CHAPTER 1

Review of the literature

1.1 Direct costs to the sheep industry

Gastrointestinal nematodes (GIN) cost Australian sheep producers more than any other disease with an estimated annual cost of $369 million (Sackett et al., 2006). Significantly, the majority of these losses are associated with production loss (87% (Sackett et al., 2006); 64% (McLeod, 1995)), rather than costs associated with treatment and prevention. Evidence also suggests that GIN contribute significantly to the occurrence and severity of flystrike, which is the second largest contributor to the cost of disease in sheep at $280 million per annum (Sackett et al., 2006). The cost of GIN to industry is influenced by sheep numbers and commodity prices; and depends significantly on estimations of decreased animal performance caused by the severity of GIN challenge.

The validity of presenting the ‘total’ cost of worms as a figure that represents the potential savings from practice change is questionable (Perry and Randolph, 1999). However, the process is valuable in demonstrating the size of the problem and assessing the benefits that may arise from improved control. Early studies, while thorough in describing methods for determining the economic impact of GIN, generally underestimated the numerous areas that GIN impacted on potential production loss (BAE, 1964, 1972). Wool production loss per year, assumed to be 113g/head in 1963 and 1970, accounted for more than half the economic costs attributed to GIN, estimated to total $281 million and $275 million (net present value, NPV) respectively (BAE, 1964, 1972). On a per head basis, the cost of GIN fell between these years from $1.78 to $1.58 (NPV) even though modelling in the later study was based on greater liveweight loss, lower wool quality and increased mortality than the earlier study. The introduction of thiabendazole in 1961 and its rapid and widely accepted adoption significantly reduced the cost of control, but was not credited for reducing production loss due to GIN (BAE, 1972).

To assess the impact of new technologies, increasing GIN resistance to drenches, and variability of seasons, these figures were updated in 1985 (Beck et al., 1985) with the cost of GIN increasing to $5.51 per head with an industry cost escalating to $670 million (NPV) due to the large national sheep flock. This estimate, informed by further study into the impact of GIN (Barger, 1982), was based on a 10% reduction in wool loss and 15% reduction in liveweight. This analysis also predicted that production loss from GIN accounted for 83% of the total cost of GIN. Seasonal variability across years may also significantly impact on the risk level associated with GIN. During periods of low risk of infection, costs may only be $4.00 per head compared to high risk seasons, with an increased the cost of $7.06 per head. Using a similar set of studies, McLeod (McLeod, 1995) attributed 64% of the estimated $293 million (NPV) cost of GIN to the Australian sheep industry to production loss. Inherent in these estimates was the calculation that the annual cost of GIN per head was approximately $9.10 per head for lambs and only $2.40 for ewes; perhaps reflecting the low wool price at the time.

The most recent review on the cost of GIN (Sackett et al., 2006) was able to build upon the earlier study of McLeod (1995) and incorporate a broader scope of variables that potentially affect costs and production loss (Table 1-1).

Table 1-1. Summary of assumptions used to estimate the cost of GIN in a northern, summer rainfall area (Sackett et al., 2006).

Control	Poor		Good	
	Weaners	Adults	Weaners	Adults
Wool loss (g)	90	175	45	90
Fibre diameter (μm) reduction	0.3	0.315	0.15	0.162
Bodyweight reduction (kg)	1	4	0	2
Fertility reduction (%)	0	6	0	3
Staple strength reduction (N/ktx)	10	10	5	0
Dags increase (%)	15	10	5	2
Cost of dags (¢)	2.5	1.5	0	0
Cost of crutching (¢/kg)	6.5	5	2.8	1
Drenches	4	3	4	3
Cost of drenches ($)	1.04	1.08	1.04	1.08
Increase in monitoring frequency	0	0	4	3
Cost of monitoring (¢)	0	0	28	21

Costs associated with GIN vary depending on climate and the sheep production system adopted (Sackett et al., 2006) (Table 1-2). Due to the number of sheep, the largest financial impact of GIN to the industry is in high winter rainfall dominant systems. In prime lamb production systems, the significant cost per head reflects decreases in bodyweight and fertility due to GIN.

Table 1-2. Summary of costs associated with GIN in the main climatic areas and production systems of the Australian sheep industry (Sackett et al., 2006).

Zone	Reduced Income ($)	Increased expenses ($)	Total ($)	Cost per head ($)
High rainfall, summer	19,980,954	2,973,541	22,954,495	5.93
High rainfall, winter	153,324,968	18,373,768	171,698,736	4.61
Sheep cereal	54,438,977	29,458,624	83,897,601	2.40
Prime lamb	82,465,267	8,092,137	90,557,404	8.51
Total	310,210,166	58,898,070	369,108,236	

Reviewing the cost of GIN over the last 45 years, it is evident that little progress has been made in reducing the cost of GIN infection. This is due to two main factors. First, increased knowledge about the broad impact of GIN on production systems and has been incorporated into recent economic analyses. Second, the adoption of anthelmintics and their management has failed to lower production loss associated with GIN. While strategic control programs have been modelled to show decreased production loss (McLeod, 1995), an increase in the most recent estimate of the cost of GIN suggest that such programs have not been adopted by the majority of industry (Sackett et al., 2006; Walkden-Brown et al., 2006). In contrast, the widespread adoption of mulesing and prevalence of chemical control has lowered both treatment costs and production loss caused by flystrike (Beck et al., 1985). Despite many new classes of anthelmintics being introduced since thiabendazole in 1962, estimated production loss has risen to be 87% of the total cost of GIN. This may be attributable to the increasing prevalence of anthelmintic resistance and the delivery failure of strategic worm control programs.

Reduced efficacy of treatments may significantly alter the cost of GIN. Comparing production attributes and disease status over 12 months in groups of sheep treated with either a benzimidazole (65% effective), a combination benzimidazole–levamisole (85% effective) or a moxidectin (100% effective) drench, Besier et al.(Besier et al., 1996) demonstrated that the cost of GIN increased significantly with increasing levels of anthelmintic resistance. Sheep given the 65% effective drench grew 450g less wool than sheep given the 100% effective treatment while sheep given the 85% effective combination drench grew 90g less wool respectively. The percentage of sheep scouring and the number of sheep deaths due to worms was also two and three times higher in the 65% effective and 85% effective treatments compared to the 100% effective treatment. The production losses in wool and sheep value equated to a cost of $6.60 and $2.45 for drenches of 65% and 85% efficacy respectively compared to fully effective treatment, highlighting both the importance of effective treatment, but also the economic threat of increased anthelmintic resistance (Besier and Love, 2003). Modelling the cost of resistance for a West Australian environment, Pech et al.(2009) predicted that an increase of initial resistance level from 2 to 10% would increase the cost of GIN by 58%, although this could abated by increasing levels of refugia. Treatment costs will also increase with increased prevalence of resistance to anthelmintics as treatment frequency will increase and effective drenches most likely being more expensive. However, as previously described, treatment costs are only a minor contributor to the total cost of GIN. The rise and impact of resistance to anthelmintic classes is further discussed in Chapter1.5.

The analyses presented clearly show the significant financial cost of GIN to the Australian sheep industry. Production loss, despite significant additional treatment options, have remained the major component of estimated financial losses over the large time period of available studies. Variations on the effect of GIN on production account for some differences between the studies, and further work is required to more accurately define the impact of GIN on all aspects of the production system. The literature also suggests that production loss will increase as resistance to anthelmintic classes increase. Of concern also is the limited impact that new anthelmintic classes have had on reducing the cost of worms. New approaches that aim to lower the production loss caused by GIN, and are able to be adopted by the industry are clearly required.

1.2 Measured effects of GIN on production

Measuring the effect of GIN challenge on animal production is beset with practical difficulties, influenced by type and number of parasite burden, management factors, environment and host species (Barger, 1982). These difficulties are exacerbated by the challenges and varying approaches to the provision of ‘worm free’ sheep for comparison. Often, the results presented from grazing studies may underestimate the true impact of GIN, with either ‘worm free’ sheep co-grazing with infected sheep and susceptible to larval challenge, or having suppressive treatments that are not entirely effective (e.g.(Johnstone et al., 1979). Penned animal studies may overstate the impact of GIN due to short time periods of measurements and acquisition of immunity that may be graduated throughout the year. Penned studies may also underestimate the effects of GIN as energy requirements are reduced in this environment (Barger, 1982). The presence of recently ingested juvenile stages of nematodes may be associated with significant production loss (Barger, 1982). Although this issue was identified in the classical study of Johnstone et al. (1979), worm egg counts of suppressive treated animals - grazed separately from other treatment groups - showed that they were still challenged by juvenile larvae and adult establishment. Studies with cattle have shown that following monthly treatment with levamisole, treated calves grazing separately gained 206kg, treated calves grazing with untreated calves gained 177kg, while untreated calves gained 168kg (Bryan, 1976). The lack of studies that compare treated animals grazing clean pastures and treated animals grazing infected pastures does not allow for the impact of L_3 larvae to be assessed. Despite the practical difficulties associated with measuring the impact of GIN, the following sections highlight the vast and varying impact that GIN have on production systems.

1.2.1 Feed Intake

A reduction in feed intake is recognized as a major feature of the pathogenesis of GIN (Parkins and Holmes, 1989) and can account for up to 40 - 90% of lost production (Van Houtert and Sykes, 1996). The level of feed intake reduction is dependant on the age of the host, stage of immunity and the burden and species of the parasite. In young sheep, reductions in feed consumption of between 10 and 30% are common and severe inappetence is demonstrated in animals that show clinical symptoms (Van Houtert and Sykes, 1996). However, when feed intake is expressed relative to body weight, effects are less pronounced (Sykes, 1983), with parasitized animals often associated with reduced rate of skeletal growth (Parkins and Holmes, 1989).

Reduction in feed intake coincides with the establishment of mature worms (Kyriazakis et al., 1994; Kyriazakis et al., 1998) and is dependant on the amount of larval challenge (Steel et al., 1980). In susceptible sheep trickle infected with *Trichostrongylus colubriformis,* no reduction in feed intake was noted at dose rates of 300 or 950 L_3 per week. Food consumption was significantly depressed with a weekly dose rate of 3000, 9500 and 30,000 L_3 with the maximal effect occurring between weeks 8 and 12 when food consumption was 71, 61 and 44% respectively of that of non-infected animals

(Steel et al., 1980). Reduction of feed intake in this magnitude due to larval challenge with *T. colubriformis* or *T. circumcincta* can occur without the presence of clinical signs (Coop et al., 1976; Coop et al., 1977). Mixed infections of *Haemonchus contortus* and *T. colubriformis* reduce intake more when compared to infections with *T. colubriformis* alone (Knox and Steel, 1999). Animals infected only with *H. contortus* do not typically show a reduction in feed intake (Knox and Steel, 1999; Wallace et al., 1998).

Recent studies have suggested that the reduction in feed intake is a component of the animals' immune response when challenged by GIN. Greer et al. (2005) demonstrated that it is perhaps the acquisition of immunity that provides the greatest challenge to maintaining food intake during GIN challenge, with feed intake resuming once immunity is required. For example, Greer et al. (Greer et al., 2008; Greer et al., 2005) trickle infected lambs with either *T. colubriformis* or *T. circumcincta* and compared feed intake of uninfected control lambs with lambs infected but immuno-suppressed by concurrent corticosteroid treatment. When compared with controls, infected lambs displayed a 30% reduction in feed intake from day 21 of infection, which continued until recovery at day 63. Feed intake of infected but immuno-suppressed lambs did not differ from uninfected controls. Feed intake also recovers immediately after anthelmintic treatment despite morphological damage to the digestive system (Angus et al., 1979). These findings suggest that the establishment of worms *per se* does not affect feed intake but with depression mediated by the immune response. Reduced feed intake appears to be a paradoxical response to GIN challenge by sheep, in conflict with the additional nutrients required by the host when challenged (Kyriazakis et al., 1998; Liu et al., 2005a). Further study to better understand the association between reduced feed intake and acquisition of immunity is required.

1.2.2 Nutrient Metabolism

Animals affected by GIN experience changes in gut morphology, the need to repair damaged tissue and an associated immune response. These changes may be connected with changes in nutrient metabolism, both in the absorption of nutrients from the gut and the endpoint of deposition. Changes in metabolism are a result of increased competition for available nutrients, with an increased demand from the immune system reducing production potential (Sykes and Greer, 2003). This section looks at major changes demonstrated in nutrient absorption as affected by GIN and effects on nutrient partitioning.

Damage caused by GIN to the intestinal tract has been associated with changes in nutrient metabolism. MacRae (1993) postulates that ‘overall metabolic consequences of the intestinal infection seems to involve the diverting of protein synthesis away from muscle and bone and towards repair, replacement and reaction to damage of the gut wall, to mucus production and to plasma or whole blood loss’. Physiological damage to the intestinal system caused by GIN is discussed in Chapter 1.3.2. Damage to the intestine does not appear to directly affect the digestibility and absorption of energy substrates, amino acids or peptides, though gastrointestinal (GI) tract site-specific differences may occur. In contrast, limited ability to absorb phosphorus, following infection with *T. colubriformis*, may result in stunted skeletal growth (Poppi et al., 1985). Of more importance is the use of absorbed nutrients in animals challenged by GIN compared to animals free of GIN challenge.

Effects of GIN challenge divert metabolisable protein from production to maintain integrity of the GI tract and mount an effective local immune response (Coop and Sykes, 2002). Demonstrating the competitive nature of GI tissue, Yu et al*.* (Yu et al., 2000) showed that this tissue when infected with *T. colubriformis* increased sequestration of amino acids by 24%. This increased demand for amino acids in the GI tract may cause the decreased levels of protein synthesis seen in muscle and within wool follicles of infected animals (Symons and Jones, 1975). The mobilisation and/or repartitioning of amino acids from muscle and wool synthesis is likely to be a result of the metabolic changes caused by GIN (Roy et al., 2003). This may be exacerbated further by the diversion of essential amino acids for production into maintenance of the GI tract and mounting an immune response. The demand for cysteine by the wool follicle is a critical factor controlling wool growth (Williams, 1995) but demand is also increased by inflammation of the GI tract caused by GIN (Adams and Liu, 2003). Differences in partitioning a mobile pool of amino acids can be manifested by animals that either (i) maintain production but fail to mount an effective immune response as measured by worm egg count (WEC) or (ii) minimise production at the expense of an apparent increased immune response. Hence, animals selected for low WEC have lower greasy fleece weights (Eady et al., 1998; Wheeler et al., 2008) as discussed in Chapter 1.3. In a production environment it is important to develop the right balance of protein use between GI tract repair, mounting an immune response, and maintaining production.

Increasing the supply of metabolisable protein to infected animals appears to facilitate a more effective immune response to infection as demonstrated by reduced WEC and the maintenance of production. In animals challenged with a moderate infection (3000 L_3/week) of *T. colubriformis*, supplementing low quality roughage diets with a source of protected protein substantially reduced production losses associated with infection and increased the rate of worm expulsion (van Houtert et al., 1995). Similar results were observed by Datta et al. (1998) in response to an increased protein supply during infection with *H. contortus* (Datta et al., 1998). Increased dietary protein improved liveweight gain, feed intake and immune response, as evident by an increase in eosinophil counts, antibody titres and reduced WEC. Stimulation of rumen microbial activity and microbial protein synthesis (and presumably rates of rumen outflow) via the addition of urea has also been shown to improve the production attributes of GIN challenged animals and limit WEC in young growing animals (Knox and Steel, 1999). Increase in energy supply has also been shown to reduce WEC during infections with *T. colubriformis* (Kahn et al., 2000). Significantly, short-term increase in protein supply to growing animals may have long-term benefits. In the study of Datta et al. (1998), animals with greater protein supply for 9 weeks maintained higher liveweight gain, increased wool production, higher antibody response to both *H. contortus* and *T. colubriformis*, and maintained lower WEC than non-supplemented animals over a 69 week period (Datta et al., 1999). Hence, protein supplementation to growing animals that minimises the nutritional restriction associated with GIN challenge may have life long consequences on productivity (Datta et al., 1999; Knox et al., 2003b). However, this effect does not appear to have been demonstrated again since this initial report.

1.2.3 Mortality

The most severe manifestation of GIN challenge is mortality, and in the case of *H. contortus*, it is probably the most important. Mortality rates as high as 68% and 31% have been recorded in uncontrolled infections in young and mature sheep respectively (Cohen et al., 1972; Gordon, 1964). While commercial production systems aim to limit mortality with anthelmintic treatment, mortality may still contribute significantly to the impact of GIN as indicated by experimental studies (Table 1-3).

Due to the pathogenicity of *H. contortus,* mortality rates are higher in areas dominated by this species and particularly so for animals less than 2 years of age. Anaemia and death are common consequences of *H. contortus* infection with the amount of blood loss determined by worm number, mass and egg production (Le Jambre, 1995). However, some infected sheep seem able to tolerate the pathogenic effects of *H. contortus* infection better than others as evidenced increased bodyweight, condition score and haematocrit (Roberts and Swan, 1982). In summer rainfall regions, mortality rates are also disproportionally high during Autumn (Barger and Southcott, 1978) for environmental reasons outlined in Chapter 1.2.

Table 1-3. Increase in mortality rate seen in animals with uncontrolled GIN challenge as opposed to animals with minimal infections when grazing.

Increased deaths (%)	Species (in order of dominance)	Reference
26-32%	*H. contortus*; *Trichostrongylus* spp.; *T. circumcincta*; *Nematodirus* spp.; *Cooperia oncophora*.	(Barger and Hamilton, 1978)
42.5%	*H. contortus*; *Trichostrongylus* spp.; *T. circumcincta*; *Nematodirus* spp.; *Cooperia oncophora*.	(Barger and Southcott, 1978)
29%	*Trichostrongylus* spp.; *T. circumcincta*; *H. contortus*	(Gordon, 1964)
22-56%	*Trichostrongylus* spp., *Teladorsagia* spp.	(Brown et al., 1985)

Adapted from Barger (1982).

1.2.4 Liveweight

Reductions in liveweight and liveweight gain are seen in parasitised animals largely as a consequence of reduced feed intake and adaptive changes in nutrient metabolism. Reduction in liveweight and liveweight gain has detrimental effects on survival, reproduction and livestock value. Reduced production during GIN infection is well documented in young sheep, both grazing (Table 1-4) and penned (Table 1-5). Although a wide variation in weight gains is found in young sheep due to reasons expressed earlier, all studies showed a significant reduction in liveweight gain.

Table 1-4. Selected studies demonstrating impact of mild GIN infections on production attributes of wool growth and liveweight gain compared to animals with no or minimal GIN challenge. Collated by Barger (1982).

Comparison	Dominant species and/or location	Reduced wool growth %	Reduced liveweight gain %	Reference
Untreated vs. drenched	*Trichostrongylus* spp. / New Zealand	23	43	(Brunsdon, 1963)
Untreated vs. TBZ 2-weekly	*Trichostrongylus* spp. / New Zealand	31	48	(Brunsdon, 1964)
Untreated vs. TBZ monthly	*Trichostrongylus* spp., *Teladorsagia* spp., *H. contortus,* / South Australia	15	32	(Banks et al., 1966)
Napthalophos vs. TBZ monthly	*Trichostrongylus* spp., *Teladorsagia* spp., *H. contortus,* / South Australia	9	15	(Banks et al., 1966)
Strategic vs. 2-weekly	*Teladorsagia* spp., *Trichostrongylus* spp., / West Australia	11	26	(Anderson, 1976)
Untreated vs. drenched, moved	*Trichostrongylus* spp. / New Zealand	-	79	(Brunsdon, 1976)
Untreated vs. 6 drenches	*Trichostrongylus* spp. / New Zealand	14	55	(Cottier et al., 1976)
Untreated vs. TBZ monthly	*Trichostrongylus* spp. / New Zealand	15	23	(McCleod, 1976)
2 drenches vs. weekly drench	Victoria	17	21	(Thompson et al., 1978)
Curative vs. suppressive	*H. contortus, Trichostrongylus* spp. / Northern Tablelands, NSW	12	16	(Johnstone et al., 1979)
Curative vs. suppressive	*Trichostrongylus* spp. ,*Teladorsagia* spp./ Hamilton, Victoria	13	14	(Johnstone et al., 1979)
Untreated vs. 6 drenches	*Trichostrongylus* spp. / New Zealand	-	58	(Morton, 1981)
Weekly vs. 3 drenches/year	*Teladorsagia* and *Trichostrongylus* spp., *H. contortus* / East Gippsland, Victoria	22	14	(Barton and Brimblecombe, 1983)

With natural mixed infections, Johnstone et al.(Johnstone et al., 1979) demonstrated that reduced weight gain was related to the frequency of parasite control and hence, WEC. This study was conducted in a summer rainfall environment with *H. contortus* dominant over the summer months. Treatment groups maintained WEC at monthly average values of 171, 221, 473 and 943 epg, and the corresponding live weight gain was 24.7, 23.7, 20.7 and 17.4 kg respectively over an 11 month period. Wool growth followed a similar pattern.

Clearly, GIN infection is associated with decreased liveweight gain in young sheep. Three factors dominate the extent of this effect. First, increased larval challenge increases production loss (Steel et al., 1980) although the extent of larval challenge without adult establishment has not been quantified. Second, production loss is dependent on the species of GIN. Mixed infections have a multiplicative effect on production rather than a simple additive effect (Knox and Steel, 1999) although increasing worm burden in these studies compared to sheep with single infections may confound this result. In production systems dominated by *H. contortus*, inclusion of effects on mortality indicates an overall effect on production is similar to challenges from *T. colubriformis* and *T. circumcincta*. Relative growth depression in infected animals adjusted for mortality may vary from 12 - 64% compared to uninfected animals (Albers et al., 1989). Third, the physiology of the host mediates production loss. This is covered in greater detail in Chapter 1.3.

Table 1-5. Reduction in liveweight gain and wool growth caused by GIN infection in young, penned sheep compared to uninfected. Adapted from Barger (1982).

Larval dose (larvae/week)	Species	Reduced wool growth %	Reduced weight gain %	Reference
17500	*T. colubriformis*	-	50	(Coop et al.)
28000	*T. circumcincta*	-	52	(Sykes et al., 1977)
9500	*T. colubriformis*	53	39	(Steel et al., 1980)
37500	*T. circumcincta*	25	9	(Symons et al., 1981)
3000 38000	*T. circumcincta* *T. colubriformis*	55	73	(Steel et al., 1982)
900 38000	*T. circumcincta* *T. colubriformis*	66	76	(Steel et al., 1982)
38000	*T. circumcincta*	25	30	(Steel et al., 1982)
3000	*T. colubriformis*	13	20	(Steel et al., 1982)
900	*T. colubriformis*	0	0	(Steel et al., 1982)

1.2.5 Wool growth

Wool growth is reduced in parasitised sheep and is associated with reduced feed intake and allocation of protein, particularly sulphur amino acids, to the immune system (Liu et al., 2003; Liu et al., 2005b). This is demonstrated by the extent of wool loss caused by GIN in a number of studies (Tables 1-5 and 1-6) and its relationship to the extent of liveweight loss. Limitation of sulphur amino acids caused by infection of *T. colubriformis* and *T. circumcincta* not only reduces wool growth, but also reduces staple strength and fibre diameter. Consequently, the number of tender fleeces from infected animals increases (Thompson and Callinan, 1981). Experiments that limit nutrition show similar reduction in fibre diameter and staple strength (Masters et al., 1998). Improving the nutrition available to an infected animal therefore lessens the effects of GIN on wool production (van Houtert et al., 1995).

Table 1-6. Measured attributes of weaners used by McLeod (1995) to assess impact of GIN with poor and good control relative to serially worm-suppressed sheep.

Measured Attribute	Reference	No or poor control	Good Control
Wool loss (GFW) (g)	(Barger and Hamilton, 1978)	450-860	
	(Barton and Brimblecombe, 1983)	1290	1460
	(Brown et al., 1985)	1040-930	
	(Lipson and Bacon-Hall, 1976)	480-1130 (13-31%)	
	(Thompson and Callinan, 1981)	760-1040	
Fibre diameter reduction (micron)	(Barton and Brimblecombe, 1983)	1.5	0.9
	(Brown et al., 1985)	1.5-1.7	
	(Thompson and Callinan, 1981)	1.33	
	(Lipson and Bacon-Hall, 1976)	0.4-1.5	
	(Albers et al., 1989)	0.39-0.79	
Tender fleeces % increase	(Thompson and Callinan, 1981)	11.8	
	(Lipson and Bacon-Hall, 1976)	4.3-38.7	
Staple Length	(Lipson and Bacon-Hall, 1976)	0.13-0.85	

In production systems dominated by *H. contortus*, wool loss is also significant but variable in magnitude (Johnstone et al., 1979). Effects of infection may also persist after treatment. Albers et al.(Albers et al., 1989) observed that a five week infection period following an intra-ruminal bolus of 11000 L_3 *H. contortus* larvae resulted in a reduction in clean wool growth of 1.4 to 15.7 % (mean reduction of 6.8%) in the four months after the infection was truncated. Over the same period, reduction in fibre diameter ranged from 0.39 to 0.79µm (mean 0.57µm), highlighting the prolonged depression in wool growth following cessation of infection. Mixed infections of *H. contortus* and *T. colubriformis* reduce wool growth more than single infections of either species (Knox and Steel, 1999), concomitant with multispecies effects on feed intake.

1.2.6 Reproduction

Studies directly linking reduced reproductive performance in sheep with GIN challenge are limited. The general consensus is that reduced fertility in sheep challenged by GIN is through the associative effects of reduced liveweight and body condition, and not directly associated with infection. Assumptions made regarding the impact of GIN on reproductive performance are generally based on effects of GIN on liveweight or body condition score. Reduction in weaner growth rate and ewe weight caused by GIN can prevent target weights and body condition scores to be met for optimal lifetime reproductive performance (Robinson et al., 2002). Inadequate pre-weaning nutrition can also affect reproductive performance. Lambs reared on a low plane of nutrition for 3 months produced 17% fewer lambs and weaned 15% fewer lambs than those reared on a high plane of nutrition over the subsequent six year period (Langlands et al., 1984a). As reproductive ability can be estimated by body condition and changes in liveweight (Dunn and Moss, 1992), it can be assumed that reproductive potential is reduced in animals exhibiting deleterious effects from GIN infection. Using these principles, Sacket et al*.* (2006) estimated that a 6% reduction in fertility for summer rainfall production areas can occur due to GIN infection.

Few studies directly link GIN to reproductive performance. In a New Zealand study with predominantly *H. contortus* infection in March and *Trichostrongylus* spp. and *Cooperia* spp. at other times of the year, infected sheep scanned fewer foetuses (12.5 per 100 ewes) and had fewer multiple pregnancies compared to control sheep with GIN – suppressed treatment (West et al., 2009). Also in this study, lambs from multiple pregnancies were 2.5kg heavier at weaning with GIN-suppressed treatment, although no effects were evident in single and triplet lambs from ewes of the two groups. Measuring the effect of GIN on reproductive ability, Fernandez-Abella et al*.*(2006) showed that ovulation rates decreased with a trickle L_3 challenge of 87% *H. contortus*, 10% *Trichostrongylus* spp. and 3% *Oesophagostomum* spp. Moderate effects on liveweight (40 vs. 38.2 kg) and condition score (3.5 vs. 3.0) between control and challenged groups were associated with fewer corpora lutea per sheep. Control sheep showed no change in ovulation rate over the experimental period (from 3.3 ± 0.6 to 3.5 ± 0.5 developing follicles) compared to challenged sheep that showed a reduction from 3.4 ± 0.5 to 2.2 ± 0.2 developing follicles, potentially representing fewer lambs born that cannot be accounted for by differences in body weight or condition score. In a separate study, sheep challenged with *T. circumcincta* showed no reduction in ovulation rate, reduction in body weight or condition score compared to control sheep, suggesting that the severity and type of infection influences reproductive performance (Jeffcoate et al., 1988). Despite recent studies demonstrating the importance of reproduction as a determinant of farm profitability, clarification on the influence of GIN on reproductive performance remains to be established. Management of sheep prior to mating to meet recommended weight and condition score targets may mask the cost of GIN on reproductive performance.

1.2.7 Milk production

Evidence of the impact of GIN challenge and consequences for lactational yield and pre-weaning growth of grazing sheep is equivocal. Investigating the impact of GIN on the pregnant and lactating ewe, Thomas and Ali (1983) found that infection with *H. contortus* larvae for a period of 6 weeks prior to and 6 weeks after lambing, reduced milk yield by 23% when compared with uninfected control ewes. There was no effect of infection on birth weight or surprisingly on weight of lambs at 6 weeks. Access to creep feed for lambs in this study most likely removed significant effects of infection. Under commercial grazing conditions, where creep feed is not generally available, effects of infection on milk yield are more likely to transcribe to reduced lamb growth and, as a consequence, reduced weaning rates (Everett-Hincks and Dodds, 2008; Jordan and Mayer, 1989).

Similar deleterious effects on maternal production have been observed in response to infection from *T. circumcincta* (Leyva et al., 1982). Milk production decreased by 17% in infected groups compared to control groups, but lamb birth weight and growth rates were not significantly affected. In this study, lamb access to additional feed may have confounded results. Weight loss in infected ewes during pregnancy and lactation was observed for *T. circumcincta* (Leyva et al., 1982) and *H. contortus* (Thomas and Ali, 1983) infection. In a grazing system with sheep artificially challenged with 3000 *H. contortus* L_3at 130-145 days gestation, milk yield (703 vs. 1043 ml/d) and lamb growth rate (130 vs. 236 g/d) were reduced with infection (Cobon and O'Sullivan, 1992). The differences were associated with lamb mortality, significantly increasing in lambs from infected ewes compared to their treated counterparts (28% vs. 12%). As differences were not detected in worm egg counts (WEC) of the lambs, it suggests that the different growth rates and mortality rates are an effect of the GIN challenge in the ewes. Differences in lamb growth rates from lambs reared by parasitised or treated ewes (78 ± 13.1 vs. 104 ± 16.1 g/day) were not significantly different from day 75 after lambing to weaning at 140 days. The low prevalence of natural *H. contortus* infections during spring lambing periods on the Northern Tablelands of NSW may decrease the potential of GIN to impact on lamb survival.

Comparing the effects of GIN infection on pre-weaning lamb production between safe and contaminated pasture, Bailey et al. (2009b) showed that preparation of clean spring lambing paddocks on the Northern Tablelands increased weaning weight. In contrast, Waller et al.(Waller et al., 1987) showed no significant difference in growth rates of lambs. Lambs on contaminated pasture and clean pasture had similar growth rates from 0 to 14 weeks (0-6 weeks 202 v 194g/d; 6-14 weeks 199 v 176g/d) despite dams of lambs on contaminated pasture having significantly higher *T. colubriformis* and *T. circumcincta* worm egg counts. It is possible that the insensitivity of lamb weight gain to maternal infection and pasture infectivity may be a result of changes in grazing behaviour such that lambs reared by infected ewes began grazing at an earlier age. These findings are similar to those found in early studies on the Northern Tablelands (Waller et al., 1987), suggesting that production potential of lambs may not be affected by parasites during spring lambing, and that GIN control of young stock is best advised at weaning.

The above studies show that although GIN impacts negatively on ewe body weight and milk production, adverse effects on birth weight or lamb weaning rate are not always observed. Improving the nutrition of infected ewes through protein supplementation does not always improve production as measured by lamb weight or lamb weaning rate although increased protein supply has been shown to decrease WEC and limit bodyweight loss in the ewe (Donaldson et al., 2001). As lactation imposes an increase in nutrient requirements, partitioning of nutrients to the immune system may be reduced commensurately (Coop and Kyriazakis, 1999). This theory is supported by Houdijk et al. (2003) who showed that increasing protein supply increased milk production without reducing *T. circumcincta* worm burden. Once maximum milk production threshold was reached, a reduction in worm burden was seen. This apparent prioritisation for milk production appears to reduce the impact of GIN challenge in ewes on lamb birth weight and growth. However, in an environment with low protein availability or *H. contortus* infection, milk yield would still be expected to be reduced alongside an increase in WEC (Cobon and O'Sullivan, 1992).

1.2.8 Scouring

Scouring is an important issue in Merino sheep grazing improved pastures and significantly impacts management and wool value (Larsen et al., 1995). Affected sheep accumulate faeces around the breech, increasing direct costs through increased crutching costs and lost wool. Affected sheep are also more disposed to fly strike with associated mortality and reduction in wool quality (Colditz et al., 2005; Morley et al., 1976). Predisposition of sheep with scouring to flystrike not only imposes financial costs, but also increases requirements for mulesing which consumers may be ethically opposed too (James, 2006). Reducing GIN challenge to reduce scouring and flystrike has been well established with several studies demonstrating that reduced worm challenge lowers the incidence of flystrike (Brown et al., 1985; Morley et al., 1976; Watts et al., 1978).

The major cause of scouring during winter and spring on improved pastures in temperate environments is the ingestion of *Trichostrongylus* spp. and *T. circumcincta* larvae (Larsen et al., 1999; Larsen et al., 1994). In one study over multiple farms (Larsen et al., 1994), controlled release capsules provided worm free treatments for comparison between infected and GIN-suppressed mature merino ewes. Severe scouring was present in 26% of infected sheep, compared to 3% in GIN-suppressed sheep. The severity of dag score was not associated with WEC (Table 1-7), suggesting that ingestion of *Trichostrongylus* spp. larvae and an associated immune response are responsible for scouring, not worm burden.

Table 1-7. Distribution of dag score relative to worm egg count (WEC) in ewes either mated or unmated, 7 weeks after lambing (Larsen et al., 1994).

Group	WEC	Number	% ewes in dag score class		
			0-1	2-3	4-5
Mated	<100	8	12.5	37.5	50.0
	100-400	26	15.3	42.3	42.3
	>400	80	12.5	38.8	48.8
Unmated	<100	11	45.5	27.3	27.3
	100-400	17	35.3	11.8	53.0
	>400	11	36.4	18.2	45.5

Increased resistance to GIN, as measured by low WEC, has been correlated with increased dag score in Romney sheep in New Zealand (Bisset and Morris, 1996), while in Australian merinos, correlations were present but low (Karlsson et al., 2004). This hypersensitivity reaction in resistant sheep creates a significant barrier for the management of GIN through the selection for WEC (Williams et al., 2010). Due to the risk of increased scouring by selecting for low WEC, both WEC and dag score traits should be in a selection index, reducing the rate of genetic progress compared to individual selection on either trait.

1.3 Lifecycle and Environmental Regulation of GIN

1.3.1 Lifecycle

Summer rainfall regions of Australia are dominated by three major GIN parasites, *Haemonchus contortus*, *Teladorsagia circumcincta* and *Trichostrongylus colubriformis*. All are members of the Trichostrongylidae family, and share a common lifecycle (Figure 1-1). Understanding the influence of climate on the free living ecology and epidemiology of these major GIN parasites is essential for developing successful Integrated Parasite Management (IPM) strategies that aim to reduce anthelmintic treatment, slow the development of resistance, and limit loss of production.

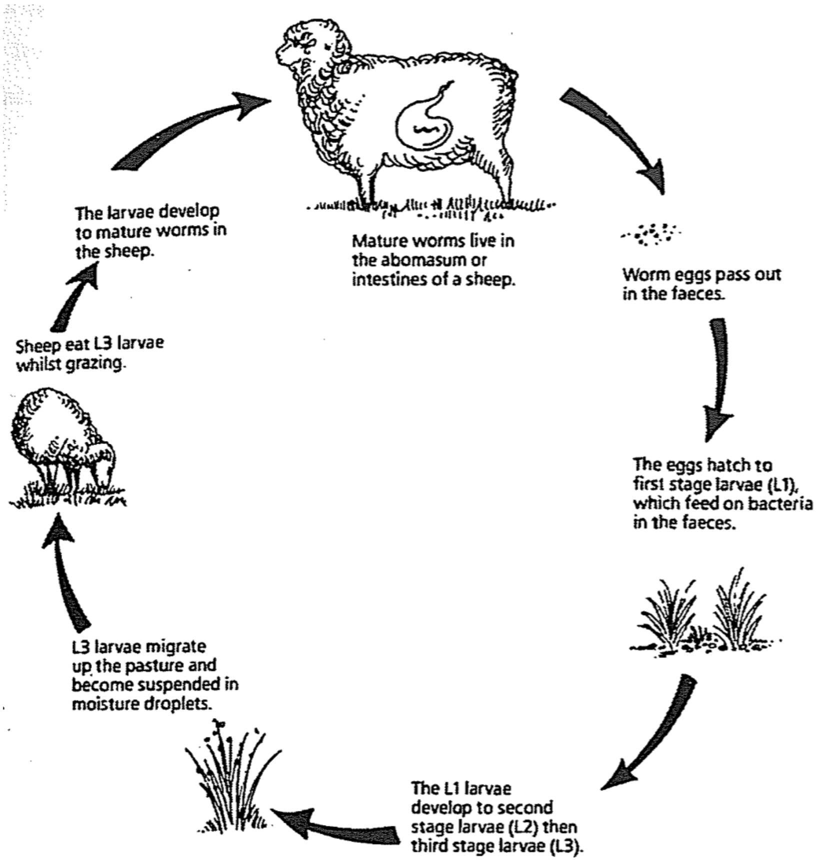


Figure 1-1. Typical lifecycle of a Trichostrongyloid parasite species of sheep (Brightling, 1994).

1.3.2 Adults

Reproduction is limited to adult male and female worms either based in the abomasum (*H. contortus, T. circumcincta*) or the anterior of the small intestine (*T. colubriformis*). Prolific egg layers, *H. contortus* can lay up to 10 000 eggs per day (Gordon, 1967; Roberts and Swan, 1981). In comparison, *T. colubriformis* and *T. circumcincta* lay 50 to 350 eggs per day (Gordon, 1967; Stear and Bishop, 1999).

Haemonchus contortus is the most pathogenic GIN and dominates in summer rainfall regions (Donald et al., 1978). During favourable weather conditions, pastures can quickly be contaminated with L_3 larvae due to the high reproductive rate of the parasite, rapidly increasing worm burden. These 'outbreaks' are often associated with mortality (Gordon, 1967). With a piercing lancet developing in the cephalic region before the final moult, *H. contortus* has been likened to an open-ended artery due to its blood sucking ability. Le Jambre (1995) showed that blood loss due to *H. contortus* is related linearly to worm number and biomass but not female fecundity. High burdens can result in greater than 400ml per day of blood lost from the host. As a consequence of increased blood loss, the central feature of the pathogenesis of *H. contortus* is haemorrhagic anaemia and resulting compensatory mechanisms as discussed in Chapter 1.4.

The pathogenesis of *T. colubriformis* and *T. circumcincta* infections is derived from niches they occupy in the digestive tract. *Teladorsagia circumcincta* develop into a mature adult within the gastric glands reducing gastric gland mass and functional cells lining the glands (Armour et al., 1966). Specifically, biochemical changes seen in response to the transplant of adult parasites accompany the acute loss/inhibition of parietal cells (Scott et al., 1998). Similar principles apply with *T. colubriformis.* With greater than 80% of L_3 penetrating the surface of the epithelium in the first three metres of the duodenum (Wagland et al., 1996), emerging worms cause considerable damage. Increased plasma loss into the gut is observed 10-12 days after infection and coincides with the onset of inappetance, hypoproteinaemia and weight loss (Barker, 1973). Resulting enteritis reduces the area available for nutrient absorption (Barker, 1975), and is associated with changes in intestinal pH and diarrhoea (Coop and Holmes, 1996). Increase endogenous protein losses into the gastrointestinal tract is also a symptom of the pathophysiology of *T. colubriformis* infection inducing protein deficiency (Bown et al., 1991).

1.3.3 Development through to infective larvae

Eggs deposited in dung hatch into first stage larvae (L_1), before moulting and becoming second stage larvae (L_2). During these stages, larvae feed on bacteria within the dung. A further moult, or part moult results in third stage larvae (L_3) which can migrate up grass blades and infect the host.

Environmental influences play a significant role in the regulation of lifecycle development and survival of free-living stages of the parasites reviewed. Differences between the species and their adaptation to climatic conditions has recently been reviewed by O'Connor et al. (2006). The major regulating factors on free-living nematode population dynamics are temperature and moisture.

Moisture

Studies show that *H. contortus* is highly susceptible to desiccation as an egg. Although faecal moisture enables development of some eggs through to pre-infective larvae, further moisture is required for continued development. Greater emergence of infective larvae has been shown when a rainfall event occurs within four days of egg deposition (O'Connor et al., 2007). Berbigier et al. (1990) found that only 6% of *H. contortus* and 36% *T. colubriformis* eggs remained viable 48 hours after deposition at 21℃ with faecal moisture falling below 5%.

Temperature

Understanding of temperature regulation on the developmental process from deposited egg to the infective larval stage is well developed. In *H. contortus,* predicted development time reduced from 26 days at 10℃ to 2.5 days at 37℃ (Smith, 1990). In field studies without limiting moisture or temperature, L_3 stages can appear 4 days after egg deposition (Cheah and Rajamanickam, 1997). Similar findings were noted for *T. colubriformis*. The ability to tolerate lower temperatures, developing from the umembyronated egg to infective L_3, is greater in both *T. circumcincta* and *T. colubriformis* than *H. contortus* as shown in Figure 1-2.

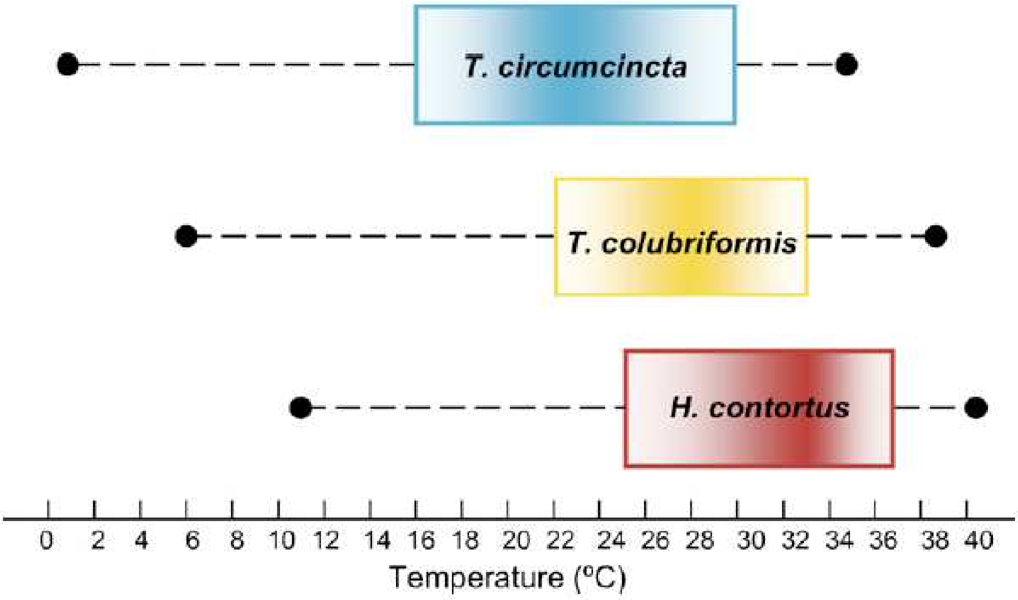


Figure 1-2. Temperature range for development of major Trichostrongylid species from unembryonated egg to L_3. Optimum temperature indicated by box, with most optimum temperature marked by high colour intensity. Dashed lines (--) extend to the upper and lower temperature limits for development (O'Connor et al., 2006).

H. contortus larvae are best adapted to warm moist weather with poor survival in cold or dry conditions. Recent research in the New England region of NSW suggests that unlike *T. circumcincta, H. contortus* and *T. colubriformis* have poor translational capacity over the winter period (Bailey et al., 2009a). The authors suggest that this has beneficial consequences for the preparation of clean lambing paddocks in spring, significantly enhancing the ability to develop integrated parasite management programs as discussed in Chapter 1.5.2

1.3.4 Infective larvae

Protected by the larval sheath, and the ability to seek favourable microclimates, L_3 are less susceptible to climatic conditions with less variation between species (O'Connor et al., 2006). Larval decay curves of Barger et al. (Barger et al., 1972) predict a population half-life of 93 days at 85% relative humidity and 12ºC and 9 days at 35% relative humidity and 28ºC. The practical implications of this are that infective larvae can remain on pasture for significant lengths of time (Anderson et al., 1978; Southcott et al., 1976). Specifically, on the Northern Tablelands of NSW, while development of larvae is limited over the winter period, larvae that develop during autumn can survive over winter and contaminate spring lambing paddocks. In winter rainfall areas, hot and dry summers decrease survival of both *H. contortus* and *T. circumcincta* L_3, allowing the preparation of clean pastures (Anderson and Dobson, 1975; Besier and Dunsmore, 1993; Callinan, 1978).

1.3.5 Infective larvae to adult

Following ingestion, *H. contortus* and *T. circumcincta* L_3 exsheath in the rumen before two further moults take place in the lumen. With adults predominantly residing in the duodenum (Wagland et al., 1996), *T .colubriformis* complete their second moult as they move towards the duodenum before L_4 penetrate between epithelial glands of the mucosa and form tunnels beneath the epithelium. This tunnelling can cause significant haemorrhage, oedema and loss of plasma proteins. For all species, the complete cycle can take between 21 – 28 days to complete. However, all species have the ability to extend this cycle by adaptation of the free-living stages to environmental conditions or lifecycle variation during the parasitic phase.

One such novel approach is the ability to arrest development. Known as hypobiosis, it has been documented at the L_4 stage in the *H. contortus* lifecycle. Arresting development at the L_4 stage in the abomasum, it prevents the production of eggs during periods when weather is unfavourable for development. In tropical and subtropical climates, it is an important mechanism to survive dry winters (Gatongi et al., 1998) and in temperate regions, to survive cold winters (Waller et al., 2004). Developmental arrest appears to be influenced more by environmental stimuli rather than the host immune response (Herd et al., 1984). Hypobiosis is only a one component allowing GIN to endure environmental variations, but with the success of modern anthelmintic against arrested L_4, it is likely to be a less effective survival strategy.

1.4 Host - Immune Regulation of GIN

1.4.1 Mechanisms of the Immune Response

Immunity is expressed as the expulsion of adult nematode populations, changes in adult nematode morphology, a reduction in the fecundity of female worms, larval developmental arrest and failure of larvae to establish (Balic et al., 2000). An animal's response to GIN infection is complex and multi-factorial resulting in induction of a Th2 type immune response (Shakya et al., 2009), with repeated infection producing immunity (McClure, 2000). Mechanisms responsible for immunity have been extensively reviewed by Balic et al. (2000) and include:

1. Mucosal mast cell hyperplasia
2. Appearance of globule leukocytes
3. Eosinophilia
4. Increased mucus production and presence of inhibitory substances in the mucus
5. The production of specific antibodies.

1.4.2 Timing and Development of Immunity

Establishment rates of *H. contortus* are reduced as immunity is acquired. Barger et al. (1985) demonstrated that peak worm burdens were reached six to nine weeks after infection and are proportional to larval challenge. Establishment of infective larvae declined from 45% in the first four weeks to insignificant levels after week nine. Interestingly, animals with a higher larval challenge (2400 – 4800 L_3/week), worm numbers were lower by week 15 than animals that received a low challenge (600-1200 L_3/week). This relationship between larval challenge and immune response is consistent with other studies, suggesting a threshold level for immune response (Dobson et al., 1990b; Windon et al., 1984).

Immunity that develops to *H. contortus* in animals exposed to moderate infections (Barger, 1988) also limits worm size and fecundity through increased lymphocyte response (Rowe et al., 2008) and elevated immunoglobulin levels (Strain and Stear, 2001). Presumably, this may also decrease blood loss and pathogenicity (Le Jambre, 1995). Immunity to *H. contortus* can also be acquired from prior infection with *T. circumcincta* (Dobson and Barnes, 1995), indicating a degree of cross-immunity between worm species.

Immunity to *H. contortus* can be lost following anthelmintic treatment, with immunity not being restored until approximately nine weeks post re-infection (Barger, 1988). Prior exposure to *H. contortus* does not appear to offer increased protection to subsequent exposure in lambs, suggesting that lambs are not capable of responding effectively to *H. contortus* antigens (McClure et al., 1998). The limited persistence of immunity to *H. contortus* has implications for production systems. Due to the fecundity of this species, *H. contortus* infections present as 'outbreaks' with mortality and deleterious effects on animal welfare. Survival of stock may be increased by the maintenance of moderate GIN populations that enable immunity to be acquired and maintained. The use of persistent anthelmintics in areas where *H. contortus* dominates may lead to loss of immunity with negative consequences if sheep are exposed to high pasture L_3 contamination after anthelmintic protection has ceased. This host-parasite interaction implies that it would be advisable to refrain from use of persistent anthelmintics unless protection extended to a period where subsequent challenge would be low (e.g. environmental conditions limiting to *H. contortus* development). Further work is required to understand the interactions between host immunity and use of anthelmintic for *H. contortus* infections.

Compared to *H. contortus*, immunity against *Trichostrongylus* species is more persistent. Barnes and Dobson (1993) showed that persistence of immunity is regulated by the duration of primary infection and age of exposure. As age increases, shorter periods of infection are required to develop immunity. Increased duration of primary infection lengthens persistency of immunity, with immunity lasting for up to 24 weeks (Kimambo et al., 1988). Seaton et al. (1989) showed that in *T. circumcincta* infections, protective immunity develops between 4 and 8 weeks of continuous infection, with infection rates reducing by 78%.

Development of a vaccine against *H. contortus* has progressed with the development of the hidden antigen approach (Knox et al., 2003a). This approach requires inoculating sheep with a gut nematode antigen, artificially inducing an antibody response directed against components on the surface of the worm gut. Separate from the acquisition of natural immunity, hidden antigen protection is persistent for several weeks following primer vaccinations (Andrews et al., 1997). While this approach has been a successful approach against *Boophilus microplus* (Willadsen et al., 1995), the requirement for continuous booster doses and the risk of sheep not responding to the vaccine threaten the commercial viability of this approach. Nonetheless, the commercialisation of a vaccine against *H. contortus* will provide an additional tool to reduce production losses from GIN parasitism.

1.4.3 Factors affecting immunity

Age and Liveweight

Immunity to GIN is not innate, with sheep exposed to larvae on pasture showing immunity from 6 – 12 months of age (Stear et al., 1999). Lower levels of immunity in young sheep are due largely to hyporesponsiveness, and not simple a consequence of limited exposure to GIN (Colditz et al., 1996). Weaning also influences development of immunity (Spedding et al., 1964), with weaning at 3-4 months of age occurring prior to the full development of immunity. While the effect of stress of weaning on immunity is unclear, nutrition appears to be a mechanism to mediate the apparent effects of weaning on immunity (Shaw et al., 1995). Weaning at 8 weeks of age onto pasture increased worm egg counts and reduced serum antibody responses to *H. contortus* antigens and liveweight by 6kg compared to lambs that remained with dams (Watson and Gill, 1991). Weaning at 4 months has no effect on response to *H. contortus* challenge compared to lambs that remained with dams (Shaw et al., 1995).

McClure et al. (1999) demonstrated a negative correlation between initial liveweight and *T. colubriformis* worm count in 8 month old Merino lambs. The correlation was strongest in sheep that initially weighed less than 22kg. The inability of lightweight sheep to mount a protective immunity supports the importance of liveweight and growth rate in young sheep on survival (Campbell et al., 2009; Hatcher et al., 2010).

Periparturient Rise

The loss of immune competence in the periparturient ewe and subsequent increase in WEC is well documented (Brunsdon, 1970), although not fully understood. Kahn (2003) proposes two stages of nutrient partitioning priority associated with the periparturient rise. First, several factors predispose the ewe to loss of immunity to GIN. It is clear that the requirement for metabolisable protein (MP) increases significantly in the periparturient ewe (Houdijk et al., 2000) with the rise in WEC associated with the increased demand for protein with the onset of lactation (Liu et al., 2003). Coop and Kyriazakis (Coop and Kyriazakis, 1999) propose that this increased demand for MP is offset by a decreased priority for MP by the GI tract immune system, resulting in increased (although tempered) WEC despite adequate supply of MP (Donaldson et al., 2001; Kahn et al., 2003). Second, nutrient partitioning priorities are altered subsequently to enable the re-acquisition of immunity in the ewe. This may be facilitated by a reduction in the total MP requirements due to decreased demand after the cessation of lactation.

As the periparturient rise has significant impacts on pasture contamination and lamb worm burdens, appropriate management at this time is important to maintain production attributes. Morris et al. (2000) found that sheep selected for low WEC had increased number of lambs born and survival to weaning. Although resistant animals are still susceptible to the periparturient rise, it is of a lower magnitude (Kahn et al., 2003). Supplementation of ewes with MP can moderate worm burdens during this period (Donaldson et al., 2001) while the most effective timing of supplementation is during the time of greatest weight loss, significantly lowering WEC and maintaining or improving productivity (Kahn et al., 2003). Although the addition of MP to meet the required demands of the animal does not fully alleviate the loss of immunity seen during this period of increased nutrient demand, the practice of supplementing animals to reduce pasture contamination and maintain production has practical merit (Kahn, 2003). Further research is required to understand the continued expression of the periparturient rise in the presence of adequate nutrient supply and in animals selected for resistance.

1.4.4 Cost of the Immune Response

Reviewing the cost of immunity, Colditz (2008) suggests six costs of the immune response. Phenotypic costs arise from 1) increased metabolic activity; 2) reduced nutrient availability due to reduced feed intake; 3) altered priorities for nutrient utilization; 4) change in size and turnover of the pool of immune cells and proteins; 5) immunopathology from inappropriate immune activation; and 6) altered efficiency of offspring to demonstrate production attributes following selection for parasite resistance. As these costs are variable due to host response, GIN challenge and species, managing productive animals in a contaminated environment is layered with additional challenges.

1.4.5 Resistance

Managing an animal’s natural resistance to GIN is one such challenge. Resistance implies an antagonistic response acting against the development and continued presence of the parasite (Riffkin and Dobson, 1979). Resistance is described as being the ability of the host to either suppress establishment; suppress development of worm infection; or limit longevity or worm fecundity. Therefore, a good indicator for an animals resistance is measured by its ability to reduce faecal worm egg count, and hence this is the principal trait for measuring (Eady et al., 1996). Immunological markers for resistance are variable (Douch et al., 1996a) limiting their potential as markers for resistant individuals. Other phenotypic correlations associated with the immune response include several antibodies, specifically IgE (Douch et al., 1996b). Additionally, haemoglobin type (Allonby, 1976; Altaif and Dargie, 1978) and haematocrit (Albers et al., 1984) are correlated to WEC with *H. contortus* infections. Genetic markers for resistance have been hampered by the difficulty in measuring the various immune responses engaged by the host. Quantitative trait locus studies have identified a number of chromosomal regions of interest (Dominik, 2005) with significant technical requirements limiting current application for the Australian sheep industry (Marshall et al., 2009).

The paradigm of increased resistance at a cost to production is highlighted when the response of the immune system is understood. Comparing divergent breeds of sheep for resistance to *H. contortus,* Shakya et al. (2009) demonstrated that resistance is associated with increased immune response. Resistant sheep had increased eosinophil count, both when measured within the abomasal mucosa and in peripheral blood, increased mast cell and globule leukocyte numbers and increased production of IgE. The immune-mediated reduction in feed intake, as shown by Greer et al (Greer et al., 2008; Greer et al., 2005) is potentially driven by the Th2 response to parasitism releasing cytokines that decrease appetite and have effects on metabolism (Figure 1-3) (Williams, 2011). Furthermore, parasite-induced diarrhoea is more pronounced in high immune responders (Meeusen, 1999).

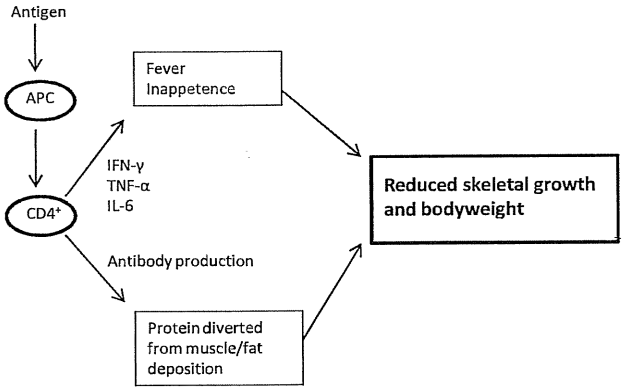


Figure 1-3. Possible mechanisms leading to immunopathology during acquisition of immunity to nematodes in young sheep (Williams, 2011).

Riffkin and Dobson (1979) proposed that sheep more able to resist establishment of *H. contortus* by virtue of their immunological competence may not necessarily be able to overcome the pathogenic effects of parasites. Their study found that sheep with a high immune response (characterised by a high lymphocyte response) to *H. contortus* challenge had a liveweight gain of 3.8kg compared to sheep with a measured low immune response to challenge that had an increased liveweight gain of 5.0kg. These correlations are supported by more recent studies with other GIN species. A singe-trait resistant selection line when compared to a control line, were 8.6% lighter at weaning, had 14.9% lower greasy fleece weight and an increased dag score despite having a WEC 16% lower than the control (Wheeler et al., 2008). Evaluating data collected from New Zealand industry breeding schemes, McEwan et al. (1995) showed negative correlations between body weight, fleece weight and dag score in Romney sheep. Measuring Merino resource flocks across Australia, the correlation between WEC and wool production traits was close to zero (Eady et al., 1998); although the authors conceded that a breeding objective based on production traits results in unfavourable WEC response. When GIN challenge is extreme, measured production attributes are more likely to be negatively correlated with WEC (Albers and Gray, 1987). It is clear that in a diseased environment, reduced WEC is not associated with increased levels of production within the flock. Changes to the environment may however reduce the immune response and minimise production cost over the long term.

To demonstrate the potential long-term benefits of selecting for resistance, Greef and Karlsson (2006) argue that resistant and control lines can only be comparable when lines are grazed separately. This method ensures resistant lines undergo less larval challenge (resulting in less challenge to the immune system), representative of an improved pasture system achievable from selection for WEC. In the first field trial study published where single trait resistant and susceptible lines grazed separately, Bisset et al. (1997) showed a 2.6 to 2.9 fold decrease in larval pasture contamination (Figure 1-4). This favourable epidemiological effect of decreasing the infectivity of pastures by worm larvae is expected to significantly improve worm control by reducing larval challenge and decreasing reliance on anthelmintic control (Besier and Love, 2003). Selecting sheep resistant to nematodes clearly reduces the larval challenge when grazed separate to non-resistant sheep but questions remain as to whether this is reflected in production attributes. In a single study including resistance in a selection index and separate grazing paddocks, it appears that production gains can be achieved by including resistance in a selection index (Greeff and Karlsson, 2006). As production systems will always exist in a diseased environment, the extent that production loss can be minimised by selecting for WEC has yet to be determined and warrants further research.

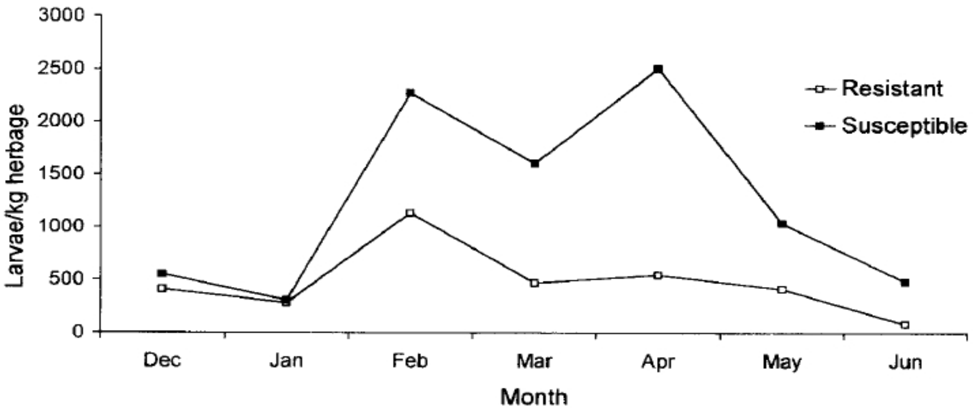


Figure 1-4. Mean monthly concentrations of infective nematode larvae infesting pasture on farmlets grazed by resistant and susceptible genotype ewe lambs (Bisset et al., 1997).

1.4.6 Resilience

The frequent inability to demonstrate improved production by breeding sheep resistant to worms suggests that other approaches to worm control may need to be investigated. Resilience, as measured by the ability to maintain production when challenged by GIN, may be one such approach. Resilience is demonstrated in sheep that show 'the ability to maintain a relatively undepressed production level when infected' (Albers and Gray, 1987), probably by minimising the cost of the immune response to GIN. Bisset et al. (1996) suggest that the definition of resilience can be expanded to include a full range of variables associated with productivity. Hence, measurement of resilience should be based on the key measures of productivity; whether it is wool growth, liveweight gain or dagginess. The term 'relative undepressed production' is accurately measured as an animal's productivity when infected compared to its productivity when not infected. Due to experimental challenges presented by this measurement, researchers in New Zealand have developed a system that compares productivity following a standard challenge (Bisset et al., 1994; Bisset et al., 1996). Although this method adequately accounts for experimental difficulties of recording individual production with and without GIN challenge, and is focused on maintaining production, its inability to account for the confounding effect of genetic potential limits it being used as a suitable experimental technique to investigate potential phenotypic markers for resilience. It is, however, well suited to rapidly select animals that display resilient characteristics.

Resilience has been measured in Merino sheep by measuring the difference between an animal when infected compared to the same animal's production when not infected (Albers et al., 1987). Sheep were given a single intraruminal inoculation of *H. contortus* and remained infected for 5 weeks. Following removal of infection, sheep were monitored for an additional 14 weeks. Significant differences for resilience measures (liveweight gain) were detected between sire groups and between sire groups with similar levels of resistance (Albers and Gray, 1987). New Zealand studies have measured resilience based on the age at first anthelmintic treatment and average number of treatments required. They demonstrated that animals selected for resilience showed improved production attributes and were capable of maintaining higher growth rates and developed less severe dagginess (Bisset and Morris, 1996). Resilience in this study may be confounded by the benefits achieved by improved birth and weaning weights. Both of the above studies show the potential benefits of improving production by improving resilience. However, both studies also showed that selecting for resilience is hindered by low heritability.

Resilience has poor heritability compared to resistance and other production traits and potentially a function of the difficulty measuring this trait. Albers et al. (Albers et al., 1987) calculated heritability to be close to zero and that a strong and positive correlation existed between resilience and resistance (Figure 1-5). The high positive genetic correlation between resistance and resilience suggests that selecting stock on resistance measurements would improve the ability to be productive under challenge (Albers and Gray, 1987; Albers et al., 1984); however, as discussed above, this has not yet been apparent. This finding is also likely to be only applicable to *H. contortus* dominant infections were pathology of infection is less influenced by immune response (Morley, 2006). Heritability for resilience was also found to be low in Romney sheep (Bisset et al., 1994). When measured in terms of drench requirements, heritability of resilience ranged between 0.05 – 0.14. This value may have been affected by the inability of the study to ensure strict criteria for selective drenching requirements.

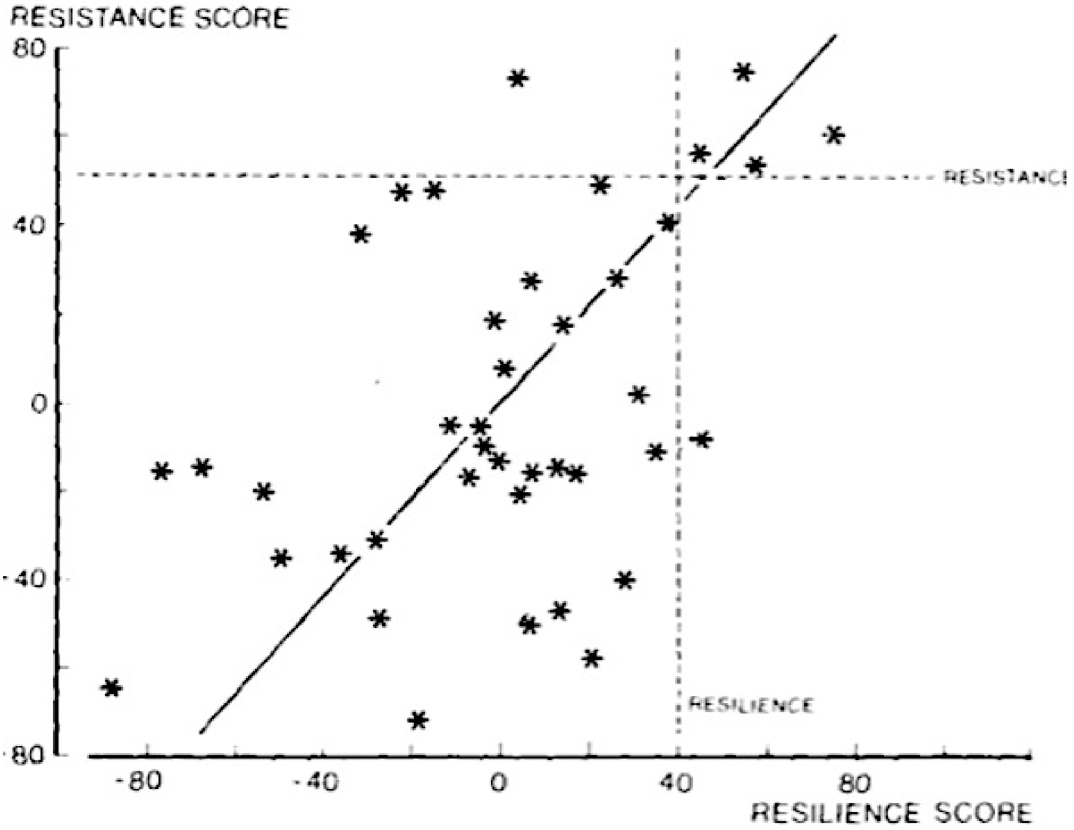


Figure 1-5. Family group means for resistance (inverse WEC) and resilience (inverse of liveweight gain while infected) on standardized scales. The solid line describes the linear relationship between resistance and resilience. The broken lines indicate culling levels when a selection intensity of 5 out of 40 is applied (Albers and Gray, 1987).

Before anthelmintic use was available, breeding for resilience was the default breeding strategy, even if unknown at the time. However, serial anthelmintic use as discussed earlier has considerably reduced the capacity of animals to be selected on resilience, resulting in animals with poor resilience maintained within the flock. Selection pressure placed on resilience traits such as fleece weight and liveweight may compromise the immune response (Eady et al.,

1998) which could have potential deleterious effects in diseased animals. A compromised immune response at the expense of production is demonstrated by Williamson et al (1995). Comparing sheep from either a line selected for increased fleece weight growth or a random selected line, it was shown that selection for increased fleece weight was correlated with a higher WEC. Selection for high fleece weight did not correspond to greater production loss due to GIN, suggesting that selection for high wool growth, although reducing resistance, does not impact on potential production in an environment where clinical signs of GIN can be controlled through regular anthelmintic treatment.

The ability of sheep to show resilience to GIN challenge has been correlated to other phenotypic traits. Investigating resilience to *T. circumcincta*, Simpson et al. (2009) have shown that resilient lambs (animals selected for high fleece weight) have lower circulating eosinophil counts during primary infection and that this reduction is more pronounced during the secondary infection compared to random-bred controls. Differences in haemoglobin type (Allonby, 1976; Altaif and Dargie, 1978), increased haematocrit (Albers et al., 1984), and various immunological parameters (Douch et al., 1996b) have also been demonstrated as indicators of resilience. However, little work has been carried out on the suitability of these markers for resilience in sheep. Genetic factors that influence the resilience of sheep to overcome the harmful effects of infection may provide a useful adjunct to selection programs (Riffkin and Dobson, 1979). Genetic markers could assist in the development of breeding stock with the aim of improving worm management whilst maintaining other breeding goals or allow improved GIN management by phenotypic selection of resilient sheep.

1.5 Managing the Impact of GIN

Traditional control of worms has depended heavily on anthelmintic intervention within the host. While increased frequency of anthelmintic intervention can successfully prevent clinical signs of disease and minimise production loss (Johnstone et al., 1979), treatment is often implemented without knowing infection status or the anthelmintic resistance status of the worm population (Walkden-Brown et al., 2006). Such an approach is likely to increase frequency of treatment and be less cost-effective while hastening the development of anthelmintic resistance (Besier and Love, 2003).

Anthelmintic-based worm control is currently based on a limited number of chemical groups (Besier and Love, 2003). The current major groups used are:

1. Benzimadazoles (BZ)
2. Levamisole/morantel (LV)
3. Macrocyclic lactones (ML)
4. Organophosphates
5. Salicyalnilides

Recently, two new classes of anthelmintic have been developed and released. Monepantel (an amino-acetonitrile derivative) will provide effective broad-spectrum nematode control where widespread resistance has developed to existing anthelmintic classes (Kaminsky et al., 2008). Derquantel (one of the spiroindole class of anthelmintics) is a mid-spectrum anthelmintic but when combined with abamectin provides a commercial broad –spectrum anthelmintic (Little et al., 2010). These new classes have demonstrated efficacies against GIN resistant to other classes, although the combination of Derquantel and abamectin has little efficacy against an ML resistant *H. contortus* L4 (Kaminsky et al., 2010). History demonstrates that new classes of anthelmintic do not reduce production loss across the industry and that resistance will develop. It is apparent that a variety of control mechanisms must be adopted to improve these outcomes. The release of new classes present an opportunity to improve management of worms and reduce the risk of developing anthelmintic resistance to these new drenches. While modelling suggests several approaches to achieve this aim (Hosking and Dobson, 2010), further improvements may be possible if these suggestions were combined with concepts outlined within Integrated Parasite Management.

1.5.1 Integrated Parasite Management

Integrated parasite management involves a three-pronged approach; 1) grazing management; 2) use of anthelmintics; and 3) utilising the natural or artificially induced immunity (Brunsdon, 1980). Although an established concept, adoption of integrated parasite management for GIN control is not widespread. Adoption of strategic control programs such as ‘WormKill’ has been widespread (Besier and Love, 2003) but its role in increasing anthelmintic resistance has rightly reduced its use. Other perceived problems include apparent complexity of integrated systems (Kahn et al., 2006). Complexity of integrated systems arises from the varying environments, worm species and resistance profiles across the sheep industry. However, if the Australian sheep industry is to reduce the considerable cost caused by GIN, integrated management systems must be understood and form a key component of managerial decision-making.

The advantages of integrated parasite management have been demonstrated by the Integrated Parasite Management in Sheep (IPMs) project (Kahn et al., 2006; Scrivener et al., 2006). Comparing sheep managed according to IPMs against sheep treated with serially administered albendazole capsules over two years and across five farms on the Northern Tablelands of NSW, no significant effects on liveweight, mortality or wool characteristics were noted. The authors also suggested that the cost of adopting IPMs would be less than typical management approaches in summer rainfall dominant regions. These results were promising but due to the variability of climate and potentially lower production in GIN suppressed sheep through L_3 exposure, further study was required to validate these results and the suitability of IPMs for adoption compared to typical practices already used by industry. The individual components of IPM, falling under the categories of prevention, detection and response have been validated as detailed below.

1.5.2 Grazing Management

Preventing infection by grazing management been identified as a suitable method of managing the impact of GIN for young stock by reducing pasture contamination levels. Pasture contamination is reduced by either the removal of infective larvae by non-host species or by restricting development of infective larvae. At the most basic level, destocking of pasture and allowing decay of infective larvae can allow the preparation of clean pastures. Time of destocking is dependant on climate and species as discussed in Chapter 1.3. Destocking can however impose limits to production, and along with perceived increase in workload of grazing management has limited adoption of grazing management principles to prevent GIN infections (Waller, 1999).

Studies consistently show that sequential grazing of pastures with cattle prior to sheep reduces faecal egg counts in sheep compared with mixed grazing or with sheep only (Bailey et al., 2009b; Marley et al., 2006; Reineke, 1994; Southcott and Barger, 1975). For example, Marley et al. (2006) demonstrated that preparing weaning paddocks by grazing with cattle prior to lambing reduced WEC in lambs compared to paddocks grazed with sheep only or cattle and sheep.

In sheep only systems, intensive rotational grazing systems are as effective at producing parasitological and production benefits as grazing with non-host species. Preparing clean paddocks for susceptible stock using ‘Smart Grazing’ is successful in both winter and summer rainfall areas (Bailey et al., 2009b; Niven et al., 2002a). 'Smart Grazing' requires intensive grazing of recently drenched adult sheep (not pregnant ewes) for 21 days. Colvin et al*.* (2008) demonstrated that intensive rotational grazing with short grazing and long rest periods, compared to typical continuous grazing systems, lowered mean WEC and required fewer anthelmintic treatments.

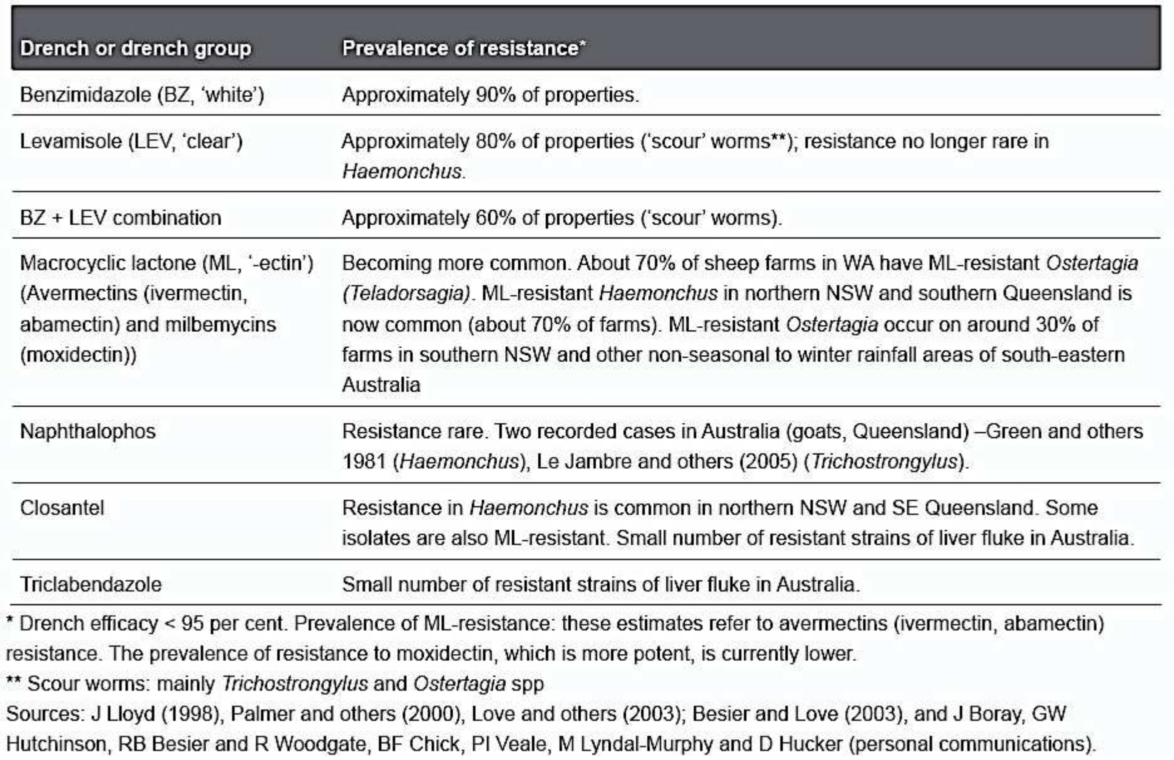
In the New England region of NSW, Bailey et al*.* (2009) demonstrated that the prevention of egg deposition on pasture in autumn, irrespective of grazing during winter, significantly reduced *H. contortus* and *T. colubriformis* infections during spring. As the climate is too cold for development of larvae over winter, this method supplies some 180 days for the decay of infective larvae, but only 90 days where worm egg deposition on pasture had to be restricted. This research translates into simple extension messages that will lower treatment frequency, but will also improve production and survival of young lambs.The results demonstrate that grazing management principles, based on the epidemiology of GIN, can assist with control of in cool temperate climates where H. contortus is the dominant parasite.

1.5.3 Breeding

Using WEC, studies have shown that heritability for resistance within-breed is moderate. Using Merino sheep with various bloodlines throughout Australia, challenged with either natural or artificial infections of *H. contortus* and *T. colubriformis*, heritability estimates ranged from 0.07 to 0.42, with a weighted average of 0.22 (Eady et al., 1996). New Zealand studies have found similar heritability for resistance of 0.21 in Romney sheep (Bisset et al., 1994). In terms of WEC reduction, Greef and Karlsson (2006) showed a reduction from 1292 to 533 eggs per gram over three years by selecting for resistance, and in earlier studies showed a reduction in WEC of 2.7% per year (Greeff and Karlsson, 1999). The success of breeding strategies that aim to reduce WEC must incorporate the cost to production, both from the reduced production potential of an animal with an increased immune response (Colditz, 2008) and the decrease in genetic gain for production attributes from including WEC weighting in a breeding index. The dichotomy of breeding for lower WEC to improve production and the evolution of resistant host-parasite systems characterised by low production attributes (Perry and Randolph, 1999) highlight the challenge that this approach faces.

1.5.4 Management of anthelmintics

The increasing occurrence of anthelmintic resistance and reduced ability to control worm populations has long been established. Prevalence of resistance is widespread (Figure 1-6), however extensive surveys of drench resistance are not readily accessible. The advent of new anthelmintic classes, both historical and current, and successful combinations of drench classes appear to reduce the threat of total anthelmintic breakdown to a long-term risk. However, applying a precautionary approach suggests that methods that minimise the risk of developing anthelmintic resistance should be considered.



Drench or drench group	Prevalence of resistance*
Benzimidazole (BZ, 'white')	Approximately 90% of properties.
Levamisole (LEV, 'clear')	Approximately 80% of properties ('scour' worms**); resistance no longer rare in *Haemonchus*.
BZ + LEV combination	Approximately 60% of properties ('scour' worms).
Macrocyclic lactone (ML, '-ectin') (Avermectins (ivermectin, abamectin) and milbemycins (moxidectin))	Becoming more common. About 70% of sheep farms in WA have ML-resistant *Ostertagia (Teladorsagia)*. ML-resistant *Haemonchus* in northern NSW and southern Queensland is now common (about 70% of farms). ML-resistant *Ostertagia* occur on around 30% of farms in southern NSW and other non-seasonal to winter rainfall areas of south-eastern Australia
Naphthalophos	Resistance rare. Two recorded cases in Australia (goats, Queensland) –Green and others 1981 (*Haemonchus*), Le Jambre and others (2005) (*Trichostrongylus*).
Closantel	Resistance in *Haemonchus* is common in northern NSW and SE Queensland. Some isolates are also ML-resistant. Small number of resistant strains of liver fluke in Australia.
Triclabendazole	Small number of resistant strains of liver fluke in Australia.

* Drench efficacy < 95 per cent. Prevalence of ML-resistance: these estimates refer to avermectins (ivermectin, abamectin) resistance. The prevalence of resistance to moxidectin, which is more potent, is currently lower.

** Scour worms: mainly *Trichostrongylus* and *Ostertagia* spp

Sources: J Lloyd (1998), Palmer and others (2000), Love and others (2003); Besier and Love (2003), and J Boray, GW Hutchinson, RB Besier and R Woodgate, BF Chick, PI Veale, M Lyndal-Murphy and D Hucker (personal communications).

Figure 1-6. Estimated prevalence of anthelmintic resistance in NSW (Love, 2007).

In recent years, the importance of a component of the GIN population not exposed to anthelmintic treatment has been incorporated into management systems. Sources of refugia to maintain susceptible alleles include both the suprapopulation or infrapopulation (Kenyon et al., 2009), although most research effort has focused on the infrapopulation. High drench frequency and low numbers of GIN in refugia accelerate the development of resistance. During the 1970's and 1980's, regular treatment to reduce production loss contributed to the dramatic increase in resistance to the BZ and LV groups (Besier and Love, 2003). Although industry estimates that between two and four drenches per year are common in pasture-based systems (Walkden-Brown et al., 2006; Sackett et al., 2006), seasonal variation may account for differences in the number of drenches applied. Maintaining worm populations not exposed to anthelmintic treatment, or in refugia, will slow the development of resistance. Maintaining a population of GIN in refugia enables adults to develop, reach maturity and produce offspring without coming into contact with a particular anthelmintic (Le Jambre, 1982). Martin et al. (1981), starting with a strain of *H. contortus* containing 5% thiabendazole resistant larvae, showed a proportional increase in the development of resistance over six generations when larvae exposure to thiabendazole was 0, 25, 70, 90 and 100%. Resistance was shown to develop rapidly when 90 or 100% of the larvae were exposed to thiabendazole, demonstrating the potential of larvae in refugia to delay development of resistance.

The success of strategic programs like 'WormKill' in reducing the number of treatments and pathogenicity of GIN infection also reduced the populations of worms in refugia. Such programs have come under strong criticism and some authors suggest they such programs should cease to be recommended (van Wyk, 2001). Le Jambre (1982) suggests that susceptible GIN should be conserved through the correct choice of anthelmintic, dosage and mode of application; integrated control; stamping out newly developed resistance; rotation of anthelmintic; and synergistic use of anthelmintics. The benefits of maintaining GIN in refugia must be balanced by the potential loss of animal performance caused by increased larval challenge. Several authors suggest that total parasite suppression is not viable and that it is better to have some production loss than to loose the ability to control worms (Barger, 1982; Besier and Love, 2003).

The development of the 'Farmacha' system is a novel method for the control of *H. contortus* and increase the number of GIN not exposed to anthelmintic treatment. Developed in South Africa, it relies on the identification of animals displaying signs of anaemia with treatment applied only to these animals. Nematode populations are often over-dispersed in flocks, with some individuals having a disproportionate number of worms, while others have limited numbers. Using these principles, anthelmintic use can be significantly reduced (Waller, 1999). Adopted in some areas overseas, trained operators can apply the concepts to successful identify and treat anaemic sheep (Burke et al., 2007). Reducing anthelmintic use and allowing a population of GIN in refugia has significantly reduced selection pressure for anthelmintic resistance (Waller, 1999). The context of large and productive systems in Australia with low labour input is in contrast to the systems where 'Farmacha' is currently adopted. Individual assessment of sheep for clinical signs of anaemia involves a high risk/cost strategy for Australian producers and is not recommended. Development of mob based faecal blood testing may allow for better targeted treatment options within the Australian sheep industry (Colditz and Le Jambre, 2008).

In areas not dominated by *H. contortus*, partial flock drenching has been practiced to increase refugia. Analogous to Farmacha, selection of undrenched sheep can either be random, or based on liveweight or animal condition. Besier et al. (2010) have developed a two-step decision process. First, a mean worm egg of the flock is used as an indication of the degree of parasitism and the proportion of the flock that needs to be treated to lower the mean worm egg count under 200 eggs per gram. Second, sheep to be treated are selected on body condition. This method does not appear to significantly lower wool production or liveweight compared to regionally typical programs. Greer et al. (2009) have also developed a decision support method to identify animals for treatment within a targeted selective treatment program, albeit more complex. This method estimates the efficiency of gross energy utilisation, with inefficient sheep (assumed due to parasitism) selected for treatment. Sheep treated via this method (mean of 2.56 treatments over 20 weeks) had no detectable difference in liveweight gain than sheep serially worm-suppressed every 4 weeks.

Modelling anthelmintic resistance, Barnes et al. (1995) explored the relationship between anthelmintic resistance and management practice. Changing anthelmintic class regularly delayed the development of resistance compared to treatment programs that changed drench class less frequently. The model also demonstrated that moving weaners to clean pastures delayed development of resistance compared to weaners not grazed on clean pastures and drenched at a higher frequency to maintain similar production attributes. This suggests that a balance must be found between optimal levels of GIN in refugia and minimal requirement for drench application. The development and use of models may be beneficial in finding these levels.

1.6 Conclusion

The impact of GIN on the Australian sheep industry is a significant economic burden and a potential limiting factor to its long-term sustainability. Despite sporadic release of classes of anthelmintic over the past 50 years, the improved ability to reduce the impact of infection through grazing management, protein supplementation and management of the host immune system, GIN still represent the most significant sheep health cost. To what extent these costs can be alleviated by management change is an important question for the Australian sheep industry and requires the need for a greater understanding of the constraints imposed by GIN.

The literature presents a strong argument that immunity to GIN, or specifically the acquisition of immunity, is associated with a cost to production. Negative or negligible genetic correlations found between animals selected for resistance and production attributes are supported by several authors as discussed in Chapter 1.4.4. This suggests that animals selected for resilience may present a better model of GIN management and maintaining production attributes. However, the lack of suitable phenotypic markers for resilience, and limited studies in the area, present an area of further research that may provide a novel opportunity for genetic improvement of flocks against GIN challenge.

The success of strategic programs in limiting production loss and relatively high levels of adoption suggest that refined IPM programs may be successful. However, despite such programs being founded on a better understanding of GIN ecology and drivers of anthelmintic resistance, the extent to which such programs reduce the development of resistance and the impact of GIN on production is yet to be determined. Further research that addresses these questions could potentially provide a tool that enables long-term control of GIN. Economic evaluation of these programs may also highlight the practical value of implementing improved GIN control programs (Morris and Meek, 1980) and create a more profitable Australian sheep industry.

CHAPTER 2

Integrated parasite management for sheep reduces the effects of gastrointestinal nematodes on the Northern Tablelands of New South Wales

G. A. Kelly, L. P. Kahn and S. W. Walkden-Brown

Accepted 21 September 2010, *Animal Production Science* 50: 1043-1052

Abstract. An experiment was conducted over 2 years on six commercial farms to quantify the costs of gastrointestinal nematode parasitism on grazing Merino ewes on the Northern Tablelands of New South Wales. To determine the effect of worm management practices, three farms implemented integrated parasite management (IPM) strategies and three farms continued to implement regionally-typical industry practice (TYP).On each farm, 120 ewes born in 2006 and 120 mature-age ewes were selected at shearing in 2007.Of these, 60 in each flock were serially treated with anthelmintics (CAP treatment) to suppress worm populations and the other 60 ewes were managed according to their respective farm management strategies (NOCAP treatment). Among NOCAP ewes, worm egg counts were significantly

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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STATEMENT OF ORIGINALITY

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CHAPTER 3

Measurement of phenotypic resilience and resistance to gastrointestinal nematodes in Merino sheep and association with production variables.

G. A. Kelly, L. P. Kahn and S. W. Walkden-Brown

Submitted to *Animal Production Science*

Abstract

A cross-over experiment was conducted to determine the effect of phenotypic resistance and resilience to gastro-intestinal nematodes (predominantly *Haemonchus contortus*) on production levels of Merino sheep. On each of six farms, 120 ewes born in 2006 and 120 older mixed age ewes were selected at shearing in 2007. Of these, 60 in each mob were serially treated with long-acting anthelmintics to suppress worm populations. The other 60 ewes were managed according to management practices employed on the farm (infected, INF). At shearing in 2008, the experimental sheep had their anthelmintic treatments switched. The experiment concluded at shearing in 2009. Resistance was determined from the average of at

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	Steve Walkden-Brown	5

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CHAPTER 4

Short Communication:

Risk factors for mortality in sheep on the Northern Tablelands of NSW

4.1 Introduction

Increased risk of mortality post-weaning has been well documented and is most strongly associated with body weight and current growth rate (Campbell et al., 2009; Hatcher et al., 2008; Pope and Atkins, 2009). In contrast, there is an absence of current published data on the rate and predictive correlates of mortality of mature sheep, with historical studies suggesting mortality of this age group to be in the range of 2 to 7% per annum (Moule, 1966; Turner et al., 1959). Recently, Kelly et al. (2010) reported that mortality in mature sheep on the Northern Tablelands of NSW is associated with management of gastrointestinal nematodes (worms) with the greatest worm-related mortality events coinciding with seasonal spikes of the blood-sucking abomasal parasite *Haemonchus contortus* (Kelly et al., 2010a). This aim of the analyses reported here was to outline the key risks associated with mortality for mature sheep on the Northern Tablelands of NSW.

CHAPTER 5

No loss of production due to larval challenge in sheep given continuous anthelmintic treatment via a controlled release capsule

G. A. Kelly, S. W. Walkden-Brown and L. P. Kahn

Accepted 1 July2011 to *Veterinary Parasitology*, in press.

Abstract: This study aimed to quantify production loss due to larval challenge in sheep administered a controlled release albendazole capsule (CRC) and thus determine the suitability of CRC treated sheep as a proxy for worm-free sheep in grazing experiments. The experiment used an incomplete 2x3 latin square design with 81 Merino wethers. Sheep were either infected (INF) with mixed oral infection of albendazole-susceptible *Haemonchus contortus, Trichostrongylus colubriformis, Teladorsagia circumcincta* (initial bolus then thrice weekly maintenance) or remained uninfected (UINF). Worm control treatments were with a CRC (CRCT), threshold treatment with a short-acting anthelmintic when worm egg count (WEC) exceeded 1500 epg (TT) or untreated (UT). The experiment was conducted in two 63-day periods (separated by a 14 day washout period) with infection treatments swapped between periods. A subset of animals was killed at the end of each period for worm counts and tissue sampling.

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	Author's Name **(please print clearly)**	**% of contribution**
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CHAPTER 6

Economic evaluation of gastrointestinal nematode infection of sheep in an Australian summer rainfall region and impact of different worm control strategies.

Abstract: Performance data from a large field study comparing production in worm suppressed and non-suppressed sheep under different worm management systems was used as input for two models to a) quantify the economic cost of gastrointestinal parasitism in a summer dominant rainfall region of Australia and b) update current estimates of the overall national cost of worm infection to the Australian sheep industry. The cost of parasitism under regionally typical (TYP) management was \$11.09 per ewe per year and was reduced to \$5.80 with management based on integrated parasite management (IPM) principles. This difference clearly validates the additional monitoring costs associated with IPM. The major factor increasing the cost of parasitism was adult mortality, with a 1% increase in mortality rate increasing the cost of parasitism by \$1.24 per ewe. These estimates suggest that the industry has underestimated the cost of worms in areas dominated by *H. contortus*. The total annual cost of GIN parasitism has declined from \$369m (2001) to \$267m (2010) in line with a sheep population that has decreased from 111m to 68m over the same

CHAPTER 7

General Discussion

7.1 Introduction

The overarching aim of this thesis was to quantify production loss from gastrointestinal nematodiasis and evaluate the extent to which it can be ameliorated by integrated parasite management approaches in Merino sheep on the Northern Tablelands of NSW. This summer-dominant high rainfall region is dominated by *H. contortus,* which aside from its pathogenicity has developed resistance to most established anthelmintic classes (excluding the recently released active monepantel). These factors, along with increasing commodity prices, underpin the need for management practice that improve parasite control and limit the rate of anthelmintic resistance development. The major hypothesis tested in this work was that gastrointestinal nematode infection (i.e. worms) present on commercial sheep properties in the Northern Tablelands of NSW induces significant production loss and that worm control utilising Integrated Parasite Management in Sheep (IPM) would reduce this loss and the overall economic impact of worms. Subsequent questions that required investigation in order to test this hypothesis were: the effectiveness of long-acting anthelmintics at establishing a proxy for worm-free sheep in a grazing environment and; the phenotypic relationships between measures of host resistance and resilience to intestinal parasitism and production. This discussion summarises how the results presented in this thesis led to the acceptance of this major hypothesis, with IPM reducing the effects of worms and providing an economic advantage over current regionally typical management.

7.2 The effect of management

Perhaps the greatest test of the efficacy of a worm control program, for a high summer rainfall region, is the ability to mitigate the effect of *H. contortus* on sheep mortality. On farms with regionally-typical management (TYP), infected sheep had higher worm egg count (WEC) and adult mortality and lower haematocrit compared to farms with IPM. The causative relationship between WEC, haematocrit and pathogenicity has previously been described (Le Jambre, 1995). A prolonged effect of high worm burden includes reduced liveweight (Chapter 5) and body tissue reserves which may further increase the risk of death. Increased monitoring linked to treatment thresholds on IPM farms prevented clinical signs of infection from developing. Mortality on TYP farms was the major factor accounting for increased cost of parasitism (as discussed in Chapter 6) which accrued through reduced income from wool and meat sales, and additional costs of replacement stock.

The importance of mortality to the difference between TYP and IPM varied between the two years of observation, with the large advantage to IPM being recorded only in the first year of the field experiment. Three factors are proposed to explain the effect of year on mortality. First, *H. contortus* development from egg deposition to infective larvae is highly regulated by climate (O'Connor et al., 2006). Using weather records for Armidale over the experimental period in the predictive model, WormWorld (Dobson et al., 1990a), indicated that the mean probability of *H. contortus* egg development to L3 in summer was 2-fold greater in year 1. Second, because of the change-over design, infected sheep in year 2 had spent the previous 12 months as worm-suppressed, and as a consequence, started year 2 being 2.8 kg heavier than their counterparts. Increased liveweight was demonstrated to reduce the risk of death (Chapter 4) and this may have led to lower mortality in year 2. Third, and least supported by empirical evidence, may have been the sociological response of the participating farmers to visiting scientists. While all efforts were made to observe and record but not influence management on TYP farms, it is possible that 'stockmanship' improved following mortality events in year 1. In sheep with curative worm management (treated when visual evidence of disease) that best typifies TYP, Johnstone et al. (1979) recorded an annual mortality rate of 4% in Merino sheep. With salvage treatment (treated to avert death) this increased to 12%. The 5% point increase in annual mortality due to worms with TYP management appears to be consistent with these earlier estimates.

Curiously, while IPM prevented worm-related mortality, it did not reduce wool and liveweight loss as expected (Scrivener et al., 2006), with these losses being similar across management groups. The minimal liveweight and wool loss observed in the threshold treatment group compared to worm free sheep in the penned experiment reported in Chapter 5 would suggest that appropriate thresholds (a key component of IPM) could significantly reduce these losses. In this animal house experiment (Chapter 5), larval differentials suggest that *Trichostrongylus* and *Teladorsagia* spp. did not contribute more than 15% of the WEC (~580 epg) in the threshold group when anthelmintic treatment was triggered. WEC continued to remain low after treatment and at the end of experimental periods, larval differentiation indicated that *Trichostrongylus* and *Teladorsagia* spp. did not contribute more than approximately

280 epg to the WEC. In the field experiment, IPM significantly reduced overall WEC compared to TYP, and WEC seldom exceeded 1500 epg, but larval differentials suggest that management had no effect on *Trichostrongylus* and *Teladorsagia* spp. burdens (as deduced from WEC) compared to TYP management. While *H. contortus* is the most pathogenic species due to its effect on mortality, *Trichostrongylus* and *Teladorsagia* spp. are responsible for greater liveweight and wool loss (Barger, 1982). Lowering treatment thresholds when *Trichostrongylus* and *Teladorsagia* spp. represent more than 40% of the infection (as determined by larval differentiation) below thresholds used in this study (page 73) may reduce the magnitude of production loss with IPM.

Sheep on IPM properties were consistently heavier and produced more wool than recorded on TYP farms. However, within-farm experimental contrast with worm-suppressed sheep was used to remove this variation from the analyses reported in this thesis. It was not the intention nor is it feasible to attribute this difference among the many aspects of property and livestock (including worm control) management. Nevertheless, higher levels of animal production on IPM farms meant that equivalent loss of liveweight and wool due to worms represented a smaller proportion of annual production compared to TYP. Therefore, if we expressed production loss due to worms as a proportion of total production, IPM would appear less constrained by worms. Because the magnitude of the reduction in feed intake due to worms is less when it is expressed per unit of body weight (Sykes, 1983), it is probable that heavier sheep would suffer a greater absolute decline in feed intake as a result of worm-induced anorexia. As a result, heavier sheep would also suffer a larger decrease in metabolisable energy available for production and therefore greater absolute losses of liveweight and wool due to worms would be expected. Hence, the similar level of wool and liveweight loss on IPM farms (with TYP) is suggestive of greater worm control compared to TYP management.

7.3 The phenotypic effect of resistance and resilience

Overall, worm infection in the field experiment reduced greasy wool growth by 170 g and liveweight by 2.8 kg. This masked a large variation in depression between the most (quartile 1) and least (quartile 4) phenotypically resistant (WEC) sheep (Chapter 3). Depression due to worms for the most resistant quartile was 48 g of wool and 1.2 kg liveweight and for the least resistant quartile was 238 g of wool and 3.0 kg liveweight. In a separate contrast informative of the variation in depression, sheep with the heaviest GFW when infected (quartile 1) lost 27 g of wool and 1.4 kg liveweight, whereas sheep with the lightest GFW when infected (quartile 4) lost 305 g wool and 2.1 kg liveweight, respectively. This phenotypic variation within the flock suggests a significant opportunity to reduce the effect of worms by improving resistance and production when challenged.

Improving host resistance has been a staple recommendation of sustainable worm control programs (Waller, 1999). However, recent advancements in understanding the links between host immunity and feed intake depression require this recommendation to be reassessed in terms of minimising the economic consequences of parasitism (Greer, 2008). On the Northern Tablelands of NSW, this study suggests that improving host resistance will be beneficial. While not increasing wool production, resistance was associated with greater weight gain, reduced haematocrit depression and reduced risk of mortality.

The benefits of phenotypic resistance may not be the same in environments not dominated by *H. contortus* or where improved worm control can be achieved through other means such as grazing management. For example, wool growth and liveweight gain was least in the more resistant sheep during the period of worm-suppression. This novel finding raises the question that improving genetic host resistance may reduce production potential when worm control can be successfully achieved by other means. On the Northern Tablelands, evidence suggests that tactical, co-species grazing strategies provides worm control that reduces WEC and anthelmintic treatments (Colvin et al., 2008). While a multi-trait selection approach may manage this possibility, further research is warranted to explore the implications of this novel finding.

This study confirms the findings of Albers and Gray (1987), demonstrating that increased resilience (production loss due to worms) is associated with a reduction in WEC. However, this trait is difficult to measure and heritability is too low to allow for substantial gain when selected as a single trait (Albers et al., 1987). Therefore, as resilience is strongly associated with wool growth and liveweight gain when infected, and was independent of WEC, these measures provide an appropriate proxy measure. These resilient sheep also have lower risk of mortality due to increased growth rates. Continuing the selection of high producing sheep under IPM management would appear to offer a strategy that would further minimise the cost of worms. Further studies could assess the possibility of increased treatment thresholds in resilient sheep and effects on production and levels of refugia.

7.4 The effectiveness of controlled-release capsules

Previous estimates on the cost of worms have been dependant on animal house and research station experiments. The value of estimating the costs of disease is the ability to then assess the advantage of management change (Perry and Randolph, 1999). An accurate estimate of the true disease costs will assist with the development of innovative ways to control parasitism.

This study presents a suitable method of estimating gastrointestinal disease costs within commercial management practices over the full production year using CRCs and long-acting moxidectin. This method has several advantages. First, observations can be made over a prolonged period of time. Short periods of observation could overstate the cost of worms as host resistance develops. Second, the dynamic nature of farm management is accounted for, with infected sheep being treated according to production targets rather than an imposed experimental timeframe or protocol. Third, the use of effective treatments removes any detectable production loss associated with larval challenge or the establishment of adult worm populations. Albers et al. state(1989):

> “In studies of the effect of anthelmintic treatment on production of sheep grazing infested pastures, conservative estimates of production loss are inevitable, since the treated group cannot be regarded as worm-free. Even at high frequencies of treatment with very effective anthelmintics, sheep will still ingest infective larvae which may undergo at least some development.”

This concern is justified, as larval challenge stimulated an immune response as identified in Chapter 5. However, the level of challenge resulted in no detectable production loss in sheep with a CRC but high worm burdens in sheep without a CRC. Hence, it can be concluded that an effective CRC (and assumedly other anthelmintics with sustained activity) can provide an effective tool to establish a proxy for worm-free sheep in a grazing environment.

In field trials, the establishment of worm-suppressed sheep is made challenging by the presence of anthelmintic resistance to albendazole. Albendazole resistance on several properties in Chapter 2 reduced the capacity of the CRC model. While some exposure to adult worms did occur on some properties early in the experiment, the revised experimental protocol (introduction of a moxidectin injectable drench) improved the model and allowed an accurate estimation of the effect of worms. The exposure to adult worms may have reduced wool and liveweight gain in worm-suppressed sheep, reducing the magnitude of production loss observed in infected sheep on TYP farms in year 1 compared to year 2. If the experiment were to be repeated, CRCs in combination with a long-acting moxidectin injection, would be preferable.

7.5 Future pathways

Adoption of sustainable practices such as IPM has been slower than socially optimal due to a range of economic and sociological factors (Pannell, 1999). Investigating adoption of Integrated Weed Management practices, Llewellyn et al. (2005) showed that the greatest influence of adoption was perceived economic benefit. Adoption of IPM is also limited by socio-cultural and psychological factors, mainly: perceived uncertainty of IPM components and their level of worm control, lack of knowledge to implement, and challenges to self-identity (Thompson, 2009). This study has addressed several of these challenges. IPM provided greater level of worm control, reduced risk of mortality and consequently provided a significant economic advantage. Additionally, IPM required less anthelmintic treatment and should limit the development of anthelmintic resistance (Besier et al., 1996). This study has provided greater knowledge about worm management to the industry that should assist with the adoption of improved and more sustainable management.

7.6 Conclusion

This study has provided a quantative assessment on the cost of worms in sheep on the Northern Tablelands of NSW. It has highlighted the importance of IPM at removing mortality caused by high *H. contortus* burdens and consequently reduce the economic constraints to production. The study has also provided a better understanding of host response to worm challenge, demonstrating the potential of some sheep to tolerate high WEC or reduce WEC compared to their cohort. Together, these results should allow more sustainable worm control practices in summer-dominant, high rainfall regions while ensuring that commercial sheep enterprises are not financially encumbered due to parasitism by worms.

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