Molan and Faraj, 2010), tanniferous bark (*Z. nummularia*) and fruit (*A. nilotica*) (Bachaya et al., 2009) and tanniferous leaves (*Anacardium humile*) (Nery et al., 2010). Extracts from non-tanniferous *C. sativum* (Egualé et al., 2007) and *Plectranthus punctatus* and *Maesa lanceolata* (Tadesse et al., 2009) plants also demonstrated reduced egg hatchability and larval development. However, whilst reduced larval development in the faeces has indeed been demonstrated for CT-rich forages (Niezen et al., 2002), it could not be demonstrated for the low-CT chicory (Schreurs et al., 2002; Marley et al., 2003; Veldhuis, Kidane, Houdijk and Kyriazakis, personal communication). Furthermore, since variation in faecal moisture can affect larval development in the faeces (O'Connor et al., 2006), the higher faecal dry matter observed for a number of CT-rich forages (Niezen et al., 2002) could impact on larval development directly. Thus, PSM in general, and CT in particular, have the potential to reduce pasture infectivity through reducing faecal egg hatchability and larval development. Delivering PSM as anti-parasitic components at the site where its action is required would be analogous to oral administration of nematophagous fungi spores to reduce pasture infectivity through its action at a faecal level (e.g. Faedo et al., 2000).

2.3. Controlling larval challenge from the pasture

To complete their life cycle, L₃ larvae need to be ingested and this is facilitated through vertical migration onto the forage and host grazing behaviour. The latter presents a greater risk of parasitism than browsing. However, since sheep would only browse if forage availability and/or quality are low, they have not evolved as browsers, in contrast to goats. Their browsing feeding behaviour can be considered an evolutionary adaptation to minimise parasite exposure, which may have reduced the need for goats to rely on acquired immunity to control parasites (Hoste et al., 2010). Reduced L₃ intake may arise from MP supplementation if substitution occurs, i.e. a displacement of forage intake due to the volume of supplemented foods offered (AFRC, 1993). However, the authors are unaware of studies quantifying this possible mode of action. Nutritional strategies that impact on larval motility may reduce the rate of vertical migration and thus reduce larval challenge. Several *in vitro* studies have shown that L₃ motility and migration ability is reduced in the presence of CT extracts (Lorimer et al., 1996; Molan et al., 2000, 2004; Manolaraki et al., 2010), and chicory-extracted sesquiterpene lactones (Molan et al., 2003a). Furthermore, Manolaraki et al. (2010) showed *in vitro* that non-CT PSM in extracts from *Pistacia lentiscus* and *Ceratonia siliqua* also have larval migration inhibition capacity. Studies performed at faecal level support the above observations: the motility of lung worm larvae extracted from faeces of deer grazing chicory was lower compared to those derived from deer grazing pasture (Schreurs et al., 2002). Thus, due to their effects on parasite motility, selected PSM may have the potential to reduce

vertical L₃ migration and thus minimise host exposure to parasites.

Typically, 50% of L₃ larvae are found on the first 2 cm of conventional grasses, whilst less than 5% will be at 5 cm or higher (Familton and McNulty, 1997). It has been suggested that the number of L₃ present at the latter stratum depends on plant structure. For example, the presence of epidermal outgrowth, such as trichomes on stems and leaves of various herbage species (Moss and Vlassoff, 1993; Niezen et al., 1998), or at larger surface area of leaves, such as chicory compared to perennial rye grass (Marley et al., 2006), may impede vertical larval migration on the sward. The consequence would be that at similar grazing depths, the grazing hosts would encounter fewer parasites, thus effectively facing reduced challenge. Scales et al. (1995) has already speculated that the latter may be one of the mechanisms responsible for reduced FEC in sheep grazing chicory.

Thus, many studies support the view that MP supplementation and grazing on PSM-rich bioactive forages can modulate parasite epidemiology (Fig. 1). Although the effects of each strategy on contamination, development and challenge differ, the overall outcome would be a reduced larval uptake, which can greatly reduce the penalty of parasitism on performance in parasite-naïve lambs (Coop et al., 1982). Indeed, the vast majority of the studies referred to in previous sections reported that MP supplementation and grazing on PSM-rich bioactive forage increased growth of lambs, kids and deer. This improved productivity is likely to have a multi-factorial basis, which is beyond the scope of this review, but it may arise from increased resilience (Coop and Kyriazakis, 1999), a production response *per se*, reduced worm mass (Vagenas et al., 2007) and possibly from a reduction in parasite-induced anorexia (Kyriazakis, 2010). Whilst the consequences of nutritional strategies on productivity are referred to where appropriate, below the focus will be on discussing whether they may have arisen from nutritionally manipulated parasite epidemiology.

3. Combining nutritional strategies to manipulate parasite epidemiology

Anti-parasitic efficacy of MP supplementation and bioactive forage feeding as nutritional strategies when used separately is usually considerably lower than that which can be achieved through the use of pharmaceuticals, although it has been argued that the latter may not necessarily be required nor desired (Ketzis et al., 2006). In the context of this review, the rationale for combining non-chemical parasite control strategies would be to modulate parasite epidemiology to a greater extent than possible when the strategies are used in isolation. Athanasiadou et al. (2008) reviewed several combinations of nutritional alternatives and other non-chemical strategies, including copper oxide wire particles (COWP) and genetic selection for resistance to parasites. COWP combined with MP supplementation or sericea lespedeza (Burke et al., 2007) additively reduced FEC. However, MP supplementation did not further reduce the already low periparturient FEC in ewes selected for low FEC (Kahn et al., 2003a,b). Also, lambs

grazing subsequently on the bioactive forage chicory and the high-protein forage sulla (Tzamaloukas et al., 2005b) or lambs fed high-protein diets combined with quebracho CT extracts (Athanasiadou et al., 2001b; Butter et al., 2000) did not show the expected synergistic effects of combined bioactive forage and MP supplementation on host resistance (Athanasiadou et al., 2008).

Here we propose that combined nutritional strategies have the potential to result in additive benefits on host resistance, if their components affect parasite epidemiology through targeting different epidemiological drivers, or the same drivers but to different extents. These drivers include different sources of infection (ewes or lambs), different processes in the parasite life cycle (contamination, development or challenge; Fig. 1) and different phases of acquired immunity to parasites (acquisition or expression of immunity). Below, we address this epidemiological framework for temperate production systems, reporting studies we have recently completed, where MP supplementation of parasitized ewes, which started prior to turnout, was combined with chicory grazing (Kidane et al., 2010a, 2009b,c). The expectation was for additive effects on resistance to parasites in lambs, since these strategies not only target different phases of acquired immunity (expression of immunity in ewes, and acquisition of immunity in lambs) but also different drivers of parasite epidemiology (ewes and lambs as infection for lambs) and different parasite life cycle processes (Fig. 1), i.e. contamination (MP supplementation and chicory grazing) and challenge (chicory grazing only).

3.1. Combining nutritional strategies in temperate production systems

Any parasite control strategy should aim to reduce pasture infectivity (Torres-Acosta and Hoste, 2008), as it is a key factor in parasite-reduced performance in growing lambs (Coop et al., 1982). As we have shown before, pasture infectivity arising from ewe and lamb FEC can be reduced through MP supplementation and chicory grazing, respectively. Their combination would be expected to result in a greater reduction in pasture infectivity, and thus a larger improvement of lamb performance. We therefore hypothesized that ewe MP supplementation and grazing of ewes with their lambs on chicory would additively lower lamb FEC and increase lamb growth. In addition, effects of chicory grazing may be more pronounced in the absence of maternal MP supplementation. The outcomes of the studies described below are summarized in Table 1.

In the first study, Scottish Mule ewes (Scottish Blackface × Bluefaced Leicester crosses) and their 24 day-old twin Suffolk cross lambs were used to assess effects of maternal MP supplementation and subsequent ewe and lamb grazing on newly established chicory on lamb FEC and growth (Kidane et al., 2010a). *T. circumcincta*-infected ewes were turned out with their lambs onto parasitologically safe grass/clover pasture, and continued to be experimentally infected for 5 weeks, during which half of the ewes received extra MP through xylose-treated soybean meal supplementation at 400 g per head per day in elevated feeding troughs. Hence, ewes were the main source of

Table 1

Lamb mean logFEC (epg, with also backtransformed means), body weight gain (BWG, g/day), final body weight (BW, kg) and number of trigger drenches required (drench, *n*) of ewes supplemented (HP) or not (LP) with high metabolizable protein (MP) xylose-treated soybean meal whilst grazing grass/clover (Grass) or pure stands of chicory (Chicory).

Feeding strategies		LogFEC	BWG	Final BW	Drench
Exp. 1 [*]	Grass-LP	2.05 ^a (111)	169 ^a	38.7 ^a	
	Grass-HP	1.96 ^a (91)	160 ^a	42.1 ^{ab}	
	Chicory-LP	1.64 ^b (42)	200 ^b	40.8 ^{ab}	
	Chicory-HP	1.62 ^b (42)	209 ^b	44.7 ^b	
	s.e.d.	0.073	16.8	2.30	
Effects (<i>P</i> -values)	MP	0.333	0.982	0.056	
	Forage	0.001	0.009	0.194	
	MP [*] Forage	0.552	0.457	0.892	
Exp. 2 [*]	Grass-LP	2.36 ^a (252)	105 ^a	24.4 ^a	
	Grass-HP	2.25 ^{ab} (196)	130 ^{ab}	29.3 ^{ab}	
	Chicory-LP	1.92 ^{bc} (91)	152 ^{bc}	28.4 ^{ab}	
	Chicory-HP	1.79 ^c (73)	168 ^c	32.3 ^b	
	s.e.d.	0.155	17.6	2.67	
Effects (<i>P</i> -values)	MP	0.297	0.141	0.048	
	Forage	0.003	0.010	0.100	
	MP [*] Forage	0.906	0.725	0.816	
Exp. 3 [*]	Grass-LP	2.03 (129)	122 ^a	27.1 ^a	2.0 ^a
	Grass-HP	2.11 (146)	141 ^{ab}	32.8 ^b	1.7 ^a
	Chicory-LP	1.83 (79)	158 ^{bc}	33.7 ^b	1.6 ^a
	Chicory-HP	1.84 (81)	187 ^d	40.0 ^c	0.7 ^b
	s.e.d.	0.138	10.6	1.63	0.33
Effects (<i>P</i> -values)	MP	0.714	0.014	0.001	0.045
	Forage	0.043	0.001	0.001	0.013
	MP [*] Forage	0.746	0.505	0.804	0.197

^{*} MP supplementation of parasitized ewes, which started prior to turnout, either preceded clean chicory grazing (Exp. 1; Kidane et al., 2010a), concurred with clean chicory grazing (Exp. 2; Kidane et al., 2009b) or concurred with already infested chicory grazing (Exp. 3; Kidane et al., 2009c). Trigger drench was used in Exp. 3 only. Within each experiment, values with similar superscript did not differ (LSD comparison, *P* < 0.05).

initial infection for their lambs. Ewes and lambs then grazed the safe pasture for an additional 6 weeks before they were able to be moved onto newly established chicory or grass/clover swards. The ewes were removed after 3 weeks whilst the lambs grazed the same pastures for another 6 weeks. Hence, ewes and lambs were sources of infection on the newly established pastures.

MP supplementation reduced ewe FEC on the safe grass/clover pastures, whilst their lambs had lower FEC in the first few weeks only and grew faster than lambs from unsupplemented ewes. On the newly established pastures, chicory grazing, but not previous MP supplementation, reduced ewe FEC, although overall ewe FEC was low. Lambs grazing chicory had consistently lower FEC and grew faster than lambs grazing grass/clover, whilst previous maternal MP supplementation did not affect lamb FEC and growth rate but there were additive effects on final body weight (Table 1). Terminal pasture larvae counts were lower for chicory than for grass/clover plots. Despite the fact that the conditions of the epidemiological framework were met, i.e. maternal MP supplementation and chicory grazing targeted the host in different phases of acquired immunity, drivers of parasite epidemiology and parasite life cycle processes (Fig. 1), additive effects on lamb FEC were not observed. We have argued that the absence of such additive effects is likely to have resulted from the sequential rather than concurrent application of these alternatives (Kidane et al., 2010a). Therefore, the subsequent two experiments assessed the impact of concurrent maternal

MP supplementation and chicory grazing on parasite epidemiology.

In the second experiment, Scottish Blackface ewes and their 31 day-old twin Scottish Blackface lambs were used to assess the effects of maternal MP supplementation and concurrent grazing on second season, parasitologically clean chicory on lamb FEC and growth (Kidane et al., 2009b). *T. circumcincta*-infested ewes were turned out with their lambs and continued to be experimentally infected for 4 weeks, whilst half of the ewes received xylose-treated soybean meal at 350 g per head per day until weaning when lambs were 14 weeks old. Ewes were then removed, and lambs grazed the same pasture for another 9 weeks. As above, ewes were the main source of initial infection for the lambs.

In contrast to the first study, MP supplementation did not affect FEC of the Scottish Blackface ewes. Maternal MP supplementation also did not affect lamb FEC but tended to increase lamb growth (Table 1). The absence of effects of maternal MP supplementation on ewe FEC in the presence of a small improvement of lamb growth may suggest that MP was not sufficiently scarce in the absence of supplementation (Coop and Kyriazakis, 1999). However, it has also been shown that resistance to *T. circumcincta* in Scottish Blackface ewes is not sensitive to MP scarcity, in contrast to that in Scottish Mules (Kidane et al., 2010b). Whilst chicory grazing also did not affect ewe FEC, it significantly reduced lamb FEC and increased growth, with additive effects of MP supplementation and chicory

grazing on final body weight (Table 1). The absence of a chicory effect on ewe FEC in the presence of a consistent effect of chicory on lamb FEC and growth rate is consistent with earlier studies (Athanasiadou et al., 2007). These results suggest that turnout on parasitologically safe chicory has great potential to affect parasite epidemiology, and that maternal MP supplementation and chicory additionally improve sheep performance (Kidane et al., 2009b). However, predicting additive effects of nutritional strategies on parasite epidemiology needs to take into consideration their interactions with host breed and/or genotype. Therefore, the last experiment in this series, the impact of concurrent maternal MP supplementation and chicory grazing on parasite epidemiology, was assessed using Scottish Mules, which have higher nutrient requirements than Scottish Blackface ewes (Kidane et al., 2010b).

Scottish Mule ewes and their 31 day-old twin Suffolk cross lambs were used to assess the effects on lamb FEC and growth of maternal MP supplementation and concurrent grazing on already-infested chicory (Kidane et al., 2009c). *T. circumcincta*-infected ewes were turned out with their lambs on grass/clover or chicory swards grazed by *T. circumcincta*-infested ewes and lambs in the previous season. Thus, ewes and overwintering pasture infectivity were initially the main sources of infection. Initial pasture infectivity did not differ between grass/clover and chicory plots, and half of the ewes received xylose-treated soybean meal at 400 g per head per day until weaning when lambs were 14 weeks old. Ewes were then removed, and lambs grazed the same pasture for another 9 weeks. Since pastures were already infested, a trigger drench was introduced; lambs were drenched when showing diarrhoea, absence of body weight gain over fortnightly intervals and/or FEC > 1000 eggs per gram.

The results from this experiment showed that MP supplementation but not chicory grazing reduced ewe FEC during the first 3 weeks post-turnout, whilst both nutritional strategies independently increased lamb growth (Table 1). This suggests that the greatest benefits on lamb growth arose from the combined maternal MP supplementation and chicory grazing, whilst even that combination may still not have been adequate for maximal lamb growth (Kidane, 2010). However, during the first 16 weeks post-turnout, maternal MP supplementation did not affect lamb FEC, whilst the latter tended to be lower in lambs grazing chicory (Table 1). This suggests that the higher growth rates due to maternal MP supplementation and chicory grazing may have arisen to a greater extent from their additional nutrient input rather than from their anti-parasitic properties. The short-lived reduction in ewe FEC arising from MP supplementation may have had a limited effect on the infectivity of already infested pastures, as often less than 1% of excreted worm eggs may eventually be picked up by grazing hosts as L₃ (O'Connor et al., 2006; Familton and McAnulty, 1997). However, it cannot be excluded that, to some extent, the benefits arising from chicory on lamb growth may have been due to reduced L₃ vertical migration (Marley et al., 2006), as the resulting lower larval intake would not necessarily result in lower FEC (Coop et al., 1982; Hong et al., 1987).

From 16 weeks post-turnout onwards, an increasing number of trigger drenches were required, which biased effects of MP supplementation and chicory grazing on FEC. However, by the end of the experiment, maternal MP supplementation and chicory grazing had resulted in a reduced trigger drench requirement of 31% and 40%, respectively (Table 1). Thus, combining maternal MP supplementation and chicory grazing has the potential to reduce anthelmintic input and improve lamb productivity. Our data suggest that this reduced drench input was mainly the outcome of improved resilience rather than modified parasite epidemiology.

In summary, combining maternal MP supplementation with chicory grazing can additively accelerate parasitized lamb finishing and reduce reliance on anthelmintics, whilst each strategy has independent, non-additive effects on parasite epidemiology that are sensitive to level of pasture infectivity and host genotype. Accounting for the latter factors in future experiments may demonstrate the expected additive effects.

3.2. Combining nutritional strategies in tropical production systems

The principles developed above could be applied to address the possibility of using (combined) nutritional strategies to control gastrointestinal nematodes in tropical production systems. Torres-Acosta et al. (2004, 2006) reviewed a number of supplementation experiments on parasitized small ruminants maintained in tropical systems and concluded that, although opportunities for nutritional improvement of host resistance and resilience exist, outcomes of supplementation studies are consistent in terms of improved resilience but appear contradictory and even confusing for effects on resistance, especially where supplementation during the wet season is concerned. For this reason, the epidemiological framework developed here may assist to identify approaches for effective tropical nutritional control strategies. As for temperate systems, the strategy of combining nutritional alternatives to control gastrointestinal parasitism in the tropics should take into account the epidemiology of the infection and the availability and composition of the feedstuffs offered, including those offered as supplements (Torres-Acosta et al., 2006).

As shown repeatedly, the epidemiology of gastrointestinal parasitism in the tropics depends greatly on environmental conditions. During the dry season survival of gastrointestinal nematodes is reduced, whereas larval development and infection pressure is consistent throughout the year in the humid tropics (Torres-Acosta et al., 2006). Availability of feedstuffs is a major issue during the dry season in the tropics, with both protein and energy being undersupplied; this would be expected to have consequence on both the resistance and resilience of ruminants exposed to gastrointestinal parasites (Torres-Acosta et al., 2006). Finally, and this is an issue that has not been considered previously, there is a high positive correlation between nitrogen content and concentration of PSM in tropical forages (Acamovic and Brooker, 2005). This implies that provision of tropical forages, such as access to foliage from leguminous trees (Nguyen et al., 2005), will provide

additional nutrients, and at the same time could have direct anthelmintic effects on gastrointestinal parasitism. The latter would be expected to have effects on parasite excretion over and above the effects that may accrue due to improved resilience. On the basis of the above observations the following predictions can be made.

Nutrient supplementation during periods when both nutrient availability and parasite dispersion is low in tropical systems, i.e. the dry season, would be expected to yield mainly benefits on resilience. This would be observed even when animals are supplemented with rumen degradable protein, such as arising from a soybean and sorghum meal mixture (Torres-Acosta et al., 2006). However, since provision of such resources is unlikely ever to be adequate in these systems, one would expect to see only small effects on resistance to parasites (Coop and Kyriazakis, 1999, 2001). Indeed, experiments recently reviewed by Knox et al. (2006) and Hoste et al. (2005) are consistent with this view. In contrast, Louvandini et al. (2006) observed that protein supplementation improved weight gain during the wet season whilst this benefit was lost during the dry season. Supplementation resulted in reduced FEC during the wet and dry season, although during the latter FEC increased at the same rate in supplemented and control sheep. For such reasons, it might be beneficial if combined nutritional strategies are applied through provision of forages that are high in both nutrients and anti-parasitic PSM, such as fodder trees (*Leucaena* and *Acacia* spp.). Combining supplementary feeding with COWP (which could be considered as a model for anti-parasitic PSM), did not reduce any further worm burdens than when applying these strategies in isolation to naturally infected browsing goats (Martínez Ortiz de Montellano et al., 2007). However, the authors identified that infection pressure was relatively low. Thus, provided that there is a significant infection pressure, one would expect to see additional effects on parasite burdens arising from the anti-parasitic effects of the PSM. This expectation remains as yet untested, but as hypothesized above it would be expected to accrue additional benefits from reduced burdens and excretion of parasites, as demonstrated through *in vivo* and *in vitro* assays (Akkari et al., 2008; Bachaya et al., 2009). However, this strategy is unlikely to accrue benefits on parasite epidemiology mainly because helminth survival and infection pressure is relatively low during dry seasons.

During the wet season and in the humid tropics, grazing and browsing ruminants could benefit from significant improvements in forage availability and diet quality, although improved resilience can still arise from supplementary feeding even in the presence of high-protein forages (Landa-Cansigno et al., 2005). At the same time, however, animals also endure a sustained helminth challenge that may affect their health, productivity and even cause death. On this basis, additional benefits would be expected if animals were given access to forages high in PSM, such as foliage from multipurpose trees (Nguyen et al., 2005). There are several indigenous plants in the tropics that are high in PSM and have the potential to affect gastrointestinal parasitism in ruminants. These plants include species of *Lepedeza*, *Acacia*, *Leucena* and *Lysiloma* as indicated above. Indeed, it has been shown that extracts from

these plants have very strong anti-parasitic effects *in vitro* (Bahuaud et al., 2006). In theory, consumption of such plants would be expected to confer advantages on both resilience and resistance of parasitized animals. However, whether this will impact on existing pasture infectivity remains to be identified. In addition, the challenge of incorporating such plants in small ruminant production systems would be to ensure that animals consume these forages, especially when they also have access to other feed resources during the wet season, and that this consumption is significantly high enough to affect gastrointestinal parasites (Brunet et al., 2008a). As many of these plants have antinutritional effects, they are frequently accompanied by reduced intake, for example as observed for cassava (*Manihot esculenta*) foliage (López et al., 2007) and other negative consequences. The beneficial effects from the consumption of forages high in PSM content must outweigh any potential negative consequences (Houdijk and Athanasiadou, 2003). To what extent this reduces exploitation of such bioactive plants as supplements in tropical small ruminant systems is currently being investigated (Brunet et al., 2008b; Martínez Ortiz de Montellano et al., 2010). Thus, high PSM forages can play a role in dry seasons through increasing resilience, and during wet seasons to increase both resilience and resistance.

4. Suggestions for further research and implications for parasite control strategies

Our systematic review of the literature for the possibilities of MP supplementation and bioactive forages to modulate parasite epidemiology (Fig. 1) has been described qualitatively; its quantitative aspects could be brought together within an epidemiological framework to predict the magnitude of nutritional strategies on pasture infectivity. In addition, the review has identified several paucities of information, which may be subjects for future studies. For example, it is not known whether MP supplementation affects egg hatching and larval development, and whether nutritionally induced variation in faeces consistency is important for egg hatching and larval development. To assess whether *in vitro* PSM effects on hatching, larval development and motility are relevant, the impact of faecal PSM on these parameters *in situ*, and its relevance under practical grazing conditions, needs to be further assessed. The increasing number of ethnopharmacological studies showing a scientific basis for traditionally used bioactive plants provides opportunities to identify novel anti-parasitic PSM.

We have discussed our recent work on combining maternal MP nutrition and chicory grazing within the bounds of our epidemiological framework. To the best of our knowledge, these studies are the only ones available to address the framework. We would like to suggest that the framework developed could be used as a basis to further assess the combination of any parasite control strategies, including nutritional ones. In particular, periparturient MP supplementation could be combined with bioactive grazing immediately post-turnout or in continuous (tropical) grazing systems, to target the complete periparturient period, and under different infection

pressures. Such studies should include methodologies to assess the impact of (combined) nutritional strategies on pasture infectivity (Kahn et al., 2003b), as there is a paucity of such vital information. In addition, optimal use of nutritional strategies may arise from targeting animals that would most benefit from them. The recently developed targeted selective treatment approach, which uses deviation from predicted weight gain as a basis to identify lambs in need of anthelmintic treatment (Kenyon et al., 2009), may be applied under temperate conditions to provide such lambs short-term access to pure stands of chicory instead. This may have the potential to further reduce reliance on anthelmintics and accelerate lamb finishing.

The ultimate aim of any parasite control strategies would be to bring the level of parasitism below the economic threshold, defined as the maximum number of adult and/or larval parasites that a host can accommodate without experiencing a decrease in production parameters (Vercruyse and Claerebout, 2001). Hence, for the economic evaluation of (combined) nutritional strategies as alternatives for parasite control, impact on resistance may be less important than impact on resilience. In discussions with end-user groups, it is often suggested that nutritional control of gastrointestinal nematodes is expensive, which stems from higher costs of supplements and crop establishment compared to the direct costs of anthelmintic drench. However, studies taking into account improved resilience and/or production responses *per se*, are showing that nutritional parasite control may indeed be cost-effective (Magaya et al., 2000; Torres-Acosta et al., 2006; Tibbo et al., 2008). Because commodity prices fluctuate within and between seasons, and variable impacts on resistance may build up infectivity over time, long-term studies are required to establish the economic sustainability of nutritional control strategies.

In addition to economic sustainability, the biological sustainability of nutritional control strategies also needs to be considered, which may be especially relevant for anti-parasitic effects of bioactive forages. It is important to establish whether nematodes can adapt to nutritional strategies, akin to developing resistance to anthelmintic drugs. For example, it has been anecdotally observed that *H. contortus* and *T. colubriformis* larvae derived from sheep fed the tanniferous tropical legume *Calliandra calothyrsus* were more infective in donor lambs than those derived from lucerne-fed control sheep (Cresswell, 2007). Although the underlying mechanisms are not known, this observation clearly highlights the importance of evaluating the sustainability of nutritional parasite control strategies. With this objective, a series of parasite traits, including hatchability, survival, infectivity and fecundity, would need to be systematically assessed using different parasite species with hosts in different nutritional environments.

Lastly, recent technological advances have opened windows of opportunity to increase our understanding of mechanisms underlying host–nutrition–parasite interactions. It is now feasible to identify effector molecules, explore cellular pathways and evaluate their importance in these interactions, which could allow identification of targets in parasite epidemiology for (combined) nutritional

parasite control. Such applications have already demonstrated effects of nutrition on medicine and immunology. For example, gene expression profiling has revealed nutritional sensitivity of genes related to ageing, metabolic disease and diabetes (Muller and Kersten, 2003). Also, in combination with *in vitro* and *in vivo* models, biomic technologies are showing sensitivity of the cascade of pathways underlying regulation of lymphocytes and macrophages to dietary amino acids (Stephen and Avenell, 2006). High throughput molecular technologies, including next generation sequencing, will enable us to obtain holistic views of complementary functions between immunity and nutrition, and thereby to dissect the complex interactions between parasites, nutrition and immunity (Athanasiadou and Huntley, 2008). Protein and gene expression profiling of nematodes and their products may reveal nutritionally sensitive targets, whilst nutritional sensitivity of host transcripts may result in the detection of biomarkers that could identify susceptible animals to target for any parasite control strategy.

In conclusion, combining two or more parasite control strategies has the potential to result in additive benefits on host resistance. This may occur if the individual strategies target different drivers of parasite epidemiology, different processes in the parasite life cycle and different phases of acquired immunity to parasites. When we used this epidemiological framework to address published studies on combining nutritional strategies, we conclude that these showed the potential to additively improve host resilience and reduce reliance on anthelmintics, whilst effects on epidemiology have to date not shown the additive results expected. Whilst the latter may have arisen from overriding effects of, for example, existing pasture infectivity or host genetics, the epidemiological framework developed here could be used to identify future research opportunities for systematically assessing the impact of any combined control strategy on parasite epidemiology.

Conflict of interest

The authors declare that there is no conflict of interest.

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