Sustainable Control of Parasites in Sheep

SUSTAINABLE WORM CONTROL STRATEGIES FOR SHEEP 4th Edition

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A Technical Manual for Veterinary Surgeons and Advisers

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FOREWORD

Worm control is a vital part of health and production management in sheep flocks in the UK, and good control is highly dependent on effective anthelmintics. Unfortunately, a direct and unavoidable consequence of using anthelmintics to control worm populations is the selection for individual worms that are resistant to the chemical group used. In some parts of the world, for example South Africa, South America and the Antipodes, the degree of resistance has reached the point where sheep farming is unsustainable in some areas. If left unchecked, anthelmintic resistance could prove to be one of the biggest challenges to sheep production and welfare in the UK.

SCOPS was formed in 2003 as the result of the industry and Defra recognising that we could not ignore this impending problem. The group is made up of representatives from across the sheep industry* working together to promote practical guidelines to sheep farmers and their advisers. These guidelines were originally produced as a result of a workshop held in March 2003, involving leading authorities in endoparasite control.

Our challenge is to get sheep farmers to recognise the threat of anthelmintic resistance and act while anthelmintics still control clinical disease on their farms. SCOPS recognises that this is not an easy task, because in most cases sheep farmers are still achieving good levels of worm control with their current strategies. Fundamental to success is that while we talk about widespread resistance being ***detectable*** on farms in the UK, this is not confused with unacceptable levels of control. This means our message is one of good news for the UK, because it is not too late to make a difference. If the SCOPS guidelines are followed, it is still possible to sustain the effectiveness of the 3-ML, and new groups, on the majority of sheep farms for years to come. With the right strategy, the development of resistance can be delayed for many years; but with the wrong strategy the loss of clinical worm control can be very rapid, potentially within a single grazing season

This manual has been updated for the third time as part of our commitment to review new research, gather feedback and field experiences and incorporate that knowledge into our recommendations. We are also very aware that with the launch of two new novel anthelmintics (4-AD and 5-SI) in 2010 and 2012 there is the real opportunity to delay resistance to the 3 original groups, while making protection of the new ones a high priority.

With your help, sheep farmers can slow the progress of resistance on their farms by changing certain practices that are highly selective for resistance, but we must act before it is too late.

Peter Baber
Chair of SCOPS

June 2012

Members of SCOPS:
NSA; NOAH; AHDA;AMTRA; RUMA; SVS; Defra; Welsh Assembly; SERAD; SAC; AHVLA; NFU; VMD; Independent consultants;

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1 Introduction – The Need for Change

1.1 Introduction

The routine use of highly effective anthelmintics, together with grazing management, has controlled worms very successfully in the majority of UK sheep flocks for nearly 40 years. However, the prevalence of anthelmintic resistance (AR) in the UK has risen sharply in recent years with an increasing number of flocks finding that one or more of the chemical groups are no longer effective against some worm species. Since the production of the first edition of this manual in 2004, several studies in Scotland, England and Wales have found evidence of "triple" resistant worm species on several farms. This is extremely worrying and underlines the urgent need for sheep farmers and their advisers to adopt strategies that will slow down the speed with which AR is developing.

As a veterinarian or adviser, you will be aware of the challenges this poses. The 'blue-print' control strategies used historically have the advantage of being easy to plan and record and are relatively cheap. Unfortunately, some elements of these practices are highly selective for AR and if we are to slow its progress, we must adopt worming strategies which reduce these selection pressures. However, persuading sheep farmers to change their practices is not an easy task because it requires much more knowledge regarding the worm populations and management options on individual farms and a fundamental change in attitude towards the balance between worm control and animal performance.

The introduction of a new group (4-AD) to the UK market in 2010, and a further new dual active containing a 5th group (5-SI), offers the opportunity for us to bring new novel groups into worming strategies. SCOPS firmly believe that if we are to extend the effective life of the older groups, (in particular the 3-ML) it is essential to integrate new groups at an early stage, while the frequency of resistant alleles in the worm population is still low. Waiting until the older groups have failed before using new groups would simply serve to accelerate the selection for AR to the new group and miss the opportunity of using them constructively to protect both themselves and the older molecules.

Resistance to anthelmintics is not the only reason for change. Much of the research on which existing strategies are based is more than 30 years old. In that time there have been significant changes in the size and structure of the sheep industry, the epidemiology of the parasites and the products available, adding further weight to the need for change.

1.2 The sheep industry

The UK sheep flock reached its peak size in the mid 1990's with just over 20M breeding ewes but this has now fallen back to just over 13M ewes as changes in EU support, low profitability and other factors such as FMD and Bluetongue outbreaks have conspired to push numbers down. At the same time, cattle numbers have also fallen and combined with very high cereal prices there are now few opportunities for the alternation of sheep, cattle and conservation, and/or the use of new leys, as a means of reducing worm burdens. As a result, and coupled to pressure to reduce overheads, in particular labour costs, sheep farmers have become increasingly reliant on the routine use of anthelmintics for worm control. It is against this background that SCOPS has been developing sustainable worm control strategies based on reduced reliance on routine anthelmintics, careful use and selection of the most appropriate product and regard to the proportion of the worm population not exposed to the treatment (*in refugia*).

1.3 The parasites

There have been noticeable changes in the epidemiology of many of the most common sheep endoparasites in recent years. We do not know if this is due to climate change, selection pressures, change in production systems or indeed a function of them all. However it is clear that our worm control strategies need to take these into account. Examples are:

- ***Haemonchus contortus* –** previously described as a problem confined to South East England, *Haemonchus* is now widespread and is frequently found as far North as Scotland. This has

profound implications for control strategies, particularly in adult sheep and the need for quarantine treatments.

- ***Nematodirus battus*** – historically seen as a spring problem, *N battus* is now seen at varying times of the year and the first case of resistance to the 1-BZ group was reported in 2011.

- ***Trichostrongylus* spp** – traditionally seen in the autumn in store lambs these worms cause 'black scour'. However, they are now frequently encountered earlier in the summer months, causing losses in younger lambs. In mild winters they have also been shown to continue to cause severe disease during the winter and early spring months.

1.4 The anthelmintics

Since the development of the worming strategies of the 1970s and 80s, the macrocyclic lactone (3-ML) group were added to the range of anthelmintics available to sheep farmers. This now includes the first broad spectrum products with persistence against some of the main worm species (moxidectin). In 2010, we also had a fourth group (4-AD) added to the armoury and a fifth (5-SI) has been launched as a dual active with a 3-ML (abamectin) in 2012.

Current research suggests that resistance to the 3-ML group is continuing to increase in the UK. The prevalence of resistance to the benzimidazole (1-BZ) group is widespread, and cases of levamisole (2-LV) resistance continue to be reported based on recent studies within Great Britain.

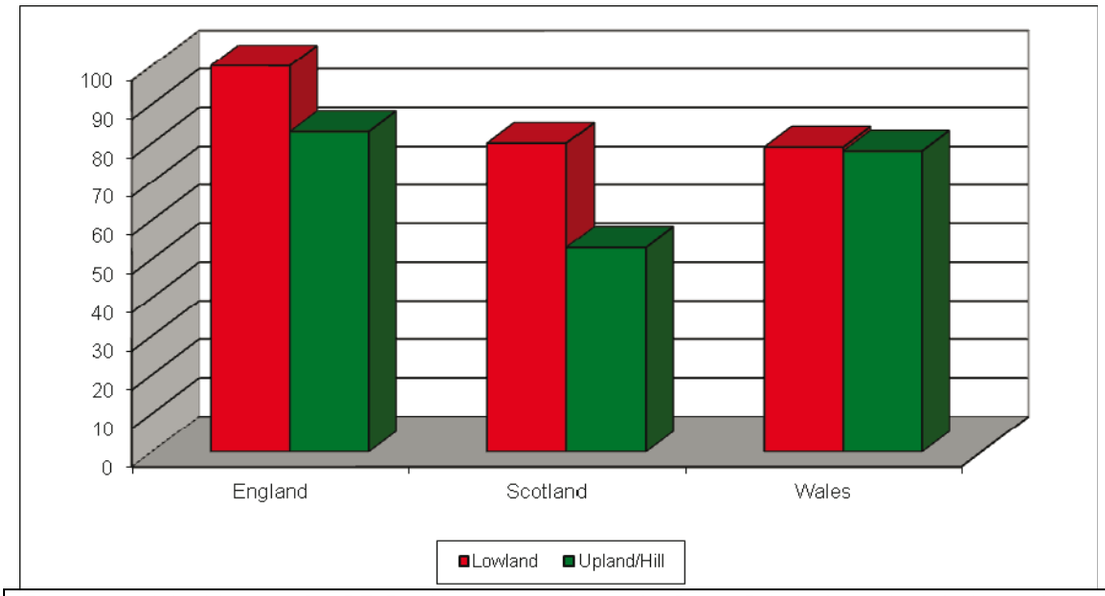


Figure 1.4.1 Incidence of 1-BZ Resistance on Farms in Great Britain based on independent studies conducted in England, Scotland and Wales

Studies by the Moredun Research Institute in Scotland since 2000 have shown an increase in 1-BZ resistance from a level of just over 20% incidence in 1991 to 80% prevalence on lowland farms and 55% on upland and hill farms.

The Wales Worm Watch project conducted in 2005 showed that 83% of all farms tested had detectable anthelmintic resistance. Resistance to 1-BZ anthelmintics was present on 80% of farms tested, with 1-BZ resistance only being more common on Hill/Upland farms (49%) compared to lowland farms (32%) with regional variations. Both 1-BZ and 2-LV resistance was present in 47% of lowland and 29% Upland/Hill flocks tested.

Studies in England and Wales, as part of the SCOPS initiative (Fig 1.4.2), indicate that resistance to the 1-BZ group can be detected on nearly 100% of lowland farms and 83% of Upland/Hill farms. Levamisole resistance (2-LV-R_ was detected on 47% of lowland farms and 17% of Hill/Upland farms, all of which also had 1-BZ resistance (1-BZ-R). In these studies conducted in 2007/2008, *T.*

circumcincta was the dominant species with 1-BZ-R detected on 97.5% of farms and 1-BZ-R *Trichostrongylus* spp present on 44% of farms. Forty (40) per cent of these farms also had 2-LV-R *T. cirmumcincta* and 50% 2-LV-R *Trichostrongylus* spp.

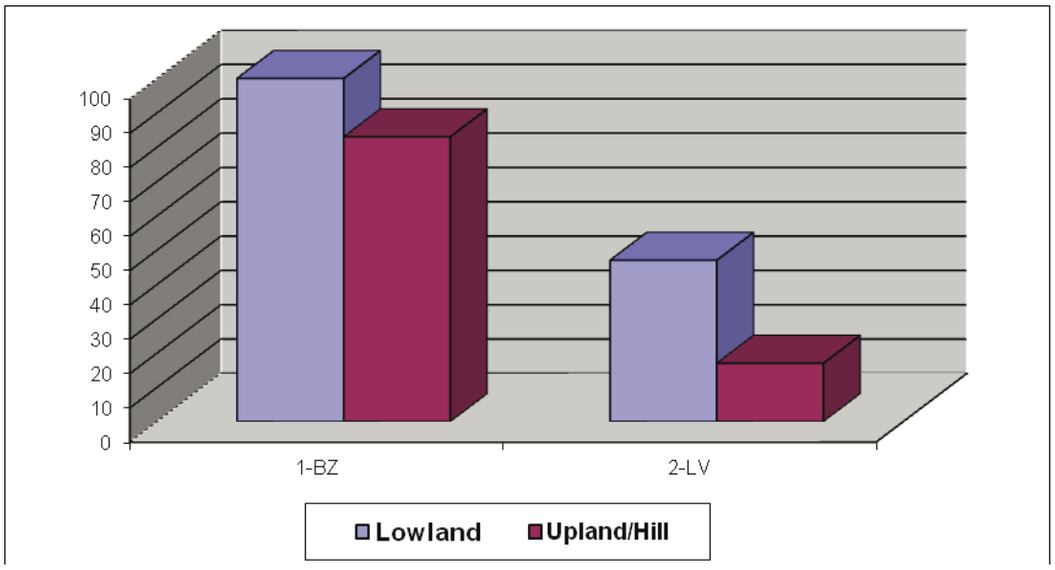


Figure 1.4.2 Resistance on Farms in England and Wales. SCOPS Study – 2007 Results.

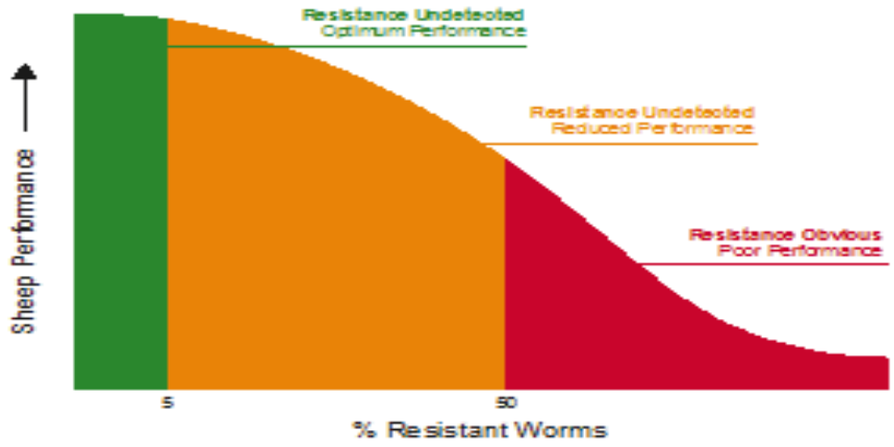
Currently resistance to 3-ML compounds can only be determined by Faecal Egg Count Reduction Test (FECRT – see chapter 8) and only limited numbers of these tests have so far been conducted within Great Britain. 3-ML resistance has been reported on an increasing number of farms in Scotland, SW England and Wales, mainly with *T. circumcincta* and where present, was associated with 1-BZ and 2-LV resistance ("triple resistance"). Although the numbers of confirmed cases are few, they are becoming more significant and numbers will no doubt continue to increase. To add to these concerns, there have been a small number of reports of moxidectin (MOX) resistance.

In a study conducted in 2010 from farms in England and Wales where Drench Tests were used as an initial means of determining anthelmintic efficacy, 12 out of 19 farms treating with a 3-ML were classified as drench failures, with efficacies ranging between 75 and 89.8%. On seven of the farms with ML drench failures, FECRTs were subsequently conducted. Three of the seven farms gave results that were assessed as indicating ML-resistance with *T. circumcincta* the species involved.
In 2011 in a continuation of this project of 16 farms that met inclusion criteria 10 had a post drench efficacy of less than 95% (7 were less than or equal to 80%) and 6 had an efficacy between 95 and 100%. This represented 3-ML drench failure on 63% of the farms.

1.5 Taking Action Early

Whilst all of these studies indicate the widespread presence of resistant genotypes on UK sheep farms, this does not necessarily indicate an associated failure to control worm populations on farms for reasons that are discussed in more detail in Chapter 5. **Detection of resistance (<95% efficacy) occurs long before the farmer will notice that a group is not working very well.** The influence we have is on how long it takes to get from being able to detect that resistance is present, to the point at which the % of worms killed is so low that the farmer is no longer getting acceptable worm control.

The Diagram 1.1 below illustrates this in terms of animal performance.



If we can persuade sheep farmers to adopt the SCOPS guidelines while the frequency of resistant alleles is still low, we can extend the timescale along the bottom of the graph. For many farms of course, it is too late for the 1-BZ group; but for a large proportion, while the 3-ML is building some detectable resistance, it is not too far advanced. Reduced selection pressures and judicious introduction of the 4-AD and new dual active 5-SI group will prolong the effective life of the 3-ML group while protecting new groups from over-use.

1.6 Pressures on the macrocyclic lactone (3-ML) Group

The situation with respect to the 3-MLs is complicated because they have three distinct advantages for sheep farmers compared with the 1-BZ or 2-LV groups.

- ❖ They are available in injectable preparations as well as oral drenches.
- ❖ They are active against some ecto as well as endoparasites and offer an alternative to dipping for sheep scab control.
- ❖ One member of the group, moxidectin, has persistent activity against some nematode species.

These features have encouraged sheep farmers to use the 3-MLs widely and have led to an increase in their inadvertent use, for example as an endectocide, when the treatment is being primarily used against sheep scab. This has significant implications for the development of AR to 3- MLs.

1.7 Protecting the activity of new anthelmintic groups

The alleles that allow parasites to become resistant to anthelmintics are believed to pre-exist in unselected worm populations (See section 5.4), therefore, the development of AR is an inevitable consequence of their use. At the workshop held in January 2009, experts discussed the prospect of new anthelmintic compounds with novel modes of action becoming available in the near future. It was considered vitally important that effective strategies were devised in anticipation of any new compounds in an attempt to prolong their effectiveness against pre-existing resistant worm populations.

The main conclusions of the meeting were:

1. Any new product(s) should be central to quarantine strategies with the aim of preventing the introduction of resistant parasites on to farms

2. New compounds should be used strategically and only where necessary. However, they **should not** be left 'in reserve' for when all other groups have failed on a farm. It is important they are integrated into worm control plans that along with existing products and with greater emphasis on management actions aimed at reducing dependence on anthelmintics.

3. For these new compounds to be integrated into control strategies effectively it is essential that there is knowledge of the AR status of the farm and every effort is made to maintain a high proportion of the worm population *in refugia.*

2 The Parasites

2.1 Nematode parasites of sheep in the UK

There are about 20 different species of nematodes of sheep commonly found in Britain, the more important of which are shown in Table 2.1 Pathogenicity varies with species, the numbers of nematodes present as well as host factors such as age (maturity), nutritional status and body condition. The tapeworm, *Moniezia expansa,* and other tapeworms for which the sheep acts an intermediate host, are also covered at the end of this chapter. The liver fluke *Fasciola hepatica* (a trematode) is discussed in Section 7.

Table 2.1 ***Nematode parasites of sheep***

Site	Species	Features	Pathogenicity (**H**igh/**M**ed/**L**ow)
Abomasum	*Teladorsagia* (*Ostertagia*) *circumcincta*	'Small brown stomach worm' 0.8 – 1.5 cm	H
	Haemonchus contortus	'Barber's Pole worm' 1.5 – 3.0 cm long and stout. Very obvious to the naked eye.	H
	Trichostrongylus axei	'Stomach hair worm' 0.3 – 0.6 cm	M
Small intestine	*Trichostrongylus colubriformis* *Trichostrongylus vitrinus*	'Black scour worm' 0.4 – 0.9 cm	M M
	Nematodirus battus *Nematodirus filicollis* *Nematodirus spathiger*	'Thin-necked intestinal worm'1.0 – 2.3 cm	H L M
	Cooperia curticei	'Small intestinal worm'0.5 – 0.8 cm	L
	Bunostomum trigononcephalum	'Hookworm'1.2 – 2.6 cm	M
	Strongyloides papillosus	'Threadworm' 0.4 – 0.6 cm	L
	Capillaria longipes	'Hairworm' 0.1-0.2 cm	L
Large intestine	*Oesophagostomum venulosum*	'Large bowel worm' 1.0 – 2.4 cm	L
	Trichuris ovis	'Whipworm' 4 – 8 cm	L
	Chabertia ovina	'Large-mouthed bowel worm' 1.4 – 2.0 cm	L
Lungs	*Dictyocaulus filaria*	'Large lungworm'. Live in bronchi, 3 – 10 cm	M
	Protostrongylus rufescens	Live in the small bronchioles. 1.6 – 4.0 cm	L
	Cystocaulus ocreatus	Live in the small bronchioles. 4.0 – 9.0 cm	L
	Neostrongylus linearis	Live in the small bronchioles. 0.5 – 1.5 cm	L
	Muellerius capillaris	'Small lungworm'. Form nodules in lung parenchyma. 1.2 – 2.2 cm	L

2.2 Life cycles of the gastrointestinal nematodes

2.2.1 The typical life cycle

The life cycles of the gastrointestinal nematodes (Fig. 2.1) are all very similar, with one or two minor exceptions, and the following description applies particularly to *Teladorsagia*, *Trichostrongylus* and *Haemonchus*.

There is no multiplication within the sheep and the life-cycle is direct i.e. no intermediate host. Adult female worms in the sheep lay eggs that pass out in the faeces and hatch; each egg releasing one first-stage larva (L1). The L1 develop and moult to second stage larvae (L2). The L1 and L2 are active and feed on bacteria in the faeces. At the second moult to the third stage larvae (L3), the cuticle of the L2 remains as a sheath, protecting the L3 but also preventing them from feeding. The L3 is the infective stage. L3 migrate on to the herbage where they are ingested by sheep. In the walls of the stomach or intestines they develop into fourth stage larvae (L4), before emerging as adult worms about 14 days later. The prepatent period (between ingestion of L3 and the appearance of eggs in the faeces) is generally between 16–21 days. Adult worms that are not expelled from the sheep by immune mechanisms or killed by anthelmintics survive for only a matter of weeks (typically less than 12) before dying naturally.

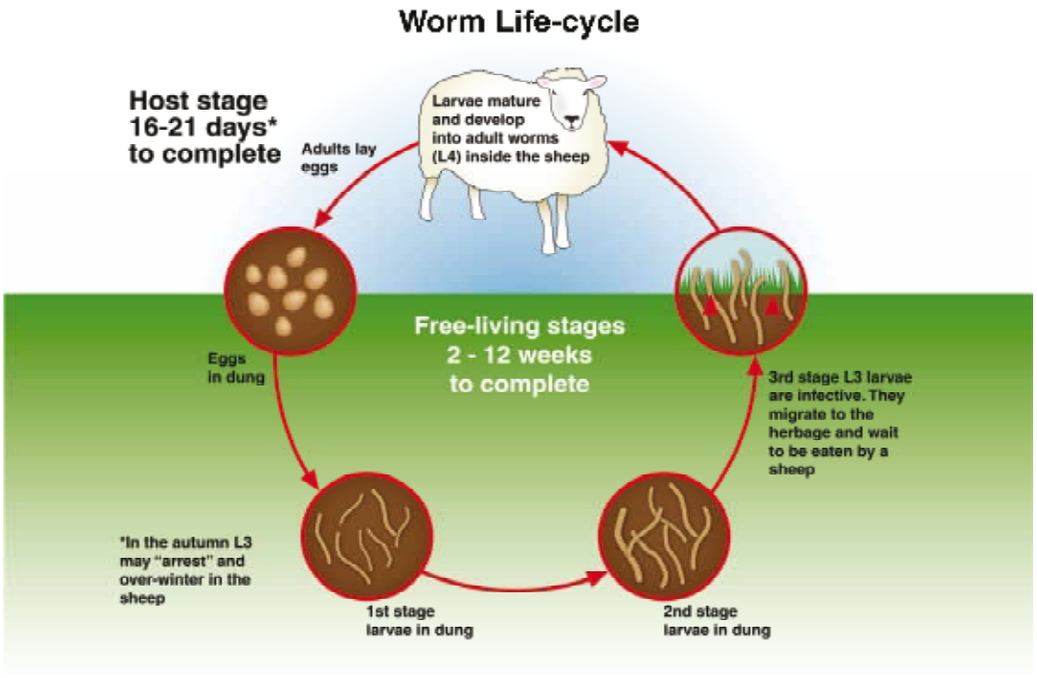


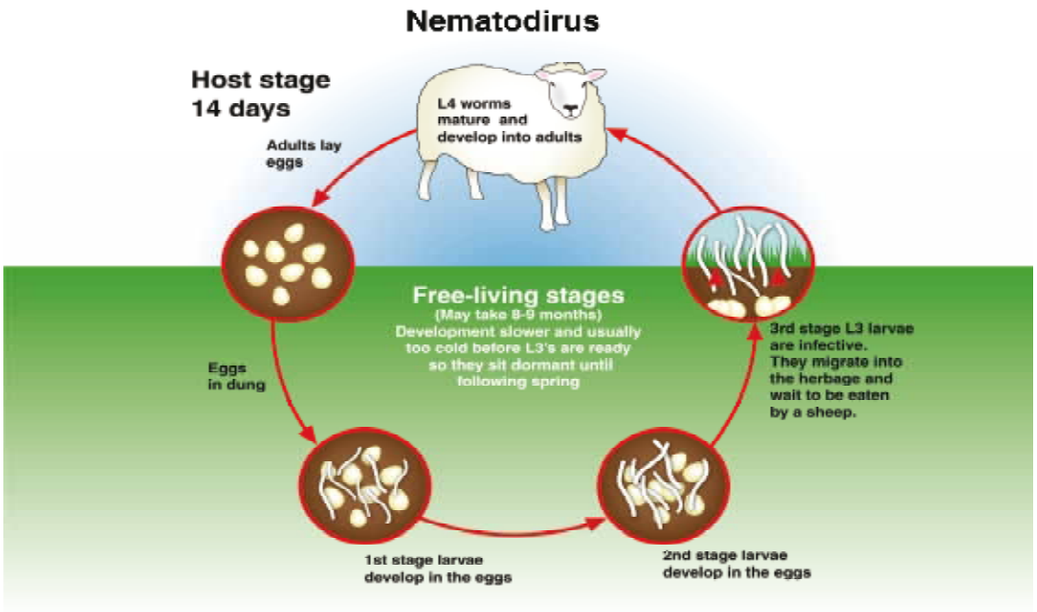
Fig. 2.1 ***The basic life cycle of the nematode parasites of sheep.***

2.3 Important variations on the basic life cycle

2.3.1 Nematodirus battus

For all *Nematodirus* spp, development to the L3 takes place within the egg. With *N battus*, hatching and release of the L3 occurs as a result of climatic stimulus, usually a period of chill followed by a mean day/night temperature of more than 10°C. The prepatent period can be as short as 14 days.

Nematodirus battus has a much slower life-cycle, with infection passed from a lamb crop in one year to the lambs born in the following year. The long survival of *Nematodirus* eggs permits this relatively long generation interval. As a result of the specific climatic requirements for egg hatching, large numbers of infective larvae can appear on pasture almost synchronously. This usually occurs between April and June each year, but can occur at other times of the year. When mass hatching coincides with the presence of 6-12 week old lambs, severe outbreaks of nematodirosis can occur (see also Section 3.5).



2.3.2 Strongyloides papillosus

The L3 has no protective sheath. L3 can infect the host by ingestion or by skin penetration. Transmission may also occur to lambs via the milk of the ewe. The prepatent period is about 9 days.

2.3.3 Bunostomum trigonocephalum

Infection of the host occurs by ingestion or through the skin. Following skin penetration the larvae pass to the lungs and then to the small intestine. The prepatent period is about 56 days.

2.3.4 Trichuris ovis

Infection of the host occurs through ingestion of the L1 in the egg. After ingestion the plugs at the ends of the egg are digested and the L1 released. All four moults occur within the sheep. The prepatent period is 1 to 3 months.

2.4 Epidemiology

Two terms are used to describe the conditions of pastures containing the free-living nematode stages. Pastures are ***'contaminated'*** if there are eggs and larvae present, but pastures are only ***'infective'*** if there are L3 present and climatic conditions are suitable for them to move up onto the herbage, where they can be ingested. Both rainfall and temperature influence the infectivity of pastures. The rate of development to the infective stage (L3) is dependent on temperature. Rain tends to increase the

infectivity of pastures by assisting in the movement of L3 out of faecal pellets or pats and by providing the film of moisture necessary for L3 to migrate onto herbage. Rainfall records have been used to predict the peak of availability of nematode larvae on pasture, and temperature records are used to predict the risk of nematodirosis in lambs.

Development of L3 from eggs deposited in early spring may take 10–12 weeks but eggs deposited later in the season develop faster. Summer-deposited eggs can give rise to L3 in just 1–2 weeks. Consequently, eggs passed onto pasture in spring and early summer tend to reach the infective stage at about the same time, resulting in high levels of pasture infectivity from mid-summer onwards (Fig. 2.2).

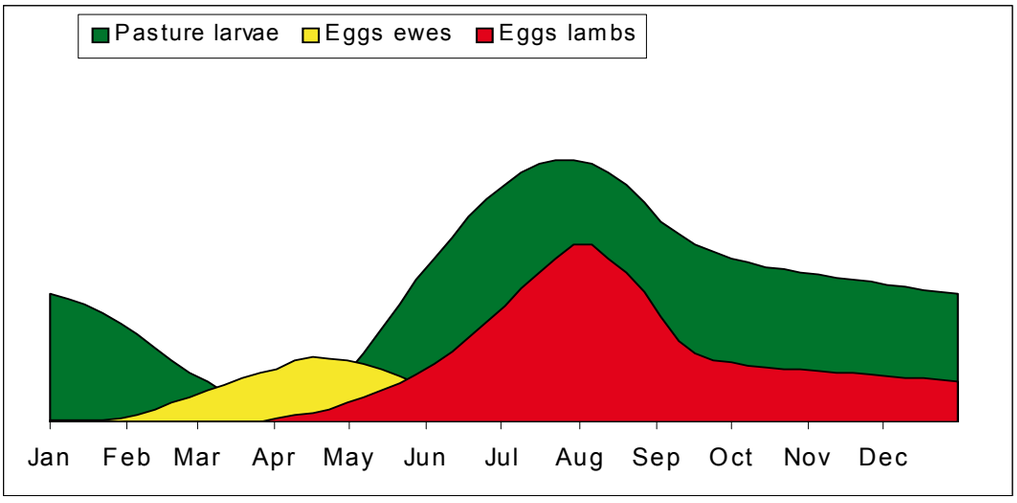


Fig. 2.2 ***The epidemiology of nematode parasitism in sheep at pasture***

L3 are most active during warm weather and, if they are not ingested, consume their energy stores and suffer high mortality rates. In autumn and winter, L3 can survive longer and some will over-winter on pasture. Some worm species are better at winter survival than others – *Haemonchus* larvae do not survive well in freezing temperatures but *Nematodirus* eggs can survive prolonged cold temperatures. Over-wintering L3 provide a source of infection to grazing sheep in late winter and early spring but do not survive long on pasture after ambient temperatures rise. Pasture infectivity tends to decline rapidly to low levels in late April or early May.
If spring-lambed ewes are placed on the pasture, contamination with worm eggs occurs first from the ewes themselves (early spring), and then later (late spring and summer) from the lambs as well. In the case of the ewes, the worms producing these eggs have survived over winter in the ewes or have developed from the ingestion of over-wintered L3 in early spring. In the case of the lambs, the worms have arisen from the ingestion of over-wintered L3 then, later in the season, from eggs deposited by the ewes. The source of the high infectivity of pastures in late summer and autumn is the deposition of eggs in spring and early summer.

This typical pattern (Fig. 2.2) is seen most clearly in the epidemiology of *Teladorsagia* and *Trichostrongylus*. The rise in pasture larval availability in early summer tends to be dominated by *Teladorsagia*, with *Trichostrongylus* spp contributing increasingly in late summer and autumn.

Haemonchus has a very high biotic potential with each female worm capable of producing up to 10,000 eggs per day. Warm and wet conditions favour the rapid development of eggs to L3 and pastures can become highly infective very quickly almost any time between mid-spring and late autumn. This means that pastures can change from low *Haemonchus* infectivity in early spring to very high infectivity in summer and autumn, causing serious, unexpected outbreaks of Heamonchosis in lambs and ewes. This proclivity for rapid generation turnover under suitable conditions compensates for the poor over-winter survival of *Haemonchus* eggs and larvae on pasture under cold conditions.

2.5 Hypobiosis (arrested development)

The abomasal nematodes *Teladorsagia* spp*, H. contortus* and *T. axei* are capable of interrupting their development at the L4 stage and persisting for long periods in a state of dormancy or hypobiosis. They then resume their development and become normal, egg-laying adults. This interruption of development occurs principally to larvae ingested in the late autumn and winter. It can be considered as an evolutionary adaptation which delays egg production (and death) until the following spring when eggs deposited on pasture have a higher chance of continuing the worm's life-cycle. In the case of ewes, most of the *Teladorsagia* population in the host between November and February exists as hypobiotic larvae. Between April and September, there are very few, if any, hypobiotic larvae and most parasites exist as adult or actively developing forms.

Hypobiosis is important in sheep for three reasons:

- When hypobiotic larvae of *Teladorsagia* resume their development, they can be responsible for clinical disease in yearling sheep, similar to type II ostertagiosis or 'winter scours' seen in cattle. (See also Section 4.4)

- The worms developing from hypobiotic larvae in ewes are an important source of pasture contamination in the spring and early summer.

- Hypobiosis is the principle way *H. contortus* survives the winter in the UK. This also has implications for the selection for AR since it means that the proportion of the Haemonchus worm population 'in refugia' in spring is likely to be very low. Any anthelmintic treatment of ewes is therefore highly selective for AR.

The small intestinal parasites, including *Nematodirus* spp, *Trichostrongylus* spp and *Cooperia* spp, are also capable of hypobiosis but this does not appear to be an important feature of their epidemiology.

2.6 Lungworms

Sheep are infected with a number of lungworm species, the most important being D*ictyocaulus filaria*. Several species of metastrongylid lungworms also occur in sheep and include *Protostrongylus rufescens*, found in the small bronchi, *Muellerius capillaris*, *Cystocaulus ocreatus* and *Neostrongylus linearis* all of which are present in the lung parenchyma forming small nodules.

The life cycle of *D. filaria* is similar to GI nematodes except that L1 pass out in the faeces and develop to infective L3. After ingestion, the L3 penetrate the intestinal mucosa and pass to the mesenteric lymph nodes where they moult. The L4 then travel via the lymph and blood to the lungs, and break out of the capillaries into the alveoli about one week after infection. The final moult occurs in the bronchioles, a few days later, and the young adults then move up the bronchi and mature.

The life cycles of the various other lungworms species are similar and indirect, requiring a molluscan intermediate host. Sheep are infected by ingesting a slug or snail containing an infective L3. Following ingestion of an infected mollusc with herbage, the larvae are freed and travel to the lungs via the lymph and blood vessels, and enter the mesenteric lymph nodes and lungs.

Disease due to lungworm in sheep is usually less severe than those seen with cattle. Infections with *D. filaria* may cause dyspnoea and coughing in grazing animals usually in the autumn. Mild infections usually of other lungworm species are not normally a problem, though heavy infections may cause bronchopneumonia and emphysema.

2.7 Tapeworms

Tapeworms are mainly of importance as the intermediate larval stages in sheep; the final hosts being carnivores. Adult tapeworms (*Moniezia* spp.) are common parasites of the intestines of sheep and are frequently diagnosed because of the presence of segments in the faeces. Infections are generally symptomless, though occasionally clinical signs including unthriftiness, diarrhoea, respiratory signs and even convulsions have been attributed to *Moniezia. Moniezia* eggs are passed in the faeces and on pasture where the onchospheres are ingested by pasture mites and develop into cysticercoids in 1-4 months. Sheep are infected by ingestion of infected mites during grazing.

Intermediate stages of *Taenia* spp. may harm the host e.g. *Multiceps* (*Taenia) multiceps,* found in the brain (*Coenurus cerebralis*), causing 'sturdy' or 'gid' in sheep. Clinical signs depend on the location and size of the cyst or cysts and include circling behaviour, visual defects, and peculiarities in gait, stumbling, non-coordinated movements or paraplegia. As the infection progresses animals may become anorexic and lose weight and death may result. With the syndrome ‘gid’ the animal holds its head to one side and turns in a circle to the affected side.
Others such as *Echinococcus granulosus* (hydatid) found in the lungs and liver may be important in public health. Hydatid infections (*E. granulosus*) in sheep are generally not associated with clinical signs but can lead local condemnation of affected organs. The metacestodes of *Taenia hydatigena* (*Cysticercus tenuicollis*) can result in liver or carcass condemnation and in heavy infections may lead to hepatitis and death in young lambs. *Cysticercus ovis* (“sheep measles”), the intermediate stage of *Taenis ovis* found in the muscles and heart, can be a significant cause of economic loss through carcase condemnation at slaughter. Such infections have become a significant problem in some areas in recent years. Eblex estimated that in 2009 *Cysticercus ovis* cost the English sheep industry £7M with a further 9% of livers affected by C.tenuicollis costing another £500,000 in lost revenue.

The larval tapeworms found in sheep (e.g. metacestodes stages of Multiceps multiceps, Taenia spp, and Echinococcus granulosus) are acquired by ingestion of eggs passed out in the faeces of the final canid hosts (dogs and foxes). The life cycle is completed when a dog of fox feeds on infected sheep viscera.

3 Disease Caused by Gastrointestinal Nematodes

3.1 Disease presentations

Disease caused by gastrointestinal nematodes may be acute in onset, with outbreaks of clinical disease in 10% of a flock or more, with some mortality. The devastating effects of such outbreaks on a flock are obvious. Gastrointestinal parasites also cause sub-clinical disease, with reduced growth rate, reduced milk and wool production and reduced body condition. Although far less dramatic, these insidious losses may involve large numbers of sheep for prolonged periods resulting in high costs to the industry.

The clinical signs of parasitism, caused by the gastrointestinal nematodes, fall broadly into two categories.

- Signs associated with gastritis and enteritis, typical of infection with *Teladorsagia* spp, *Trichostrongylus* spp and *Nematodirus* spp

- Signs associated with blood loss as a result of infection with *Haemonchus contortus*.

3.2 Teladorsagia (Ostertagia) spp

Confusingly, the sheep nematodes previously referred to as *Ostertagia* spp have been reclassified as *Teladorsagia* spp, but they are still widely known by their previous name and the disease they cause, ostertagiosis, is still retained.

Ostertagiosis is characterised by inappetance, diarrhoea, dehydration, weight loss and death. As a result of the reduced feed intake and dehydration, the sheep appear 'hollow', with very little rumen-fill. Smaller burdens of parasites may be responsible for poor weight gains in the absence of clinical signs. The poor weight gains are a consequence of reduced appetite, reduced feed intake and losses of plasma protein into the gastro-intestinal tract. Disease results from damage to the abomasal mucosa caused by larvae as they emerge from the gastric glands where they develop, and by the presence of adult worms on the mucosal surface.

Ostertagiosis is typically seen in lambs during their first season at grass and usually occurs from mid-summer onwards, associated with the ingestion of relatively large numbers of infective larvae over a short period (type I ostertagiosis). In yearling animals during the winter months, type II ostertagiosis may occur as a result of the synchronous resumption of development of large numbers of hypobiotic larvae that were acquired during the previous autumn grazing.

3.3 Trichostrongylus spp

Heavy infections of the small intestinal *Trichostrongylus* spp (principally *T colubriformis* and *T vitrinus*) cause inappetance, diarrhoea, rapid weight loss and death. The common name of the worm (black scour worm) describes the clinical picture. The disease is usually seen in store or replacement lambs during the autumn and winter months but can also occur in lambs from late summer onwards.

At lower levels of infection, poor growth rates, sometimes accompanied by soft faeces, are the common signs. Chronic infections of *T. colubriformis* are accompanied by reduced food conversion efficiency (FCE).

In the case of the abomasal parasite *T. axei*, diarrhoea, ill-thrift, weight loss and death can occur if large numbers are present.

3.4 Haemonchus contortus

Infections with *H. contortus* are characterised by a regenerative anaemia due to the blood-sucking habits of the worms. Both larval and adult forms of the worm feed on blood and each adult worm is capable of removing about 0.05 ml of blood per day by ingestion and seepage from the lesions. A sheep with 5000 *H. contortus* may lose 250 ml of blood daily.

In acute infections, resulting from the ingestion of many infective larvae over a short period of time,

animals are weak and are likely to collapse if driven. Pallor of the mucous membranes is striking, but it should be assessed by inspection of the conjunctivae rather than the oral mucosa or skin where differentiation from a normal appearance is difficult. Hyperpnoea and tachycardia are also present. The onset of clinical signs may be so sudden that affected animals are still in good body condition. Acute Haemonchosis can be a cause of sudden death.

In sub-acute infections, sub-mandibular oedema ('bottle-jaw') may develop as a result of hypoproteinaemia. Clinically, the condition can resemble fasciolosis (Section 7). Chronic infections are characterised by a more general failure to thrive, with weight loss, poor body condition, sub-mandibular oedema, lethargy and weakness. The chronic nature of the blood loss leads to an exhaustion of iron reserves, and the development of a microcytic anaemia. The degree of anaemia can be assessed using the FAMACHA test (See section 8) diarrhoea is not associated with *H contortus* infection; in fact affected sheep may be slightly constipated.

Haemonchosis can occur in both adults and in young sheep. When lactating ewes are affected there can be a profound depression of milk production leading to lamb deaths and to poorly grown lambs that depend on grazing for survival and then become, themselves, heavily parasitised. Over recent years, the incidence, frequency of reports and geographical range of haemonchosis have all increased possibly as a consequence of climate change. It can now be found in all parts of the UK.

3.5 Nematodirus battus

Nematodirosis, due to *Nematodirus battus* infection, is an example of a parasitic disease where the principal pathogenic effect is attributable to the larval stages. Following ingestion of large numbers of L3 there is disruption of the intestinal mucosa, particularly in the ileum, although the majority of the developing stages are found on the mucosal surface. Development to L4 and then L5 is complete by 10–12 days from infection and this coincides with severe damage to the villi and erosion of the mucosa leading to villous atrophy. The ability of the intestine to exchange fluids and nutrients is grossly reduced and, with the onset of diarrhoea, the lamb rapidly becomes dehydrated. In severe infections, diarrhoea is the most prominent clinical sign. As dehydration proceeds, the affected lambs become inappetant, diarrhoeic and thirsty, often congregating around drinking troughs. *N battus* is a major cause of parasitic gastroenteritis in lambs in the spring and on occasions during the autumn**. This pattern of events appears to be changing, presumably as synchronised hatchings of L3 occur both earlier, or later in the year than normally anticipated, and especially where these coincide with the presence of parasite-naïve or susceptible lambs.**

3.6 Numbers of worms associated with disease

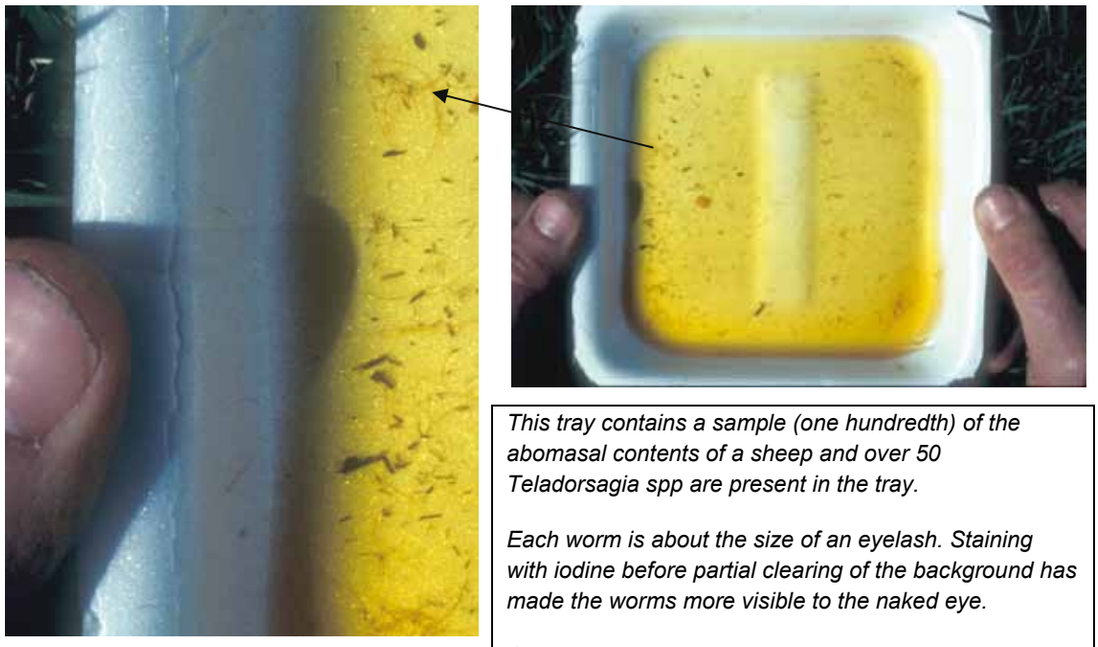
If gastrointestinal parasitism is suspected as the cause of an outbreak of disease in a flock, a post-mortem examination and worm count should be performed, preferably on two or three animals. It is not sufficient to attempt to visualise the number of worms in the abomasum or small intestine because, with the exception of *H. contortus*, the worms are difficult to see and counts are impossible.

Field techniques for worm counts have been described and are highly recommended. As well as providing an instant diagnosis, they can be used by a veterinarian to demonstrate the parasites to the sheep owner. Immature worms will often be missed, or under-estimated, in field counts but will be detected in worm counts done in laboratories.

The numbers of worms present provide definitive evidence to support the diagnosis of parasitic gastroenteritis. In many cases, there are worms of different species present. Although the species vary in pathogenicity, it is acceptable to consider their effects to be additive. A points system has been developed as a guide to interpreting worm counts: -

Teladorsagia spp	3000 worms = 1 point
Trichostrongylus spp	4000 worms = 1 point
H contortus	500 worms = 1 point
Nematodirus spp	4000 worms = 1 point
Immature worms	4000 worms = 1 point

A total of **2 points** in a young sheep is likely to be causing measurable losses of productivity although clinical signs and deaths are unlikely unless the total exceeds **3 points.** In adult sheep, the thresholds will be correspondingly higher. This system is only intended as a guide. It is important to remember that, for some species, such as *N battus*, the immature worms are much more pathogenic than the adults.



This tray contains a sample (one hundredth) of the abomasal contents of a sheep and over 50 Teladorsagia spp are present in the tray.

Each worm is about the size of an eyelash. Staining with iodine before partial clearing of the background has made the worms more visible to the naked eye.

One worm is arrowed.

Fig. 3.1 ***Worm counts can easily be done in the field.***

3.7 Immunity (acquired resistance) to gastrointestinal nematodes

3.7.1 Development of immunity

Following exposure to worm parasites, lambs gradually develop immunity against them. The onset of immunity can lead to the expulsion of much of the adult worm burden and the prevention of establishment of most incoming infective larvae. In lambs, this effect is most obvious with *N battus* infection, where adult parasites are typically expelled 3–4 weeks after the first infection, particularly if the number of infective larvae ingested is high. For most other parasites, immunity develops more gradually, following repeated or continuous ingestion of infective larvae over 2–4 months.

Immunity is not 100% effective and small worm burdens persist in immune sheep. If sheep are removed from pasture and kept in a worm-free environment, or dosed with anthelmintics continuously or at high frequency, the immunity wanes. Then, even adult sheep can become highly susceptible again. Therefore, small burdens that persist in most adult sheep are important in continuing to stimulate the immune system and in maintaining an effective immunity. As well as regulating worm numbers, immune sheep also exert some suppression on the growth and reproductive capacity of the worms in their gastrointestinal tract, so worms in immune sheep tend to be smaller and to produce fewer eggs than worms in naïve sheep.

Lambs start to demonstrate immunity against parasites from 4–5 months of age, the immunity increasing in strength with age and continued exposure to larval challenge. After a full year of grazing, most sheep have a high degree of immunity, although high levels of challenge can overwhelm immunity to parasites, particularly during the first year of life.

3.7.2 Resistance and resilience

Resistance to parasites is the ability of sheep to limit the rate of establishment, growth, fecundity and survival of worm parasites. Conversely, ***Resilience*** is the ability of sheep to continue to grow,

maintain condition, lactate and/or reproduce despite being parasitised. We would, of course, like sheep to have both, and in good measure! Most research has been directed at resistance to parasites and ways to enhance it through nutrition and selective breeding (see below). The immunity to parasites we are discussing here concerns the development of resistance, rather than resilience. This resistance is not innate in sheep – it is acquired following exposure to parasites. Consequently, the expression of immunity of sheep to worm parasites is often referred to as *acquired resistance*.

3.7.3 Immunity and nutrition

Feeding high protein feeds can enhance immunity. While there appears to be no effect of nutrition (within limits of reasonable levels of nutrition) on the rate at which immunity develops in young sheep, diets containing feedstuffs high in digestible undegraded protein (*e.g.* soya bean meal) significantly improve the strength of acquired resistance. This research has not yet been converted into specific recommendations for the use of supplementary feeds as an adjunct to parasite management in sheep, but the general relationship between nutrition and the expression of acquired resistance should be considered when planning worm control strategies.

3.7.4 Periparturient relaxation in immunity (PPRI)

There is a relaxation in immunity in adult ewes at about lambing time, which persists for a few weeks of lactation. The consequence of this relaxation is that worms produce more eggs, adult worms are not expelled, a lower proportion of incoming infective larvae are rejected and hypobiotic larvae (of *T. circumcincta* and *H. contortus*) that resume development are also less likely to be expelled. As a result, worm numbers rise and the FEC rises. The PPRI typically commences 2–4 weeks before lambing and persists for 6–8 weeks, after which time ewes recover their immunity and worm numbers and FECs tend to fall towards their pre-lambing levels. The cessation of lactation brings a rapid return of the ewe's normal immunity.

The PPRI is variable both in terms of the time of onset and in degree between sheep and between flocks of sheep. Several factors are known to influence it. For example, it is less marked in single-bearing/single-rearing ewes than multiple bearing/rearing ewes and it can be diminished by dietary supplementation with feeds high in undegradable digestible protein (UDP) - see also Fig. 6.1.

3.8 Breeding for resistance to parasites

There are variations between individual sheep within a flock in the strength of their acquired resistance to parasites. Part of this variation is genetic, and it is therefore theoretically possible to selectively breed for sheep that are more resistant to internal parasites. In flocks that have undergone selection for low FEC, lambs developed stronger acquired resistance and had lower FECs and lower worm burdens than lambs in unselected flocks. Adult ewes in selected flocks had a smaller rise in FEC during the PPRI and their lambs had lower FECs at weaning. However, work is still on-going because there is a cost to the animal in mounting the immune response, which can result in reduced performance.

It is important to note that such selection programmes do not confer significant advantage over lambs in unselected flocks until they are 4–5 months of age or more. This means that as a tool for worm control, genetic resistance will be of the greatest benefit when applied to breeds involved in producing ewes rather than terminal sires. A flock of ewes that has been sired by rams that are more resistant to worms will cause less pasture contamination with worm eggs at all times of the year, including at lambing. This reduction in contamination will provide substantial benefits to their lambs.

This selection for parasite resistance can only really be done effectively in flocks breeding rams. Even those commercial sheep producers who breed their own ewe replacements cannot achieve any significant genetic improvement in their flocks by ewe selection if the sires they use to breed ewe replacements come from another flock. If such producers wish to improve the genetic resistance of their flocks they must either breed rams themselves or buy rams from a breeder who has been selecting for resistance to worms.

Selection for low FEC is practiced in some ram-breeding flocks in the UK, but most of these flocks are terminal sire breeds (Suffolk, Texel, and Charollais). More recently, some breeders of hill-breed rams have started selecting rams for low FEC and incorporating them into EBV (Estimated |Breeding Value) scoring systems to help breed for worm resistance. This is a trend that should be encouraged for breeding ewes. Breeders interested in learning more about breeding for resistance should contact the AHDBs *Signet Breeding Services* (www.signetfbc.co.uk).

Evidence from selection in Romney sheep in New Zealand indicates that substantial and useful improvement can be made over a 10-year period, with selected flocks requiring substantially fewer anthelmintic treatments. Selection for low FEC does not appear to lead to significant correlated responses in resilience to parasites (as opposed to resistance). Experiments have produced conflicting results about the existence of correlated responses between low FEC and production traits such as growth rate. Research has indicated that lambs with low FEC's do not always perform better than the lambs with high FEC's and lambs which perform well when left undrenched do not always have low FEC's. What is clear, however, is that if selection for low FEC is pursued as the only or dominant trait, then the opportunity to continue selection for other traits is foregone. Breeders are advised to combine moderate selection pressure for low FEC with continued selection for production traits, such as litter size, maternal ability, growth rate and fat depth.

4 Anthelmintics Used Against Gastrointestinal Nematodes

(See SCOPS Leaflet 'Know Your Anthelmintics' at www.scops.org.uk)

Sheep anthelmintics have either a broad or narrow spectrum of activity.

4.1 Broad-spectrum anthelmintics

The broad-spectrum anthelmintics can be divided into five groups on the basis of chemical structure and mode of action (Table 4.1.). These groups are:

❖ **Group 1 - BZ**, **Benzimidazole** ('white').

All are effective against nematodes and are ovicidal although individual generic products may vary in efficacy against some nematode species, particularly *N. battus*. Most are efficacious against tapeworms. After administration, the 1-BZ passes into the rumen, which acts as a reservoir, allowing gradual release into the bloodstream. 1-BZs act by inhibiting tubulin activity in intestinal cells of nematodes or tegumental cells of cestodes, preventing uptake of glucose. The longer the time it stays in the animal the more effective it is. *There is one 1-BZ anthelmintic (triclabendazole), which is narrow spectrum (liver fluke only) and differs from all the other 1-BZs in many respects – but is classed with them because of its chemical structure.*

❖ **Group 2 - LV, Levamisole (LV)** ('yellow')

This group now just comprisesthe imidazothiazole, levamisole (2-LV). 2-LV acts on the nerve ganglion of the parasite, causing paralysis and the therapeutic safety index, compared to other anthelmintics, is low. Animals given levamisole may be hyperactive for a few minutes. Toxic signs, due to a stimulant effect on nerve ganglia, may manifest as salivation, bradycardia, and muscular tremors and in extreme cases death from respiratory failure. Injectable levamisole may cause inflammation at the site of injection. Levamisole is rapidly absorbed and excreted and most of the dose is lost from the system within 24 hours. Therefore, it is not essential to maintain high concentrations in the sheep for protracted periods. Levamisole is not ovicidal.

❖ **Group 3 - ML**, **Macrocyclic lactones** ('clear')

Includes the avermectins (ivermectin/doramectin/abamectin) and the milbemycins (moxidectin). These compounds are highly lipophilic and following administration are stored in fat tissue from where they are slowly released. They act on glutamate gated Cl- channels and γ-aminobutyric acid (GABA) neurotransmission sites in nematodes, blocking interneuronal stimulation of inhibitory motor neurones, leading to a flaccid paralysis.

❖ **Group 4 – AD, Amino-acetonitrile derivatives (orange)**

Launched on to the UK market in 2010, this was the first new anthelmintic group for over 30 years and is effective against all nematode species that are resistant to the three original groups above. Monepantel is the first of the derivatives to reach the market. Its mode of action is similar to the paralysis of the 2-LV group but it acts via a previously unknown nicotinic acetylcholine receptor site which is nematode specific. This confers a very high safety index.
Monepantel is currently available as a POM-V product only.

❖ **Group 5-SI, Spiroindoles (purple)**

Derquantel, from the new spiroindole group, is available from 2012 as a dual active preparation combined with abamectin, a 3-ML. This is the first time two broad spectrum anthelmintics have been combined into a product for the UK market. Derquantel is a nicotinic cholinergic antagonist, having a novel action which blocks neuromuscular transmission and inducing flaccid paralysis in the nematode. The product is currently available only as a POM-V.

Table 4.1. ***Anthelmintic preparations for sheep***

Compound	Spectrum of Activity	*Activity against*			Comments
		Tela Trich Nem Coop Chab Oes	*Haemonchus contortus*	*Fasciola hepatica*	
Group 1 BZ, Benzimidazoles					
Albendazole	Broad	+	+	+ > 10 w	50% higher dose rate required for fluke
Fenbendazole	Broad	+	+		
Mebendazole	Broad	+	+		Variable activity against *N. battus*
Ricobendazole	Broad	+	+	+ > 10 w	50% higher dose rate required for fluke
Oxfendazole	Broad	+	+		
Triclabendazole	Narrow			+ > 2 d	
Group 2 – LV, Levamisole					
Levamisole	Broad	+	+		Injectable and oral formulations
Group 3 – ML, Macrocyclic lactones					
Ivermectin	Broad	+	+		Endectocidal activity. Injectable and oral formulations
Moxidectin	Broad	+	+		Endectocidal activity. Persistent activity against some nematodes. Injectable and oral formulations
Doramectin	Broad	+	+		Endectocidal activity Injectable only.
Group 4 – AD Amino-Acetonitrile Derivatives					
Monepantel	Broad	+	+		
Group 5 - SI Spiroindoles#					
Derquantel	Broad	+	+		
Substituted phenols and salicylanilides					
Closantel	Narrow		+	+ > 6 w	Persistent activity against *H contortus*.
Nitroxynil	Narrow		+	+ > 6 w	Injectable only. Stains wool.
Oxyclozanide	Narrow			+ > 10 w	

 # Only as a dual active product in conjunction with abamectin a 3-ML

See full product listings updated annually at www.scops.org.uk

4.2 Narrow spectrum anthelmintics

The substituted phenols (nitroxynil) and the salicylanilides (closantel, oxyclozanide) are narrow spectrum anthelmintics. They are effective only against trematodes (*Fasciola*) and blood sucking nematodes (*Haemonchusa*). They act by uncoupling oxidative phosphorylation at the mitochondrial level, reducing the availability of ATP, NADH, NADPH. In the host they bind to plasma protein, which increases the duration of activity against blood sucking parasites. The fasciolicides are discussed further in Section 7.

Praziquantel is a quinoline-pyrazine and is active against the tapeworm, *Moniezia expansa*. The drug acts on cell membrane permeability leading to damage to the parasite integument. Praziquantel is only available in combination with levamisole (2-LV).

4.3 Combination Anthelmintics

'Fluke and worm' combinations have traditionally been used extensively by sheep farmers. Products available include combinations of Triclabendazole with 2-LV, 3-ML and MOX; Closantel with 3-ML and 1-BZ; Oxyclozanide with 2-LV. While these can be a useful tool when it is necessary to target both parasite groups, they are often used as an insurance, without consideration of whether treatment of both fluke and worms is really needed. This is likely to accelerate the development of anthelmintic resistance (AR) on farms because it will kill susceptible parasites unnecessarily.

4.4 Multiple Active Anthelmintics

The UK will not use the 'combination' definition for products containing more than one broad spectrum roundworm compound. The first such product, derquantel + abamectin (Startect™) was launched on to the market in March 2012. It, and any other subsequent such products will be described as 'multiple actives' so they can be differentiated from the 'fluke and worm' group above. The objective is to avoid confusion, allowing prescribers to distinguished from the avoid using the combinations except where necessary allowing us to discourage inappropriate use.

4.5 Activity against Nematodirus battus

The 1-BZ group possesses high activity against the adult and immature larvae of *N battus,* although some of the earlier 1-BZs (mebendazole) have variable activity against immature stages. The 3-MLs have variable activity against *Nematodirus* species, including *N battus.* Both ivermectin and moxidectin given orally have activity against adult and immature stages of *N. battus*, whilst doramectin given by injection at increased dose rate is active against adult and L4 larvae of this species. Moxidectin (oral or injectable) has no persistent activity against *N battus*.

4.6 Activity against hypobiotic larvae

Albendazole, fenbendazole, oxfendazole, levamisole, doramectin, ivermectin, moxidectin monepantel and the dual active containing derquatel + abamectin are effective against arrested fourth stage larvae of the abomasal parasites.

4.7 Injectable formulations of 3-MLs

Ivermectin (IVM), doramectin (DOR) and moxidectin (MOX) are available for sheep either as injectable formulations, or oral drenches (not DOR). Administration by injection leads to better absorption and a longer half-life than oral treatment.

Only products containing MOX have licensed claims for persistent activity in sheep (although all injectable 3-MLs have persistent activity against some, but not all, worm species). MOX prevents re-infection with 3-ML-susceptible *Teladorsagia* spp and *H contortus* for 5 weeks. A longer acting injectable formulation of moxidectin provides protection for approximately 14-16 weeks for these abomasal species. The period of protection from re-infection with *Trichostrongylus colubriformis* is much shorter and re-infection of animals on pasture contaminated by parasites other than these remains possible. MOX has no persistent activity against *Nematodirus battus.* These products also have activity against sheep scab. Their increasing use for the control and treatment of scab is cause for concern with respect to the acceleration in the development of AR.

4.8 Persistent activity of closantel

Closantel will prevent the establishment of all (susceptible) *H. contortus* larvae for four weeks after dosing and will reduce establishment rates of larvae for at least one further week.

4.9 Cestodes (tapeworms)

The BZs are generally effective in controlling tapeworm infections. Praziquantel is a specific treatment for tapeworm infections only.

4.10 Activity against ectoparasites

The MLs are also active against sucking lice (*Linognathus* spp), nasal bot flies (*Oestrus ovis*) and mange mites (*Psoroptes*, *Sarcoptes, Chorioptes*) when given by injection. Oral formulations of MLs have no activity against these mites. There is little or no activity against chewing lice (*Bovicola ovis*) (also called biting lice, which is the common from found in the UK), ticks or keds. A diagnosis, differentiating sheep scab from biting lice is therefore essential to avoid off-target use.

Table 4-2. ***Activity of sheep anthelmintics against lungworms, tapeworm and ectoparasites***

	Activity against		
Compound	*Lungworms*	*Tapeworms*	*Ectoparasites*
Broad-spectrum			
Benzimidazoles (1-BZ)	+	±	-
Levamisole (2-LV)	+	-	-
Macrocyclic lactones (3-ML)	+	-	±
Amino-acetonitrile derivatives (4-AD)	-	-	-
Spiroindoles (5-SI)	+	-	-
Narrow-spectrum			
Salicylanilides and substituted phenols	-	± *	±
Praziquantel #		+	

** not licensed for cestode activity in the UK.*

 # only available in combination with LV

4.11 New Novel Anthelmintic Compounds

Since the last update of this manual, we have seen the launch of the fourth group of broad spectrum anthelmintics in the UK (4-AD) The active molecule is monepantel and it was launched on to the UK market in March 2010 (Zolvix™). In 2011 another new product was launched in New Zealand (Startect™) which is a 'Dual Active' combining the only member of the new novel chemical group (the spiroindoles (5-SI)) derquantel, with abamectin (an 3-ML). The product was launched in the UK in March 2012.

Despite these additions to the chemotherapeutic armoury, it remains imperative that the activities of existing groups of chemicals are maintained for as long as possible through management actions designed to reduce the dependence on anthelmintics. It is also vitally important that effective strategies are devised for the integration of these actives in an attempt to use them to both prolong the effectiveness of the original groups, in particular the 3-MLs and also protect them against the rapid development of AR.

5 Anthelmintic Resistance (AR)

Resistance to all the main anthelmintic classes has been exhibited by nematode populations in most sheep-rearing countries over the last twenty years.

5.1 What is resistance?

Resistance is the heritable ability of the parasite to tolerate a normally effective dose of the anthelmintic. The parasite is considered resistant if it survives exposure to the standard recommended dose of the anthelmintic and the ability to survive is passed on to its offspring. Resistance can be viewed as drug tolerance, since 'resistant' individuals can often be removed by exposure to higher dose rates of anthelmintic up to the maximum tolerated dose.

We can measure anthelmintic resistance in a number of ways. These include field tests, such as a simple Drench Test as an indication, to the more accurate Faecal Egg Count Reduction Tests (FECRTs) and laboratory assays such as Larval Development Tests (LDT) and Egg Hatch assays (EHAs) (Section 8 has details of these techniques). A fully effective anthelmintic is expected to reduce the FEC to zero after administration. If the reduction is 95% or less, then we say that resistance has been detected. (Point B in Fig. 5.1)

Under field conditions however, anthelmintics will apparently continue to give clinical responses in parasitised sheep when the reduction in faecal egg count (FEC) is substantially less than 95%. Consequently, sheep farmers remain unaware that resistance to an anthelmintic is present until the reduction reaches 80% or less (point C in Fig 5.1). Beyond this point there are significant production penalties from poor worm control and the severity of the resistance will increase rapidly if the anthelmintic remains in use.

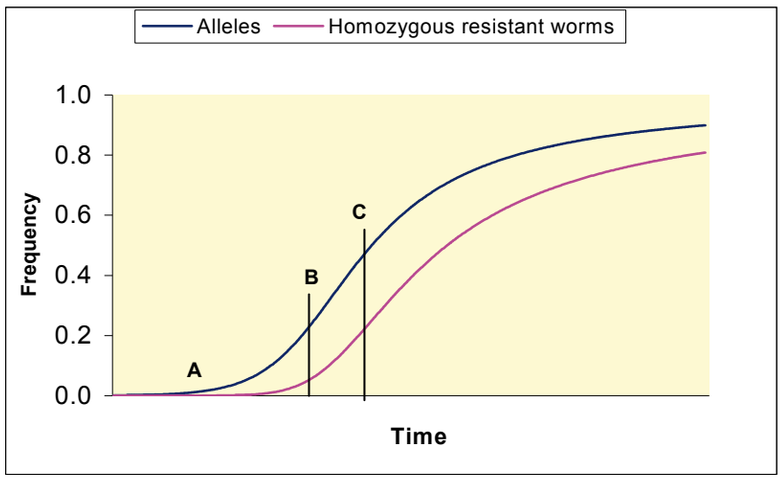


Fig 5.1 The rate at which AR appears in a flock

Point A, resistance alleles are at very low levels; B, resistance detectable in tests (95%); C, resistance apparent as a clinical problem (<80%)

This distinction between the detection of resistance using FECRTs, LDTs etc. at the 95% level and farmers seeing apparent failure at the 80% level is vital to the slowing of the development of anthelmintic resistance. By detecting resistance at an early stage sheep farmers can employ the SCOPS recommendations to prolong the time taken for the worm population on their farm to move from point B to point C on the graph. This means the activity of the wormer group(s) concerned can be maintained for longer.

5.2 The UK situation

In the UK, anthelmintic resistance has been detected in a number of species of sheep nematodes. Based on surveys conducted in Great Britain since 2000, a large proportion of lowland farms have 1-BZ resistance and a smaller, but a significant proportion has 2-LV resistance. The prevalence amongst hill farms may be lower than lowland farms. 3-ML resistance is now being reported in parts of GB, and further emphasises the importance of exercising some control over its development and spread between flocks, before it becomes widespread throughout the country. Key issues are:

- Benzimidazole resistance has been reported in *Teladorsagia (Ostertagia) circumcincta, Haemonchus contortus, Cooperia curticei* and *Trichostrongylus* spp.

- Levamisole resistance has been reported in *T circumcincta, C curticei* and *Trichostrongylus* spp.

- ML resistance has been reported in *T circumcincta* in a number of sheep flocks in parts of Great Britain. In a number of flocks with 3-ML resistance reported, there has also been 1-BZ and 2-LV resistant parasites on the same farm ("triple resistance"). There have also been a very small number of reports of early moxidectin (MOX) resistance, usually manifest as a reduced period of persistency

- **Multiple Resistance** - The emergence of 'triple' resistance' on a small number farms is of concern and presents a challenge in terms of correct advice and management. However, as often only one species, mainly *T. circumcincta*, is involved acceptable control may still be achievable by appropriate monitoring and careful management.

In one of the recent SCOPS studies (2008), data from 6 farms where resistance to one or more groups of anthelmintics was identified by either FECRT or LDT is shown below. (Table 5.2). On two farms "triple" resistance (i.e. to all three anthelmintics groups) was identified by FECRT, and on one farm moxidectin resistance was suspected based on an early return to egg laying at 28 days post treatment. On all of the farms, resistance was present in one or more genera but most commonly in *Teladorsagia*.

TABLE 5.2 FECRT results for 6 farms in the SCOPS project

Farm	% Reduction in Faecal Egg Count				
	1-BZ	2-LV	3-ML	Genus	Additional Comments
A	6	80	84	*Teladorsagia*	Resistance in Cooperia to 1-BZ and to 2-LV in *Trichostrongylus on LDT*
B	0	0	0	*Teladorsagia*	Resistance to 2-LV in both *Cooperia* and Tr*ichostrongylus on LDT*
C	0	99	100	*Teladorsagia*	Resistance to 1-BZ in *Cooperia, Trichostrongylus & Haemonchuson LDT*
D1	60	100	36 (77)	*Teladorsagia*	(77) refers to FECRT to Moxidectin at +28days
D2	21	14	70		2007 result for D1 (same flock)
E	100	93	96	*Teladorsagia*	2-LV resistance in Trichostrongylus on LDT
F	80	100	90	*Teladorsagia*	

❖ **New novel groups**

Resistance has not been reported to either of the newly introduced anthelmintics (4-AD and 5-SI). Modelling studies have demonstrated the benefits of strategic use of these new actives in delaying resistance development to both the new actives themselves and to existing chemical groups if certain prerequisite criteria are met.

5.3 Side resistance

Anthelmintics within the same class share the same mode of action. When resistance appears to one anthelmintic in a class, other anthelmintics in the same class will also be affected. Thus worms that are resistant to, for example oxfendazole, are also resistant to other 1-BZ anthelmintics, such as fenbendazole, ricobendazole and albendazole. Worms that are resistant to ivermectin will also show side-resistance to doramectin and moxidectin. In practice, moxidectin usually demonstrates higher efficacy against 3-ML-resistant parasites than ivermectin, although there is evidence that it has less persistence.

5.4 Resistance selection mechanisms

5.4.1 Anthelmintic resistance may be inevitable, but can be delayed

The genes, or alleles, which allow parasites to be resistant to anthelmintics are believed to be in existence in unselected worm populations (see the text box on page 26 for a detailed description). Consequently, for all anthelmintics that have been developed to date, it appears that the development of AR is an inevitable consequence of their use but its development can be delayed. There are several factors that have been shown to influence the rate at which AR appears in a worm population, and they are discussed below. It is our improved understanding of these factors that has led to the development of new guidelines for anthelmintic use, which are discussed in Section 6. Additionally, knowledge of the resistance status to the different drug groups, the worm species involved and at what stage in the season, can greatly influence the advice given to maintain effective control and manage resistance development.

5.4.2 The size of in-refugia populations

In any parasite ecosystem, there are two sub-populations of worms; the parasitic and the free-living. It is only the parasitic sub-population (the parasites within the host) that can be exposed to any anthelmintic treatment. Worms that are in the free-living sub-population (eggs, L1, L2, L3 - see Section 2) are not exposed to the anthelmintic and are said to be *in refugia* (Fig 5.2.). Any worms in sheep that are not treated also contribute to the *in refugia* sub-population. One of the important factors influencing the rate at which resistance develops in a worm population is the relative size of the exposed population and the unexposed or *in refugia* population. In general, the larger the *in refugia* population in comparison to the exposed population, the more slowly resistance will develop. This is of particular importance with very fecund worm species, such as *H. contortus*, where a few surviving individuals may populate the next generation rapidly especially when the refugia population is small, such as in spring.

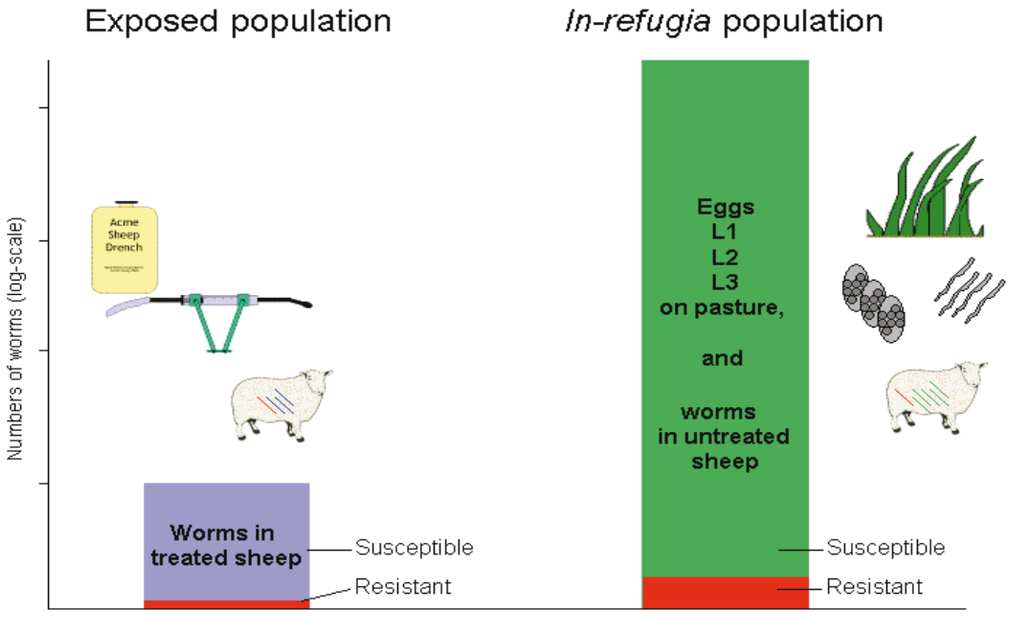


Fig 5.2 ***The exposed and in refugia worm populations***

The worms inside the dosed sheep are exposed to the anthelmintic. Worms that are free-living on pasture, or are adults or immature in untreated sheep are in refugia. The in refugia population is typically 100 to 10,000 times larger than the exposed population and the relative sizes of these two populations influences how rapidly AR develops. There are resistant and susceptible worms in both populations but only the susceptible worms in the exposed population (in blue) are removed by treatment.

5.4.3 Frequency of treatment

The more frequently treatment is given, the faster AR develops. The underlying principle of selection for AR is that ***treatment gives the resistant worms a reproductive advantage over the susceptible worms, f***or 2-3 weeks after dosing. This is because, until L3 ingested after dosing develop into egg-laying adults, the only eggs being passed in the faeces of dosed sheep are from worms which survived treatment. As the interval between dosing becomes shorter, approaching the pre-patent period of the worm, the susceptible worms have less and less opportunity to produce eggs and most, or all, pasture contamination occurs with eggs from resistant parasites. If this strategy is continued the susceptible population is progressively replaced with a resistant one.

However, the frequency of dosing does not exert its effect on AR development in isolation.. For example, if the *in refugia* population is small, replacement happens faster and AR may appear after relatively few treatments. Conversely, where there is a large *'in refugia'* population the selection pressure of a similar number of treatments is much lower. Modelling studies have suggested that a strategy of two treatments, combined each time with a move to low-contamination pasture, selects for resistance as rapidly as five treatments without using low-contamination pasture. Similarly, persistent products with sustained activity may select for resistance towards the end of their period of activity if drug concentration levels decline slowly to sub-optimal levels (the "tail" effect). The lessons from these studies are that not all high-frequency dosing strategies are equally bad, and that seeking to reduce dose frequency alone, is unlikely to be enough to slow the development of AR.

5.4.4 Re-infection after dosing ('dilution')

After dosing, resistant parasites in the sheep enjoy a period of reproductive advantage over the susceptible parasites, the extent of which depends on how quickly the sheep become re-infected with L3 from the unselected population on pasture. If the pasture is highly infective, and the sheep are highly susceptible, re-infection occurs quickly and selection for resistance is minimised. An adult worm burden derived from the unselected population of larvae *in refugia* is re-established within 3-4 weeks.

If re-infection is delayed, the resistant survivors will enjoy a longer period of reproductive advantage. Re-infection could be delayed if the pasture has a low level of contamination, if climatic conditions do not favour the movement of L3 onto pasture (too dry, for example), if the sheep has a relatively strong acquired resistance or if the sheep have been treated with a persistent anthelmintic. In New Zealand, it is believed that the anthelmintic treatment of ewes that display strong immunity, or regain strong immunity soon after anthelmintic treatment, has contributed significantly to the development of AR.

5.4.5 Anthelmintic dose rates

In the past, under-dosing of sheep with anthelmintics was probably common-place, because either the weight of the sheep was under-estimated, instructions for dose calculation were misleading or dosing equipment was faulty. This is now recognised as a very significant factor in the development of resistance to 1-BZ and 2-LV anthelmintics particularly. The reasons why dose rates are important are discussed in more detail in the text box on page 26.

5.5 Reversion to susceptibility

Reversion, by definition, is the return towards susceptibility of a resistant nematode population in the absence of the selecting drug. It will occur only if there is active selection (natural or otherwise) against resistance alleles.

Normally, in unselected populations of worms, resistance alleles are either absent or are present at very low frequencies and it could be assumed that these alleles have a selective disadvantage for fitness. If anthelmintics are used and any resistance alleles are present, they will increase in frequency. If anthelmintic use is discontinued, natural selection might be expected to reduce the prevalence of resistance alleles in favour of the fitter, fully susceptible parasites and the population would, theoretically, revert towards full susceptibility.

If, however, anthelmintic use continues, further genetic selection in favour of the resistant parasites tends to make the resistance alleles less deleterious to survival. This process of 'learning to live' with the new alleles is called co-adaptation. In parasite populations where co-adaptation to resistance alleles has occurred, the resistant worms are no longer less fit to survive or reproduce than susceptible parasites. If anthelmintic use is discontinued at this stage, reversion to susceptibility does not occur.

Supportive data on the occurrence of reversion in the field are limited. Reduction in resistance to 1-BZ in populations of 1-BZ-resistant nematodes following exposure to levamisole has been reported although 1-BZ-resistance rapidly returned when treatment was re-introduced. In a long-term study in the UK on anthelmintic reversion, 1-BZ-resistance remained present over a 15-year period during which only anthelmintics of different classes were used.

5.6 Rotation of anthelmintics

In the past sheep farmers were advised to rotate between anthelmintics of different classes, changing classes every one to two years. This strategy was intended to prolong the effective life of each anthelmintic by allowing reversion to susceptibility to occur when the anthelmintic was not in use. However, this was only likely to be effective when AR was in the very early phase of resistance development, when gene frequencies were very low, long before AR was detectable in the worm population on the farm and when natural selection might reduce the prevalence of parasites containing resistance alleles (point A in Fig 5.1 and 5.5 above).

Now that we have widespread BZ-resistance and increasing incidence of resistance to the 2-LV and 3-ML anthelmintic groups, this strategy is unlikely to be effective, unless individual farms are monitored for resistance regularly. It should certainly not override any of the SCOPS recommendations in terms of targeting parasites, the use of narrow spectrum products and quarantine treatments.

As the SCOPS principles have been developed on UK farms, it is clear that in the majority of cases, products from two or more of the broad spectrum anthelmintic groups will be required during any one season. For example a 1-BZ may be used for lambs against *Nematodirus*; this is followed by either 2-LV or a 3-ML for lamb treatments during the season; closantel may be used against *Haemonchus contortus* in ewes and lambs on "at risk" farms and monepantel and MOX, or derquantel (DQL) + abamectin (ABA) are used as quarantine drenches. This integration of the chemical groups, using the right product at the right time is a key element of SCOPS principles and underlines the need for individual farm advice and plans. See case studies at www.scops.org.uk

5.7 Using two or more actives (Multiple-actives)

Products containing combinations of broad-spectrum anthelmintics (1-BZ+2-LV, 1-BZ+2-LV+3-ML, for example) have been marketed for many years in some parts of the world. In the UK the first such product has been launched in 2012 - the dual-active product 5-SI + 3-ML.There are two main justifications for the use of such products. Firstly to enable control of nematodes in the presence of single or multiple drug resistance. Secondly, to slow the development of resistance to the component classes Ideally, such combinations of anthelmintics should be used when resistance alleles are at very low frequencies and therefore all the anthelmintics in the combination are still fully effective. Unfortunately, in many countries where they are now marketed, they were introduced long after resistance alleles had become highly prevalent in most flocks. By that time, the benefits of the combined treatment were much reduced, compared to those that might have accrued had they been introduced early in the life of the anthelmintics. This is important to note with respect to the UK where the frequency of 3-ML resistant alleles may still be quite low, although more recent data suggests this situation is changing, with reports of 3-ML resistance increasing , making the early integration of the new product groups combined with management strategies that ensure high efficacy combined with high levels of refugia imperative.

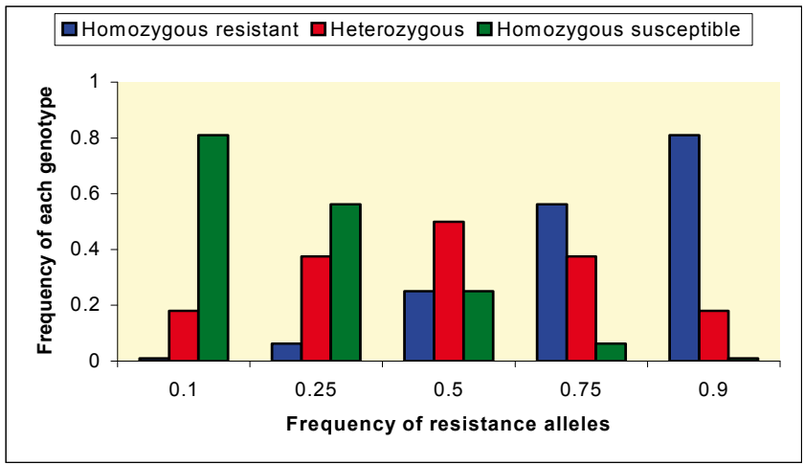
It is also permissible in the UK to dose sheep with two broad-spectrum anthelmintics (of different classes) at the same time provided there are no known contra-indications to their sequential administration**. The two products must not be mixed prior to administration** and, consequently, we refer to this use of two products as 'sequential treatment'. Sequential treatments have an important role when very high levels of efficacy are required. The main application for this strategy in the UK is with quarantine treatments (Section 6). It should not be assumed, however, that all parasites will be killed, because in some cases there will be worms with resistance to both products.

5.8 Spread of AR between farms

Previous discussion has assumed that resistance alleles occur in worms on all farms albeit, sometimes, at a very low frequency. It is possible that on some farms 'closed' populations of nematodes exist that have no alleles for resistance. On such farms, the greatest risk for the appearance of AR may be the importation of resistance alleles in worms in sheep from other flocks where resistance occurs. On other farms, resistance alleles may occur, but may be kept at very low frequencies by the judicious use of anthelmintics. The importation of resistance alleles from other flocks may lead to a dramatic increase in the frequency of those alleles, leading to the appearance of AR in the flock many years earlier than might have been the case had the introduction not occurred.

Undoubtedly spread between farms has been a significant factor contributing to the appearance of AR on many farms in the UK, and has been associated with frequent importations of sheep, often from multiple sources, and usually without effective quarantine treatments on arrival. Surveys in Scotland have suggested that only 15% of farmers treat purchased sheep in a manner that is likely to inhibit the importation of 3-ML resistance, if it existed in the purchased sheep. To prevent the introduction of resistant worms (and *Haemonchus contortus*), effective quarantine treatments are critical. The details of approaches to quarantine are provided in Section 6.

Fig 5.3 ***Frequency of resistance alleles by genotype***



When resistance alleles are rare, most of the resistance alleles are in heterozygous parasites and very few in homozygous-resistant parasites. For this reason, low dose rates are likely to select more heavily for AR than full dose rates when AR is in the very early phase of development.

5.9 Other Causes of Anthelmintic Failure

Anthelmintic resistance is not the only reason that anthelmintics sometimes appear to fail to control worm parasites. Other reasons include:

- **Dosing with insufficient anthelmintic due to:**
  - underestimation of the animal's weight
  - poorly maintained dosing equipment
  - poor administration technique
- **Failure to follow the manufacturer's instructions:**
  - not storing the products correctly
  - using products beyond their *use-by* date
  - mixing anthelmintics with other products
- **Rapid re-infection of animals after treatment from highly infective pastures**
- **Use of the incorrect drug for the target worms and/or mis-diagnosis**

The Genetic Basis for Anthelmintic Resistance

Alleles, loci and genes

The different forms of a gene at a specific position on a chromosome is called an *allele*. The position at which it occurs is called a *locus* (Latin for 'place'). The word *gene* can refer to either the locus or the allele. Generally, it is acceptable to substitute the word *gene* for *allele*. Worms are diploid creatures – meaning they have paired chromosomes. When both alleles at the same locus on each pair of chromosomes are the same, the worm is homozygous for that gene. When they are different (e.g., one allele for resistance to anthelmintic, and the other for susceptibility), the worm is heterozygous.

Resistance alleles pre-exist in worm populations

Anthelmintic resistance is now accepted as a pre-adaptive phenomenon, in that the allele or alleles that confer resistance already exist within the worm population before it has ever been exposed to the anthelmintic in question. In the absence of the anthelmintic, natural selection keeps the resistance alleles at a very low frequency because, presumably, the resistance alleles make the worms carrying them less fit for survival than fully susceptible worms.

The introduction and continued use of an anthelmintic, however, confers a survival advantage on the resistant worms. This allows them to reproduce at higher rates than susceptible worms, and their frequency within the population increases. Eventually the frequency of worms with a resistant phenotype becomes so high that anthelmintic resistance is said to have 'appeared' or to have 'developed' in the flock. This is likely to be the time at which resistance to anthelmintics is first detected in laboratory or field tests, or when the anthelmintic fails to cure clinically-affected sheep. In fact, by that time, AR has already been present in the population for a substantial period, as the current methods of detection are relatively insensitive (Fig 5.1).

When anthelmintic resistance in worms behaves as a recessive trait, only homozygous worms survive a full dose of anthelmintic. Heterozygous parasites are killed by the anthelmintic. Low doses of anthelmintic, however, may allow the heterozygotes to survive. It could be said that low dose rates enable the trait to behave as a dominant trait, rather than a recessive one.

Dose rates

When AR alleles are rare, homozygous AR parasites are very rare and most resistant alleles will be in heterozygous parasites (Fig 5.3). Full dose rates of anthelmintics reduce the rate at which AR develops, compared to low dose rates, because they kill the heterozygotes and thereby remove most of the resistant alleles from the worm population. For example, when the resistant-allele frequency is 1 in 10^4, 99.99% of the resistant alleles in the worm population are in heterozygous worms. When anthelmintics are administered in this phase of AR development (point A on Fig 5.1), full doses (killing all heterozygotes and all homozygous susceptibles) are expected to significantly delay the emergence of AR compared to low doses (which allow heterozygotes to survive, but kill homozygous susceptibles).

As resistance alleles become more prevalent in the worm population, homozygotes become relatively more common (Figure 5.3). Once resistance alleles are no longer rare, a point is reached where there is little difference in the rate at which AR continues to develop between full doses and low doses (where only homozygous susceptibles are killed). The fact that resistance to 3-MLs in *T. circumcincta* and *H. contortus* appears to be under the control of a single, dominant allele may explain why 3-ML resistance tends to appear very quickly in flocks where it occurs. In many cases, it has appeared where under-dosing does not seem to have been a contributory factor.

Use of two chemical groups

When resistance alleles are rare, (point A on Fig 5.1) the number of parasites in the population with resistant alleles to two, unrelated, products is exceedingly low. For example, if 1 in 10^4 parasites are resistant to 1-BZ, and 1 in 10^4 are resistant to 2-LV, then we expect only 1 in 10^8 will be resistant to both.

Using combination products, or two products in sequence, will remove all or nearly all of the resistance alleles from the exposed population and keep the resistance alleles very rare. By contrast, when half the worms are resistant to 1-BZ and half are resistant to 2-LV, we expect one quarter of the worms to be resistant to both. Combined treatment may then provide improved clinical responses for a few years, if used carefully. The major benefit from combination treatments may then be the opportunity to reduce the usage of 3-ML anthelmintics, thus preserving their efficacy, without losing the benefits to productivity of effective worm control.

6 Anthelmintic Resistance – The SCOPS Guidelines

The key factors which define the rate of AR development on which the SCOPS principles are based can be summarised as:

- The proportion of worms on a farm that carry resistant alleles
- The frequency of anthelmintic use
- The efficacy of each treatment
- The proportion of the total worm population in the animal at the time of treatment
- The speed with which any surviving parasites are subsequently diluted with unselected parasites in refugia.

Table 6.1 SCOPS guidelines for anthelmintic use and worm control in sheep

Guideline	Comment
1. Work out a control strategy with your veterinarian or advisor.	**The need for specialist consultation is greater now than before. Decisions about the judicious use of anthelmintics in worm control programs are complex, and will require on-going consultations**
2. Use effective quarantine strategies to prevent the importation of resistant worms in introduced sheep and goats	**Introduction of resistance alleles is considered a major cause of AR in UK flocks. The recommended treatments also prevent the importation of *Haemonchus contortus*.**
3. Test for Anthelmintic Resistance (AR) on your farm	**Knowing which products (chemical groups) are effective in a flock is fundamental to an effective control strategy.**
4. Administer anthelmintics effectively	**Administer the right dose in the correct way, and exploit opportunities to enhance drug efficacy to ensure maximum kill rates.**
5. Use anthelmintics only when necessary	**Understand the trade-off between tolerating some level of parasitism and minimising selection for AR. FEC monitoring has an important role.**
6. Select the appropriate anthelmintic for the task	**Consider narrow spectrum treatments whenever possible. Alternate chemical groups in appropriate ways.**
7. Adopt strategies to preserve susceptible worms on the farm	**Aim to reduce the heavy selection for AR imposed when treating sheep with strong acquired immunity or when dosing on to low contamination pastures.**
8. Reduce dependence on anthelmintics	**Use alternative control measures when possible. These include grazing management, risk assessment and using rams that have been selected for resistance to nematodes.**

6.1 Work out a control strategy with your veterinarian or advisor

Developing a cost effective, reliable and sustainable strategy for worm control is becoming increasingly complex. On-going consultations between farmers, their veterinarians and advisors will be needed to combine an expert knowledge of worm parasites with a practical and detailed understanding of the individual farm and its sheep flock. This relationship needs to evolve, so that the farmer bases tactical decisions within the context of an agreed strategy. This will need to be updated by advice and interpretation of analyses, such as FECs and AR tests, which give up to date information on the status of the flock

6.2 Avoid introducing resistant worms – use quarantine treatments

The objective of quarantine treatments is to reduce the probability of any AR worms being introduced onto the farm. (If any resistant worms do survive the quarantine treatment, then their numbers should be so low that the emergence of AR is greatly delayed.) Quarantine should be applied to sheep to all in-coming sheep. This includes those purchased from other flocks (including rams), ***and*** sheep, which have been grazing on other farms (or common grazing) where the resistance status is unknown or likely to be different from the home farm. The recommendations also apply to any goats introduced to the farm because they carry the same worms as sheep. Importantly, the recommended strategy will also prevent in-coming sheep bringing *H. contortus* on to a holding that does not have this worm species.

There are three steps in the recommended quarantine protocols:

6.2.1 Step 1 – Treatment

All sheep brought onto the farm should be treated with anthelmintics likely to remove all worms – both resistant and susceptible genotypes.

The underlying principle of quarantine treatments is that sheep are treated with two broad spectrum groups with the lowest frequency of resistant worms in the UK. The assumption is that in-coming sheep are carrying 1-BZ-resistant, 2-LV-resistant, and 3-ML-resistant parasites. It is particularly important to try to exclude the rarer genotypes, because it is more likely that these represent a genotype currently absent from the farm. To achieve this, sheep should be treated with two anthelmintics (either MOX (3-ML) and monepantel (4-AD), or the DQL (5-SI) and ABA (3-ML) dual active.

The principle behind these treatments is that MOX or ABA will remove all parasites that might be resistant to 1-BZ and/or 2-LV (and to some extent those resistant to 3-ML), and the 4-AD (monepantel) or 5-SI (derquantel) will remove all parasites including those resistant to 3-ML. MOX and ABA as opposed to other 3-MLs are recommended because it is likely that fewer 3-ML-resistant parasites will survive treatment with these 3-MLs than will survive treatment with doramectin or ivermectin.

A treatment for sheep scab is included since it is assumed that this will also be a threat with all in-coming sheep.

Drench with a wormer from either the

4-AD or 5-SI groups.+

Inject with moxidectin 1%

Footnotes:

1. *4-AD monepantel (Zolvix™) ; 5-SI derquantel + abamectin (Startect™)*
2. *If sheep have, or will be given Footvax, product contraindication requires that the moxidectin 1% is replaced. Suitable products are either 2% moxidectin OR doramectin OR plunge dipping in an OP (if the dipping + 4 AD option is used than a moxidectin drench should also be given).*
3. *In the case of short keep store lambs, withdrawal periods can be an issue and the only option in terms of sheep scab may be to make sure they are kept away from the rest of the flock, including avoiding any contact with vehicles, equipment etc.*

6.2.2 Step 2 - Holding in Yards

Hold sheep off pasture for 24-48 hours, until any worm eggs present in the gut have passed out in the faeces.

After sheep have been treated, they should be held away from pasture for 24, or preferably, 48 hours. This time period allows worm eggs produced by worms before treatment to pass out in the faeces. After 24 hours, about 90% of the eggs will have been passed and by 48 hours, 99% will have gone. Sheep should have access to feed and water throughout the period that they are held off pasture.

Faeces passed in the 24-48 hours post-treatment should not be applied to pastures that will subsequently be grazed by sheep or goats. Dispose by incineration, or by application to ground that is not grazed or only grazed by cattle.

6.2.3 Step 3 - Turnout to dirty (contaminated) pasture

Sheep should be turned out to pasture contaminated with worm eggs and larvae, to minimise the impact of any worms that survive treatment on the farm's AR status.

Any parasites that survive the treatment with two actives may be resistant to both. While this risk of this is very small, the consequences for farms introducing them are potentially very serious. Therefore, every effort should be made to reduce the impact of introducing any 'super-resistant' parasites.

After the period of confinement off pasture, sheep should be turned out to pastures with high levels of worm eggs and larvae, representative of the worm population of the farm. This is to ensure that any eggs produced by worms before treatment and passed in the faeces, will be diluted by the pre-existent free-living stages on the contaminated pasture. This will have the effect of (a) keeping the introduced resistant genes at a low frequency in the free-living population and (b) encouraging rapid re-infection of introduced sheep with home-farm worms as quickly as possible thus shortening the period when introduced worms are dominant. This is why oral MOX should be used wherever possible unless the risk from sheep scab necessitates use of injectable MOX. If contaminated pastures are not available, sheep should remain under restriction (step 2, above) for 72 hours before release onto a small pasture. The efficacy of the quarantine treatment should then be assessed by FEC sampling at least 10 sheep where possible, 14 days after treatment. If FECs are more than zero, treatment with a highly efficacious anthelmintic should be repeated until 14-day post-treatment FECs are zero. At that point, the sheep can be released onto other farm pastures. The small pasture field contaminated by the eggs of surviving worms should be avoided for grazing until it can be quickly and heavily contaminated by grazing with high FEC sheep from the home flock.

6.3 Test for AR on your farm

Evidence being gathered in the field supports the view that it is vital to know the resistance status for each anthelmintic drug group on an individual farm before the most appropriate treatment strategies can be decided. Early detection of reduced efficacy means that efforts can be concentrated on reducing selection pressures to help maintain efficacy for longer. Consideration should also be given to the species of nematode concerned since results will vary according to the species and hence also the time of year the test is carried out. The methods for testing are described in Section 8.

6.4 Administer anthelmintics effectively

6.4.1 Dose at the rate recommended for the heaviest in the group.

All sheep should be dosed at the rate recommended for the heaviest sheep in the group. Scales should be used to weigh two or three of the biggest sheep. If the weight range is such that the lightest sheep might receive more than a double dose, divide the group into two and then calculate a dose rate for each of the two sub-groups based on the heaviest in each.

Where two anthelmintics are being administered e.g. for quarantine treatment, the full dose rate for each drug must be used.

6.4.2 Check the dosing gun

Dosing guns should be checked regularly to ensure that they are delivering the required dose. For drenches, this should be done by delivering two or more 'doses' into a graduated measuring device (e.g. a 20 ml syringe), immediately before dosing commences. Use the anthelmintic not water, because the higher viscosity anthelmintic will be a better 'test' for the equipment.

6.4.3 Dosing technique

Dosing guns are designed to deliver into the oesophagus and not into the buccal cavity. If anthelmintic is administered into the buccal cavity and then swallowed, some or the entire dose may by-pass the rumen and go direct to the abomasum because of the action of the oesophageal groove. Anthelmintic that enters the abomasum is absorbed and metabolised very rapidly. This means that the parasite may have insufficient exposure to the anthelmintic to provide the expected level of efficacy.

Injections should be given either subcutaneously or intramuscularly at the recommended site of injection, following manufacturer's instructions. When given subcutaneously, care should be taken to ensure that the needle is inserted correctly by parting the fleece, and should be withdrawn from the skin with pressure applied at the point of insertion for several seconds to prevent leakage. For injectable, long-acting moxidectin, for example, the site of subcutaneous injection is the base of the ear.

6.4.4 Restrict feed before dosing

Where a period of feed-restriction is unlikely to be harmful (but NEVER for ewes in late pregnancy), the activity of 1-BZ and 3-ML anthelmintics can be enhanced by withholding food for 24 hours before dosing (access to water must be maintained). The slower rate of digesta flow from the rumen prolongs the availability of the anthelmintic for absorption by both the sheep and the parasite, and can significantly improve anthelmintic efficacy and reduce selection pressure for AR.

6.4.5 Do Not Mix

Anthelmintics must not be mixed with any other products prior to administration.

6.5 Use anthelmintics only when necessary

6.5.1 Dosing of ewes at tupping

There is a strong case for withholding anthelmintic treatment from ewes at tupping, or dosing only those individual sheep that appear to require treatment on the basis of low condition, or FAMACHA score (see section 8.2.5). Pre-tupping, very few adult ewes will have significant worm burdens and FECs are likely to be very low because they have a strong acquired resistance to worms. Treatment at this time selects heavily for AR because any worms that survive the anthelmintic treatment from this small population will enjoy a prolonged period or reproductive advantage, during which they dominate worm egg production. In addition, there is concern that removal of the ewes' worm burden may temporarily reduce the strength of her acquired immunity, thus being counterproductive.

It is recommended that only lean, immature or clinically affected ewes, are treated at this time.

The other exception is where *H. contortus* is known to be present on farm and where preventative treatment may be required. Any treatment of ewes during the autumn and winter months will exert a powerful selection pressure, because most of the worm population that survives over winter with this parasite does so as hypobiotic L4 in the sheep, rather than as L3 on pasture, thus the *'in refugia'* population is relatively small. FEC monitoring and a knowledge of each farm's *H. contortus* status will assist with the decision making process.

6.5.2 Dosing of ewes at turn-out

For most of the season, healthy adult ewes have high levels of acquired immunity. However, during the period of the peri-parturient relaxation of immunity (PPRI), their immunity wanes and FECs rise. (Section 3). Treatment at this time may have less serious consequences for the development of AR, but the timing of dosing and the choice of anthelmintic are both important. If ewes are still

experiencing the PPRI when the effect of anthelmintic dosing ceases, they are likely to become re-infected quickly, particularly if pastures are reasonably infective. Under these conditions, selection for AR is minimal, but the benefit of treatment in terms of pasture contamination (Fig. 2.2) is also minimal. Ewes that are treated early in the period of the PPRI show only a short duration of reduced egg output before resuming the expected, but delayed, peri-parturient rise in FEC.

In the past, repeated treatments have been advised in order to eliminate the rise in FEC altogether (Fig. 6.5). This strategy will reduce pasture infectivity for the lambs later in the season, but will also ensure that the end of the PPRI coincides with anthelmintic treatment, and there may be a prolonged period before ewes re-establish a nematode infection from the *in refugia* population. This is highly selective for AR worms.

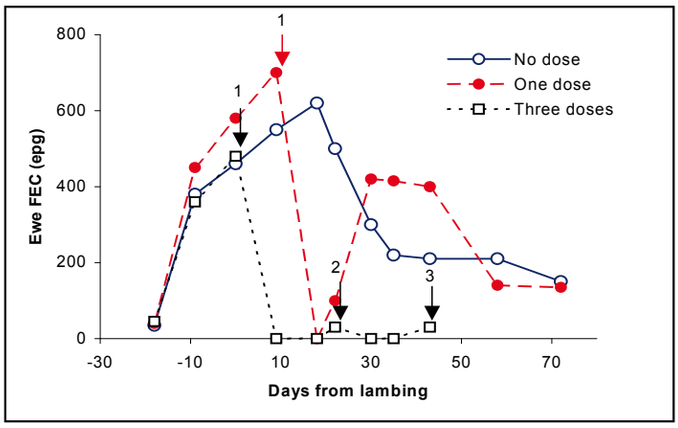


Fig. 6.5 ***Faecal egg counts of ewes grazing infective pastures after turn-out***

Peri-parturient rise in FEC is delayed by one treatment but is not necessarily eliminated unless a treatment with a persistent action or prolonged period of protection is given

The strategy adopted is therefore a compromise between reduction in pasture contamination for lambs and avoiding high selection pressure for AR. Two possible options are available:

- Leave a proportion of the ewes untreated, to populate the paddock with eggs from unselected parasites (Section 6.7, part-flock treatment, targeted selective treatments (TSTs),

or….

- Treat early in the post-lambing phase to ensure that ewes become re-infected before their immunity is fully restored.

Both of these approaches increase the risk of parasitic disease for lambs grazing the pastures later in the season. This is clearly an area where careful planning is necessary to develop strategies that give acceptable levels of worm control without undue selection for AR. This is particularly true when using long acting formulations of MOX that provide persistent action and long periods of protection against some species of nematodes for up to several months. Wherever possible these products should be used prior to lambing or early in the PPRI.

6.5.3 Treatment of lambs

Lambs are often treated frequently to eliminate the negative effects of gastrointestinal parasitism and ensure high growth rates. A number of strategies can be used to reduce the selection pressure for AR when treating lambs.

- Research carefully the need for preventive anthelmintic treatment for nematodirosis. Where farm and field histories suggest that the risk is significant, consider using 1-BZ or 2-LV anthelmintics instead of 3-MLs. Check 1-BZ effectiveness by a drench test 9-10 days post-treatment.

- ❖ Use FEC monitoring to help predict the need for treatment against *T. circumcincta* and *Trichostrongylus* spp.

- ❖ On farms where lamb treatments have been at very high frequency, such as every three weeks, explore strategies to extend the period between treatment to four or five weeks, or more.

Look for management strategies which avoid the build-up of infectivity from mid-season. Avoid frequent treatment of lambs on the same fields as those where ewes were suppressively treated during lactation because there will be low numbers of larvae from unselected parasites and AR can be expected to develop more quickly.

6.5.4 FEC monitoring to optimise the timing of anthelmintic use

FEC monitoring provides information about the worm status of a flock of sheep and can help in the decision about the need for treatment with anthelmintics. If grazing sheep have high FECs, and the faecal samples have been collected appropriately, one can safely assume that worm burdens are high and that treatment is justified. Unfortunately the corollary is not always true and low FECs require careful interpretation. See Section 8 for details on performing and interpreting FECs.

6.6 Selecting the appropriate anthelmintic

6.6.1 Use narrow spectrum anthelmintics where possible

Unnecessary exposure of worms to an anthelmintic can lead to increased selection pressure for anthelmintic resistance without providing any improvement in worm control.

Using narrow-spectrum drugs, for example, when one worm species is the target (e.g, *H. contortus*), is one option. Closantel or nitroxynil, which have a narrow spectrum of activity against *Haemonchus* and *Fasciola, are examples.*

On some farms, *Teladorsagia* and *Trichostrongylus* may be highly resistant to 1-BZ products while *Nematodirus* worms are susceptible to that class. In these flocks, the 1-BZ group could be considered as a narrow-spectrum anthelmintic against *Nematodirus.* This would avoid the off- target exposure of *Teladorsagia*, *Trichostrongylus* and others, to the three other broad-spectrum classes of wormer.

6.6.2 Avoid off-target use in combination products

Similarly, the use of combination products (flukicide plus broad-spectrum wormer) active against liver fluke and nematodes should be avoided when only liver fluke is the target for control. Instead, the narrow-spectrum flukicide should be used alone.

6.6.3 Use of Larval Culture / PNA staining with FEC

Consider the use of larval culture and larval differentiation in conjunction with FEC to identify and target pathogenic nematode species. PNA staining can now also be used to identify *Haemonchus contortus* in faecal samples. See section 8 for details.

6.6.4 Rotation of anthelmintic group

Reversion is unlikely to occur once resistance has been detected in a worm population (Section 5). Now that we have widespread 1-BZ-resistance and increasing incidence of resistance to the 2-LV and 3-ML anthelmintic groups, rotation is unlikely to be effective, unless individual farms are monitored for resistance regularly. Rotation between anthelmintic classes should certainly not take precedence over other more important decisions about selection of anthelmintics. In particular, the quarantine strategies for introduced sheep described earlier in this section should be applied as a priority. Similarly, the option to use of a narrow-spectrum treatment (such as a 1-BZ against *Nematodirus*) should be considered wherever possible.

6.6.5 Using anthelmintics with persistent action

There are two sheep anthelmintic products on the UK market with persistent action - moxidectin (MOX) against *T. circumcincta* and *H. contortus*, and closantel, against *H. contortus*. There is now also a long-acting, injectable formulation of MOX giving greater periods of activity of approximately 14-16 weeks for these species respectively. While it may be thought that anthelmintics with persistent action have the potential to hasten the development of AR, because they continue to prevent the

establishment of L3 for extended periods after dosing, there are other factors to consider. MOX as a milbemycin, is more efficacious against 3-ML-resistant parasites than the avermectins (ivermectin and doramectin), so fewer ML-resistant parasites will remain in the sheep after dosing with MOX. This suggests that MOX may be preferred to avermectins, particularly when the post-dosing larval intake from pastures is low. MOX does, however, delay the re-infection of dosed sheep with some parasites after treatment and may select for AR in the 'tail' phase of its sustained activity.

Treatment with different formulations of MOX may take the place of two or more treatments of a short-acting anthelmintic when pasture infectivity is high and when sheep are susceptible to re-infection. It is not clear if one dose of MOX will select for AR more, or less, than more doses of 3-MLs.

There is no clear-cut answer as to whether MOX should be used or avoided for peri-parturient ewes. However, it is clear that a) the persistent effect of MOX should be avoided at the stage the ewe's immunity is likely to return and b) MOX should not be used exclusively (year on year) for the lambing dose c). Leaving 10% of the single bearing/fittest ewes untreated will protect the *in refugia* population.

In the case of closantel, the use of the narrow-spectrum anthelmintic to control *H. contortus* is almost always preferable to using a broad-spectrum drug, when only that species is the target for control. However, the use of closantel at times of year (e.g. autumn / winter) when the population of *Haemonchus* 'in refugia' is low is likely to be highly selective for AR.

6.7 Preserve susceptible worms on the farm (*in refugia* population).

The 'dose and move' strategy has been widely recommended in the past because it was a successful, cost-effective method of achieving good worm control. When pastures with low levels of worm eggs and larvae become available for grazing, best use is made of them by dosing sheep with anthelmintics before placing them on the field. This ensures pasture contamination remains low for an extended period providing a period of productivity uninhibited by parasite infection, without the need for repeated anthelmintic treatment.

Unfortunately, this strategy is also likely to select for AR, because any worms surviving treatment will enjoy an extended period of reproductive advantage over unselected parasites. All the time the sheep remain free of re-infection from the low contamination pasture, any surviving worms are resistant and contaminating the pastures with their eggs. Without the dilution effect of a heavily contaminated pasture the frequency of resistant genes in the free-living population can increase quickly and the cleaner the pasture, the faster the resistant-gene frequency increases.

The benefit of the low contamination pasture may persist for weeks or months but levels of contamination will build and the worms will have be a more-resistant population than was present earlier in the season. Sheep grazing this pasture will then be infected with a selected population of parasites, with a higher resistant-gene frequency than before treatment. The repetition of such events around the farm over several years will lead ultimately to a highly resistant population of parasites, despite the farmer having 'enjoyed' the benefits of good worm control in the meantime.

How, then, can the potential benefits of low contamination pastures be exploited without selecting heavily for AR? Two approaches can be used: (1) part-flock treatment and (2) delay the 'move' after the 'dose'.

6.7.1 Part-flock treatments and Targeted Selective Treatments (TSTs)

Some animals in the flock can be left untreated, allowing a pool of unselected (unexposed) parasites to produce eggs that are passed out on to the low-contamination pasture. It has been suggested that leaving about 10% of the flock untreated before such a move will be sufficient to provide a large enough dilution effect to delay the development of AR. However, this depends on the treatment given to the remainder of the flock being highly efficacious (See below).

For example, if a treatment given to 90% of a flock only reduces FEC by 90% in treated sheep, eggs from resistant worms will be passed in approximately equal numbers to eggs from unselected worms. If the anthelmintic is 99% efficacious, unselected worm eggs will outnumber selected (resistant) worm eggs by 10:1 and, if the efficacy is 99.9%, unselected worm eggs will dominate the egg counts by 100:1. The cleaner the destination field, the more important the recommendation becomes, and the more important it is that the treatment approaches 99.9% efficacy.

Farmers looking to exploit low-contamination pastures should therefore be encouraged to use highly efficacious treatments and to leave about 10% of the flock untreated.

Farmers may be concerned by this recommendation on two counts. The first is - which sheep to leave untreated, and the second is the lost opportunity to keep a field 'clean'. On the first count, omissions could be done at random or could deliberately target sheep in good condition. One danger of selecting only sheep in good condition is that they may have substantially lower FECs than average. On the second count, the concern is well based, but the strategy is effectively a compromise between some loss of worm control and a high risk of selection for AR.

Work is ongoing in this area. In particular, workers on an EU funded PARASOL project looked to see if they could determine more accurately those animals that should targeted for treatment (Parasol website - www.parasol-project.org). Obvious indicators are animals in low body condition; reduced growth rates and/or body weight or those with signs of scouring.

6.7.2 Delay the 'move' after the 'dose'

An alternative to part-flock treatment is to allow the treated flock to become 'lightly' re-infected before allowing them access to the low contamination pasture. This will ensure that soon after the move, contamination of the 'clean' pasture with eggs from unselected parasites will recommence. The reproductive advantage offered to the selected (resistant) parasites will be short (the pre-patent period minus the number of days the sheep were withheld after dosing) and then will depend on the degree to which the sheep became re-infected after dosing.

The number of days for which dosed sheep should be allowed to graze contaminated pasture before being given access to the 'clean' grazing will depend on variations in pasture infectivity (number of infective larvae available on pasture) and climatic factors. If the pastures are of high infectivity and the sheep reasonably susceptible to parasites (less than one year old, for example) then 4–7 days of grazing may be a satisfactory compromise between making best use of the 'clean' pasture resource and reducing the selection pressure for AR.

NB. Sheep treated with moxidectin will not become re-infected with Teladorsagia or Haemonchus for five weeks after dosing (longer for the long acting 2% LA product), so the strategy described above would not usefully reduce selection pressure on 3-MLs in those worm species. Partial flock treatments are the only option in this case.

6.8 Reduce dependence on anthelmintics

6.8.1 Strategic Prophylactic Treatments (SPTs)

Anthelmintic treatments should ideally be targeted, and based on appropriate FEC monitoring programmes on a whole flock basis (see section 8.2). As worm burdens in both ewes and lambs fluctuate throughout the year, treatments should be strategically aimed at identified potential periods of risk rather than following more conventional, suppressive treatment strategies.

6.8.2 Use grazing management

The objective of management practices is to minimise the reliance on and use of anthelmintics, by avoiding exposure to parasite burdens that would lead to clinical disease and loss of production. At the same time, management needs to allow the sheep to build up immunity to the parasites if it is to remain on the farm beyond the first grazing season. To achieve these objectives, it is necessary to understand the basic principles of risk assessment for pastures, sheep and systems and to be able to relate these to the management and monitoring tools available to the farmer. See Section 8 for guidelines.

6.8.3 Use rams that are bred for resistance to worms

In flocks that are breeding their own replacements, the resistance of the flock to worms can be increased by using rams that have been selected for worm resistance. However, in commercial finished lamb producing flocks that buy in females and finish lambs at less than 5 months of age, there is unlikely to be any advantage in using selected terminal sires. As indicated in section 3.7.5,

genetic resistance will be of the greatest benefit when applied to breeds involved in producing ewes rather than terminal sires. This is because a flock of ewes that has been sired by worm-resistant rams will cause less contamination of pastures with worm eggs at all times of the year, including at the time of lambing. The reduction in contamination will then provide substantial benefits to their lambs.

6.8.4 Graze forages with anthelmintic properties

Grazing on bioactive forages, such as chicory, birdsfoot trefoil, and sainfoin have been shown to reduce the negative effects of parasitism in sheep. However, much still needs to be learned about using bioactive forages in practical production systems. It is not yet known whether bioactive forages act directly against incoming or established worms or whether they work indirectly by improving the nutritional status of parasitised animals. Work is now underway in the UK to evaluate such crops and their ability to reduce worm burdens in sheep. Chicory is the most promising bioactive forage and can be incorporated into normal grass leys or sown in conjunction with clover and/or grasses. Studies have shown that grazing on chicory can result in a reduction worm numbers, improved performance and reduced worm egg excretion in lambs grazing with their mothers. Drought resistance is also an important property of chicory, which contributes to nutritional requirements in the latter part of the season. Importantly this also coincides with the time we normally see the highest pasture larval challenges to lambs.

7 Liver Fluke

Liver fluke disease (fasciolosis) is caused by the trematode parasite *Fasciola hepatica*. Disease can result from the migration of large numbers of immature flukes through the liver, or from the presence of adult flukes in the bile ducts, or both. Liver fluke can infect all grazing animals (and man) but mainly affects sheep and cattle. It is most pathogenic in sheep.

7.1 Life-cycle

Compared to other helminths the life-cycle is complex, involving an intermediate host, the mud snail *Galba* (*Lymnaea) truncatula* and several free-living stages. The role of the snail, which prefers muddy, slightly acidic conditions, particularly areas associated with poor drainage, means that the incidence of liver fluke is far greater in the wetter areas of the country and in years when there is high summer rainfall. With the capacity of the snail to multiply rapidly (100,000 offspring in 3–4 months) along with the multiplication of the parasite within the snail, there is potential for very large numbers of parasites.

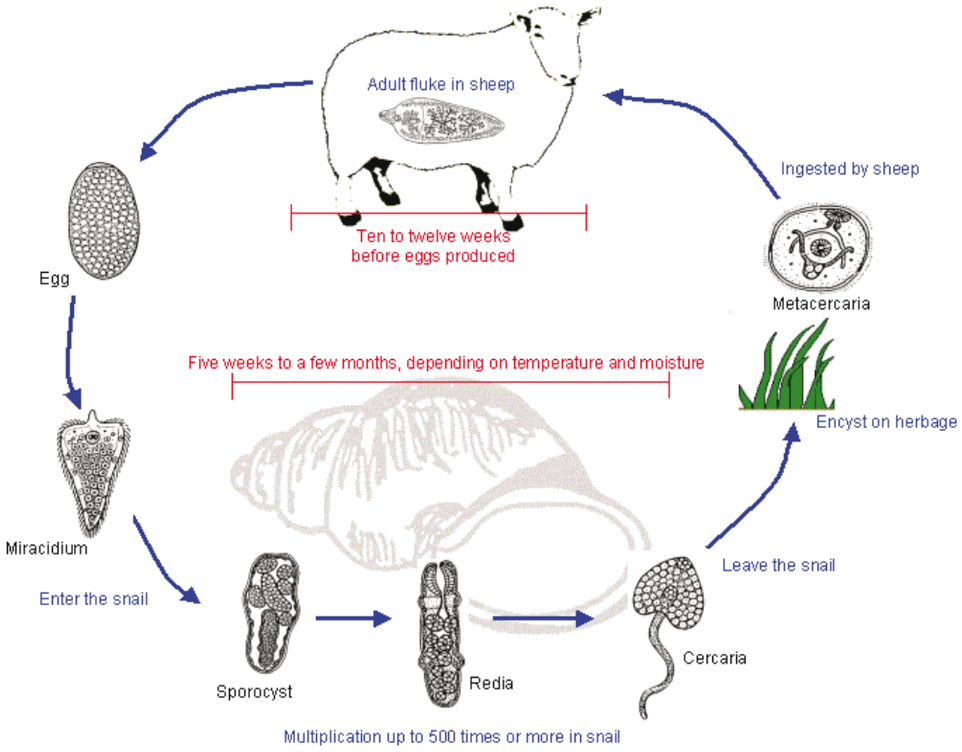


Fig. 7.1 ***Life-cycle of the liver fluke, Fasciola hepatica.***
(Drawings courtesy of Drs Oldham, Jacobs and Fox)

Adult fluke lay eggs that are passed out onto pasture in the faeces. At suitable temperatures, a miracidium develops within the egg, hatches and migrates in thin films of moisture, actively seeking the snail host. Miracidia can only survive for a few hours outside the snail. Within the snail they undergo two further developmental stages, including multiplication, eventually becoming infective cercariae, which emerge from the snail when the temperature and moisture levels are suitable. The cercariae migrate onto wet herbage, encysting as metacercariae, the highly resilient infective stage of the liver fluke. Following ingestion, the young flukes migrate to the liver, through which they tunnel, causing considerable tissue damage. The infection is patent about 10–12 weeks after the metacercariae are ingested. The whole cycle takes 18-20 weeks.

7.2 Epidemiology

The hatching of fluke eggs and the multiplication of snails depend on adequate moisture and temperatures greater than 10ºC. Such conditions usually occur from May–October in the UK although patterns have been changing in recent years. The incidence of fasciolosis is highest in years when

rainfall is above average during May–July. The epidemiology of liver fluke is often viewed as the result of two distinct cycles of snail infection and pasture contamination.

❖ *Summer infection of snails*

In wet summers, snail populations multiply rapidly and snails are invaded by hatching miracidia from May–July. If wet weather continues, the snails shed massive numbers of cercariae onto pasture during July–October. Conversely, if the climate in May–July is dry or cold, fewer snails appear, fewer fluke eggs hatch and levels of contamination in the autumn are much lower. Clinical fasciolosis resulting from summer infection of snails arises usually from ingestion of large numbers of metacercariae over a short period of time in July–October.

❖ *Winter infection of snails*

Less commonly, snails can become infected in late summer or early autumn and development within infected snails is delayed as the snails become dormant and hibernate. The cercariae are then not shed onto the pasture until the following spring. This can produce an initial and significant infection in herds or flocks in the spring.

7.3 Fasciolosis

Liver fluke disease in sheep occurs in three main clinical forms – acute, subacute and chronic fasciolosis. Which form occurs depends on the numbers of infective metaceriae ingested and the period of time over which they are ingested. Recent milder winters and wetter summers have seen changes patterns in parasite epidemiology and reported disease with earlier seasonal reports of acute disease. Table 7.1outlines the clinical signs and treatment options for each form of the disease:

Table 7.1 ***Diagnosis and treatment of fasciolosis in sheep***

Disease type	Peak incidence	Clinical signs	Fluke numbers	FEC (epg)	Treatment
Acute	July to December	**Sudden death** or dullness, anaemia, dyspnoea, ascites and abdominal pain.	1000+ mainly immature	0	Triclabendazole. Treat all sheep and move to a lower risk (drier) pasture if possible OR re-treat after 3 weeks. Further deaths may occur post-treatment from liver damage incurred.
Subacute	October to January	**Rapid weight loss, anaemia,** submandibular oedema and ascites in some cases.	500-1000 adults and immatures.	<100	Treat with a fasciolicide active against mature and immature fluke. If sheep cannot be moved to lower risk pasture, re-treat after 5-8 weeks.
Chronic	January to April	**Progressive weight loss, anaemia,** submandibular oedema, diarrhoea and ascites.	200+ adults	100+	All fasciolicides are active against the mature fluke involved in chronic disease. Treat and move to lower risk pasture.

7.4 Treatment and control

Control programmes must take into account the farm history, topography, geographical location and the prevailing weather. Most programmes rely heavily on flukicidal treatments. The choice of product and frequency of use will depend on the level of fluke challenge, the time of year, and the management and husbandry systems on the farm.

It is important to use the appropriate drug for each situation and to base treatments on fluke forecasts.*(see www.nadis.org.uk for regional forecasts)* Most flukicidal drugs on the market are effective in treating chronic fasciolosis, because they kill adult fluke, but few are effective in treating acute fluke infections in sheep caused by the immatures migrating through the liver (Table 7.2). Triclabendazole (TCBZ) is generally the drug of choice but as resistance to flukicides can occur with repeated and frequent use, alternatives should be used wherever possible, particularly in late winter and spring, in order to reduce the potential for the development of TCBZ-resistance.

Fluke burdens can be monitored in sheep flocks by *post-mortem* examinations when the opportunity arises, or with FECs. Flocks should be monitored before a fasiolicide is used unless there is a history of fluke infection on the farm. Continued monitoring can help determine the need for repeated treatments. For treatment in late summer and autumn, a fasciolicide that is active against immature fluke is recommended. Treatment may need to be repeated in winter (January). If a spring treatment is required (April - June), then a flukicide with adult activity only can be used reducing the selection pressure associated with TCBZ.

The use of combination fluke and worm products should be discouraged as it can lead to off-target selection for resistance to broad-spectrum anthelmintics in nematodes, or fasciolicide resistance in *F hepatica*. However, there is some evidence that closantel-BZ combinations have a synergistic activity that may enhance their activity against resistant *F hepatica* (and *H contortus*), and also help delay the emergence of resistance to either class of compound.

Where fluke infection is present, identification and exclusion of snail habitats from livestock offers some measure of control. Drainage eliminates the snail and offers an effective means of control, but the proliferation of environmental schemes to protect wetland areas has reduced the opportunities for this to be implemented. Simply keeping stock off the wettest fields in the autumn and the winter, when the incidence of disease is at its highest, can reduce the risk from fluke.

Table 7.2 ***Efficacy of flukicides available for use in sheep in the UK against susceptible fluke populations*** *(adapted from Fairweather and Boray, 1999).*

	Age of fluke (weeks)													
Flukicide	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
Albendazole										50 - 70%		80 - 99%		
Oxyclozanide														
Nitroxynil							50 - 90%			91 - 99%				
Closantel														
Triclabendazole (TCB)		90 - 99%					99 - 99.9%							

7.5 Resistance to fasciolicides

7.5.1 Resistance in the UK

TCBZ is the most widely used flukicide because of its activity against immature fluke. Unfortunately this has led to the development of resistance in several countries and reports of suspected resistance in the UK continue to increase. Currently there are no validated field-based methods for the detection of fluke resistance and confirmation is extremely difficult. As a consequence, reported cases of TCB-resistance in the UK are very much anecdotal. An EU funded project DELIVER has evaluated an FECRT for fluke resistance investigations and several other in vitro and immunological methods have been investigated and reported but have yet to be validated for field use. Resistance, where it appears or is suspected, usually manifests firstly as a failure to kill the youngest immatures with subsequent re-appearance of fluke eggs in the faeces earlier than would be expected if the drug retained full efficacy. As resistance develops eventually adult fluke are able to survive treatment as well. The possibility of other reasons for flukicide failure should always be considered, particularly if animals are in poor condition or may be suffering from liver damage.

Where resistance is suspected to a particular product, then an alternative flukicide listed in Table 7.2 should be considered, taking into account the variations in activity against immature fluke between products. However, it is also advisable to consider the other possible reasons for apparent failure because it is likely that although some cases are due to resistance, the situation is not as clear cut as resistance in roundworms. Firstly, there are no validated tests for resistance in liver fluke. A simple post treatment Faecal Egg count (FEC) is not conclusive and other methods are still under investigation. Secondly, there are a number of other reasons why treatment may not be fully effective and appear to fail. These include:

- Pastures with very heavy infestations can mean that farmers are caught out by the speed which animals become re-infected following treatment.
- Triclabendazole (TCBZ) is widely used because it kills early immature fluke and historically has been highly effective when used correctly. It does, however, have to be partly

metabolised by the liver before it can work properly. If the liver is already damaged through a high fluke burden or other concurrent disease this has the potential to reduce efficacy.

- Inaccurate dosing through underdosing and/or badly calibrated and maintained equipment – the same old story, but so often the root cause of an apparent failure.
- Incorrect product choice – for example the use of an adulticide in the autumn leaving large numbers of immature flukes untouched to continue to cause disease.

7.5.2 Preventing the development of resistance

Rotational use of TCBZ, closantel or nitroxynil should be considered where flukicides are used strategically, although additional treatments may be required in years when TCBZ is not used. Opportunities to avoid the use of TCBZ should be exploited whenever alternate drugs will give satisfactory levels of control. For example the use of closantel or nitroxynil 3 weeks post-housing; and/or treatment of chronic infections in the spring with an adulticide.

7.6 Quarantine

7.6.1 The need for quarantine treatments

Quarantine treatment strategies for liver fluke in introduced sheep, cattle or goats should be for farms considered “at risk” in conjunction with a veterinarian or advisor.

There are three different scenarios for treatment:

1. Sheep may be introduced onto a farm with no known snail habitat and, therefore, no history of fluke infection. The risk of introduced fluke establishing on the farm is very small (or zero, if there is no snail habitat) and treatment in this case is intended to remove any fluke in the sheep for the sake of their health. Treatment with a flukicide active against immatures is advised, with FEC monitoring in subsequent months to detect any small residual burden. The consequences of introducing small numbers of fluke, or resistant fluke, are not serious in the long-term.
2. The farm may have areas considered to be a suitable habitat for snails but no history of fluke infection. The risk of introduced fluke establishing on the farm is considered to be significant so treatment is aimed at removing all fluke, including any resistant fluke.
3. Liver fluke may be endemic on the farm, so introducing small numbers of fluke will not be serious, particularly if wildlife reservoirs exist. However, if the endemic fluke are fully flukicide - susceptible, the consequences of introducing resistant fluke are potentially serious.

7.6.2 Choosing a treatment strategy

The following factors should be considered when choosing a quarantine treatment strategy.

- ❖ Resistance to TCBZ is increasing in the UK but, in most cases treatment with TCBZ will remove a very high proportion of susceptible flukes of all stages.
- ❖ Treatment of TCBZ alone will not remove TCBZ-resistant fluke.
- ❖ Treatment with closantel or nitroxynil is expected to prevent the output of fluke eggs for at least 8 weeks and probably more, provided the fluke are susceptible to the drug used. If the introduced sheep are infected with young immature fluke, treatment will have to be repeated after the immatures are old enough to be killed by these products (see Table 7.2). In this context, it may be worth considering the use of two doses of closantel given 6 weeks apart (nitroxynil a minimum of 7 weeks apart for sheep
- ❖ Resistance to closantel and to nitroxynil has been reported in other countries.
- ❖ Treatment with more than one product with activity against immature flukes (closantel, nitroxynil, TCBZ) will reduce the risk of introducing fluke with resistance to any one product. It is <u>not</u> recommended, however, that two products are used at the same time, because of the potential risk to the health of the sheep.
- ❖ Sheep can pass fluke eggs for up to 3 weeks after adult fluke are killed. It is advised that sheep be kept on quarantine pastures or pastures with no fluke habitat for at least 4 weeks after treatment.
- ❖ FEC monitoring can be used to determine the need for treatments subsequent to the initial one.

8 Techniques and strategies

8.1 Detecting anthelmintic resistance

Testing for anthelmintic resistance is a vital part of the SCOPS recommendations. Early detection is essential because it encourages the adoption of practices which will sustain the effectiveness of anthelmintics. However, it is also important to balance the positive advantages of early detection of AR with the danger of over-stating the situation which may deter farmers from taking appropriate action.

Although not reversible, the presence of AR is dynamic. Detection of AR on a farm will vary according to season and the worm species/ strains present at the time a test was applied and the test's specificity and sensitivity in detecting resistant alleles within the worm populations. It is important, therefore that we do not assume we have full knowledge of the situation on an individual farm on the basis of one test for AR.

The presence of anthelmintic resistance can be detected in flocks in a number of ways. These vary in terms of their cost, complexity and robustness and are outlined below in terms of this hierarchy, starting with the cheapest and most simple, the Drench Test:

8.1.1 Post-dosing faecal egg counts ("Drench Tests")

A quick indication of the efficacy of an anthelmintic can be gauged by laboratory testing faecal samples from 10 sheep following after treatment. The time after treatment depends on the anthelmintic used: **7 days after 2-LV, 10-14 after 1-BZ and 14-16 days after a 3-ML**. In practice, this means checking either 7 days for 2-LV, or 14 post treatment for 1-BZ and 3-ML products. The test is merely an indicator of anthelmintic inefficacy and not necessarily anthelmintic resistance per se, as many other factors can influence test results. The utility of this test is improved if faecal samples from 10 sheep in the dosed group are collected and submitted on the day of dosing, to provide a rough estimate of the reduction in FEC achieved (and to confirm there was a measurable epg before treatment). The advice about faecal collection in Section 8.2 should be followed.

8.1.2 Faecal Egg Count Reduction Tests (FECRT)

A more structured on-farm test can be conducted in which a number of different anthelmintics are tested against a control. Fifteen to twenty ** sheep are randomly allocated to control or treatment groups, which might include a 1-BZ, 2-LV, and 3-ML. (In Australia, ivermectin at half-dose is used in order to detect 3-ML resistance as early as possible, but this represents an off-label use of the product in the UK.). FECs are performed prior to treatment on at least 10 of the control sheep and the 2-LV sheep after 7 days, then from all sheep in the control and 1-BZ and 3-ML groups at 14 days. AR is suspected if the percentage reduction in FEC of a test group compared with treatment controls is < 95%. Results may differ according to whether arithmetic or geometric means are used in the calculations. Where necessary, the advice of an expert should be sought with interpretation of the results.

In a modification of the FECRT, pre-dose FECs are not performed, and results are based on the percentage reduction in mean FEC in the treatment groups compared to the controls.

***NB. Sheep that have not been dosed within 30 days (or longer if MOX has been previously used), and a mean FEC of 200 epg or more is recommended before starting the trial.*

8.1.3 Larval Development Tests (LDTs)

A range of *in-vitro* tests has been developed to avoid the use of animals in testing for resistance. The two most commonly used are the egg hatch assay (EHA) for the 1-BZ anthelmintics, and the larval development test (LDT) for 1-BZ and 2-LV classes. There are no *in-vitro* tests yet available for ML resistance. Farm visits are not necessarily required and the samples can be sent by post direct to the laboratory. However, currently these tests are relatively expensive, precluding their widespread use, Sensitivity is generally considered higher than with the FECRT so AR may be detected when the frequency of resistant alleles within the worm populations is still low. Interpretation is, however, not straightforward and requires expert input.

8.2 Faecal Egg Count (FEC) monitoring

To monitor FECs, you can use a suitably equipped and trained veterinary practice, a commercial service or adopt a DIY approach using the FECPAK system. (see Appendix)

FECs can be used to:

- Help determine the need to treat
- Test the efficacy of a treatment
- Give information on the amount of contamination going onto the pasture

8.2.1 Guidelines for collection of faeces

These guidelines are for the estimation of the mean FEC of a group of sheep. A 'group' in this context refers to a flock of sheep of the same age and reproductive status grazing together in the same field and with the same anthelmintic-treatment history. The easiest way to sample a group is to loosely gather them in the corner of the field for 5-10 minutes, then let them walk away. Fresh dung samples can then be collected from the pasture.

❖ At least 10 sheep in the group should be sampled. The wide variation in FEC between sheep grazing together in the same field means that random sampling effects have a significant impact on the confidence limits surrounding the estimate of the group mean FEC. Even if 10 sheep are sampled, the confidence limits are wide. This number is generally considered to be an acceptable compromise between repeatability and cost (Fig. 8.2).

❖ The sheep should be healthy and have had full access to pasture and/or feed before sampling because counts are reported as eggs per gram (epg) of faeces and variation in faecal output will affect the count. If sheep have been held off feed for more than a few hours before sampling, or if any sheep included in the sample are inappetant due to illness, the FEC will be difficult or impossible to interpret. A high count may be incorrectly assumed to reflect a high worm burden. **For this reason, FECs should not be used as a diagnostic aid when PGE is suspected in cases where sheep are profoundly ill**. A worm count as part of a post-mortem examination is a much more appropriate way to estimate worm burden in such cases.

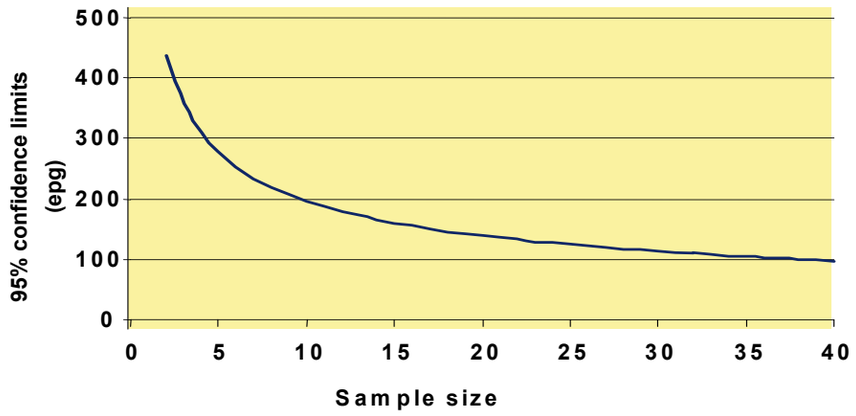


Fig. 8.2 ***Confidence limits around an estimate of mean FEC become narrower as the sample size increases***

❖ Samples should be fresh when collected (less than one hour old) and kept cool (not frozen) in an airtight container or plastic bag, before delivery to the laboratory within 48 hours. If the faeces are too old some eggs will have hatched and the reported egg count will be an underestimate.

❖ Some laboratories pool the 10 samples and report the average of the 10 animals as a single count. This is acceptable and can substantially reduce the cost, but the faecal samples should still

be kept separate until they arrive at the laboratory. The technicians can then ensure the pooled sample is prepared with equal amounts of faeces from each individual sheep.

8.2.2 Larval Culture and Differentiation

FECs are reported as counts of worm eggs per gram of faeces. Eggs of most strongyle genera of interest (*Teladorsagia*, *Trichostrongylus*, *Haemonchus*, *Oesophagostomum*, *Chabertia, Cooperia, Bunostomum*) cannot be differentiated except those of *Nematodirus*, which are very much larger than eggs of the other strongyles. *Trichuris, Capillaria* and *Strongyloides* eggs are also readily differentiated.

It is often useful to know whether FECs are dominated by worms of one particular genus or not, particularly on farms where *Haemonchus* occurs. If so, larval culture and differentiation can be performed, usually using the faeces left over from the FEC. This technique takes a further 7 to 10 days.

Larval differentiation involves hatching the eggs in the sample, culturing and identification of the larvae. Usually, 100 larvae are counted, and the percentage of each genus reported. However, the eggs of each genus do not hatch equally because the temperature at which the culture is performed may favour the hatching rates of one genus over others. It is safer, therefore, to use the larval culture results as a general indication of the worm genera present, rather than a precise determination of the proportion of the FEC contributed by each genus.

8.2.3 PNA Staining

A recently described fluorescent microscopy technique for the differentiation of *H. contortus* eggs from other species, using the lectin binding characteristics of nematode eggs has become available. The laboratory-based technique uses a fluoroscein isothiocyanate (FITC)-labelled peanut agglutinin (PNA) Lectin binding exhibits a genus specific pattern, with *Haemonchus* spp. staining strongly positive with PNA. The test is available via AHVLA laboratories.

Other nematode speciation techniques are also under development. Species-specific molecular probes have been developed for identifying *Telodorsagia*, *Trichostrongylus Haemonchus and Cooperia* at all stages and offer the potential for a rapid and cost-effective means of identifying these important genera from eggs within 24 hours.

8.2.4 Interpretation of FECs

FECs have some limitations and should be viewed as ‘additional diagnostic information’ to be considered with history and clinical signs. Careful interpretation is particularly important where the FEC is low.

- With some genera (e.g. *Nematodirus*) egg production is not strongly related to the size of the worm burden. The fecundity of adult female *Teladorsagia* of sheep is inversely density dependent, i.e. egg production per worm is higher when the number of worms in the gut is lower. FECs are better correlated with worm burdens of *H. contortus* and with burdens of *Trichostrongylus* spp in young animals.

- Nematode genera and species within genera differ in their fecundity and pathogenicity. *H. contortus*, for example, is very pathogenic and is also highly fecund. Tolerable burdens of *Haemonchus* may produce FECs that would be considered dangerously high for *Trichostrongylus*.

- As sheep grow older they develop an immunity that reduces worm fecundity, so egg count becomes a less reliable indicator of the size of a worm burden.

- Faecal egg production per worm varies with the time of year, particularly those present in fit, healthy sheep in good body condition and with a strong immunity. Generally, egg production is highest when larval intake is lowest.

- In outbreaks of acute helminthosis, egg counts may be low because the infection has not yet become patent. This is particularly true of acute *N. battus* infection in lambs and in acute

Haemonchosis in sheep of any age where the pre-patent larvae are capable of causing severe disease and death. When interpreting FECs, always remember that the eggs were produced by worms picked up by the sheep three or more weeks earlier. FECs provide no information about the numbers of pre-patent larvae present.

Despite these limitations, FECs can be used to help decide if anthelmintic treatment is necessary, or can be safely delayed or omitted. On some farms, FEC monitoring may allow anthelmintics to be better timed, and therefore used more efficiently, rather than less frequently. On other farms where anthelmintics are used excessively, FEC monitoring may provide a farmer with the necessary additional information to reduce anthelmintic frequency, while continuing to manage the risk of disease outbreaks or lost productivity.

Faecal consistency and appearance also provide clues to possible species identity and presence. Pelleted faecal samples with moderate to high FEC are generally indicative of *H. contortus* infections. Dark, foul-smelling diarrhoeic faeces are suggestive of *Trichostrongylus* infections.

Low egg counts of *N. battus* may still be significant as pre-patent larvae can cause severe illness and death in young susceptible lambs and females of this species have a low fecundity.

The following table (Table 8.2) provides a guide ONLY to interpretation of **low**, **medium** and **high** faecal egg counts in sheep.

Worm Species	Faecal Egg Counts (FEC)		
	Low	Medium	High
Mixed (*H. contortus* absent)	<250	250-750	>750
Mixed (*H. contortus* present)	<500	500-1500	>1500
Haemonchus contortus	<500	1000-5000	>5000
Trichostrongylus spp.	100-500	500-1500	>1500
Nematodirus battus	50-150	150-300	>300

Table 8.2 A Guide to the Interpretation of Faecal Egg Counts (epg)

8.2.5 The FAMACHA test for Haemonchosis

In acute infections, resulting from the ingestion of many infective larvae over a short period of time, animals are weak and are likely to collapse if driven. Pallor of the mucous membranes is striking, but it should be assessed by inspection of the conjunctivae *using the FAMACHA* © assessment system (Kaplan *et al*. 2004), rather than the oral mucosa or skin where differentiation from a normal appearance is difficult. Hyperpnoea and tachycardia are also present. The onset of clinical signs may be so sudden that affected animals are still in good body condition. Acute Haemonchosis can be a cause of sudden death.

Work in Australia is also looking at Faecal Occult Blood (FOB) testing as a means of predicting the severity of *H. contortus* infections. This utilises a dipstick type of approach and uses the fact that blood can be detected in host faeces as a result of worm feeding activity *before* (a few days) there is a significant rise in epg due to egg laying activity of adult female worms. This small time advantage could be very useful under field conditions and help to both improve performance but also contamination of pastures through early treatment.

8.3 Risk management for pastures

	HIGH	MEDIUM	LOW
SPRING	**Ewes and lambs in the previous year** **For *Nematodirus* carried ewes and lambs in the previous spring** **Goats the previous year** **Store/ewe lambs the previous autumn/winter**	**Grazed only by adult non lactating sheep the previous year** **Grazed by ewes and lambs previous spring but then conserved and aftermath not grazed by sheep *(NB Nematodirus still high risk)***	**New leys / seeds or forage crops** **Cattle or conservation only in the previous year**
SUMMER	**Ewes and lambs in the spring**	**Adult non lactating sheep only in the spring** **Cattle or conservation in the spring**	**Cattle or conservation only in the first half of the grazing season** **Forage crops or arable by-products**
LATE SEASON / AUTUMN	**Ewes and lambs all season**	**Grazed by cattle since mid season** **Grazed by mature dry ewes since weaning mid-season**	**Cattle or conservation only in the first half of the grazing season** **Forage crops or arable by-products**

8.4 Other management actions

8.4.1 Weaning

Action can be taken from late June, when lambs can be moved on to less contaminated areas after weaning, thereby avoiding the high levels of infectivity on pastures they have grazed with their mothers since turnout. Ewes can be left on the heavily contaminated grazing, while lambs require a much smaller area, for example an aftermath or pasture grazed by cattle since turnout.

8.4.2 Grouping lambs by age

Keeping lambs in tight age groups at turnout has benefits when it comes to the need for treatment and the utility of FECs in determining treatment requirements and other management decisions, for example weaning and withdrawal times post treatment when drawing for market.

8.4.3 Mixed grazing and Reduced Stocking Densities

The level of contamination on a pasture can be reduced by grazing cattle, ***(not goats),*** and sheep together. This effectively reduces the stocking density of the host species, but can make pasture utilisation more difficult. A system of rotation between the cattle and sheep during the season would address this though has practical issues.

8.4.4 Nutrition

It is well documented that sheep under nutritional stress are less able to withstand a challenge from internal parasites. This should be considered as part of the overall management plan, using condition scoring to determine the need to drench mature sheep as an integral part of a parasite control strategy. In addition, it is now known that ewes fed a ration that has high levels of undegradable protein are less affected by the PPRI and as such produce much lower numbers of worm eggs post-lambing. Similarly, creep feeding of lambs provides additional nutritive support and may help delay early exposure to larvae on pasture.

8.4.5 Grazing By Mature Ewes

Mature ewes, in good body condition can be used post weaning to reduce the level of contamination on high risk pastures that have carried ewes and lambs since the spring. These animals have very low worm burdens themselves and are therefore producing very low FECs; however, they are ingesting large quantities of infective larvae and are effectively killing them off, thus reducing the overall level of contamination on that pasture for late in the season and/or next spring *(NB this does not affect the Nematodirus risk the following spring).*

8.4.6 Alternative and Bioactive Crops

See 6.8.4

8.5 Additional risk factors

8.5.1 Rainfall and temperature

In dry years, the levels of infective larvae on the pasture are lower, but once it rains, there tends to be a huge increase in infectivity as the L3 larvae emerge from the dung. It is common, therefore, to see heavy worm burdens in the autumn and winter following a dry summer. *Nematodirus* has a life cycle that is highly dependent on temperature, as it generally requires a period of cold followed by warm spell before it will hatch. This is why in springs when the weather changes suddenly from cold to warm, there are mass hatchings of overwintered larvae resulting in a large number of nematodirosis cases. In dry years, a late surge in *Nematodirus* in June may be due to the desiccation effect of a very dry spring, with a mass hatch occurring after warm June rainfall.

8.5.2 Previous exposure

Lambs will normally develop immunity to gastrointestinal nematodes by the time they are 5-6 months old. However, this is an ***acquired*** immunity that is dependent on sufficient exposure to the parasites and at this age is not as strong and effective as in adult ewes. For example, lambs kept on clean grazing, or kept indoors for long periods of their early life, may remain naïve to parasite challenge and succumb to PGE when subsequently exposed, irrespective of their age. An example would be pedigree ram lambs that have been pushed hard on concentrates and wormed regularly so they have had little exposure worms before being put out to work on a commercial farm.. This can also be an issue for hill lambs when they are moved down from low challenge hill grazings to heavily infected lowland farms,

8.5.3 Concurrent disease

The ability of sheep to withstand a challenge from parasites will be impaired by concurrent disease. Of particular note is the effect of coccidiosis on *Nematodirus* and vice versa. This will also apply to disease caused by nutritional deficiencies (for example cobalt deficiency is implicated in the inability to withstand parasite challenges) or previous damage to the GI tract due to other parasitic disease.

8.6 Managing Multiple Resistance

Management actions become even more important on farms where resistance to two or three of the current broad spectrum groups is confirmed. Increasingly we are realising that resistance is not a black and white situation so it does not necessarily mean the end to sheep farming on a holding. However, action must be swift and positive. Key areas to consider are:

- Knowledge of which worm genera are resistant to which anthelmintic groups is essential. Based on recent field data it is probable that resistance will vary between genera and hence also the time of year, which will have a significant influence on effective strategies available.

- Changes to the production system (e.g. lambing date, introduction of creep feeding or rotational grazing / lower stocking densities) may be necessary as a means of avoiding high levels of challenge and/or pasture contamination.

- Introduction of new genetics to increase resistance to worms and the consideration of the place for resilience take on more importance.

- Expectations may have to be actively managed – i.e. it may be necessary for the farmer to realise that the potential levels of productivity are reduced. This means that the adviser necessarily gets involved in the economics of continuing the sheep enterprise given the limitations multiple resistance will impose.

- The use of the 4-AD and new 5-SI dual active products is essential, but it is imperative they are integrated into the farm strategy rather than simply used as substitutes for the original 3 groups. This is because if there is good knowledge of the AR status, worm genera involved and regular monitoring, the high level of efficacy of these new compounds can be used to prolong the life of the existing products where the frequency of resistant worms is not too high. See case studies at www.scops.org.uk for practical examples.

8.7 Systems of Production

System	Features / risks	Implications for Control
Early Lambing (January born)	If housed and finished intensively or turned out on to clean forage crops, these lambs will not come into contact with worms. If turned out to pasture then the risk should be assessed, but will come mainly from an early hatch of *Nematodirus*.	Drenching is unnecessary with many of these systems for both lambs and ewes. Note, however, that female replacements from these flocks may remain naïve to parasites if not exposed and this requires management.
Creep Feeding at Grass (Feb/March born)	This system tends to be most at risk from *Nematodirus*, partly due to their age relative to the risk, but also because high stocking rates increase the risks and the chances of concurrent coccidiosis. Conversely, the majority of the lambs tend to be finished before the main risk period for Teladorsagia. Drenching frequency in these lambs is usually relatively low, with many capable of finishing without treatment in monitored flocks	Tight grouping according to age / control of coccidiosis. Attention to warnings of *Nematodirus* risk and drenching with a BZ if there is a high risk forecast. FEC monitoring to keep a check on strongyle and coccidia counts. However, these are of limited value for *Nematodirus* due to the high levels of damage that surges of hatching L3 larvae can inflict.
Main Season (March – May born)	These lambs are also at risk from Nematodirus on high risk pastures. Few of these lambs will be finished by weaning, so they will be on the farm in the latter part of the season. It is not unusual to see scouring in these lambs when they are moved to fresh green keep. This is often confused with a worm burden.	Tight grouping according to age and attention to warnings of Nematodirus risk and drenching with a BZ if there is a high risk forecast. FEC monitoring pre- and post-weaning at 3-4 week intervals. Identification of lower risk pastures from July onwards a priority for weaned lambs.
Store lambs **(September onwards)**	Store lambs are frequently challenged by high worm burdens on grass in the autumn and are often of unknown history having been purchased from a variety of sources. Scouring due to nutritional stress (changes) or previous gut damage is common and often confused with the need to treat. Sorting lambs into groups according to their body weight and condition will help general management as well as parasite control measures.	Homebred stores should be moved to safer pastures after weaning. Purchased stores will need to be quarantined (see Section 6). FEC monitoring is an invaluable tool for these sheep. Worm burdens should be monitored at regular intervals throughout the autumn and winter.
Hill Flocks	Overall stocking rates are low, but when brought on to in-bye grazing for lambing etc. the effective stocking density can be high for short periods. Opportunities to handle are limited and can determine times when these sheep are drenched or monitored. Endectocides are also frequently used in these flocks which can inadvertently exert selection pressure for ML resistance.	There is a high temptation to drench at set times when the sheep are handled. However, FEC monitoring can be used to determine the need to treat, including for liver fluke and should be encouraged. Identification of high risk in–bye pastures and times of year will help in devising programmes. Careful use of endectocides with reference to the *in refugia* worm population and the need to dilute any selection effects as much as possible post treatment.

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