Development of Host immunity

Following exposure to helminths, lambs will gradually acquire immunity to these parasites. This ability of the host to develop an immune response is key to the sustainable control of these parasites. An understanding of the mechanisms involved is important if we are to harness this as a management tool and reduce reliance on anthelmintics. Immunity to helminths, as with other pathogens can be split into two functions:

- **Innate (inborn) immunity.** This is thought of as the first line of defence and directs the subsequent development of the adaptive response. It is not specific to particular antigens, but involves barriers such as the epithelia (e.g. of the gut), monocytes, macrophages, lymphoid cells etc.

- **Adaptive (acquired) immunity** involving T and B lymphocytes which are activated in response to antigens of specific pathogens. Subsequent exposure to that antigen will induce a 'memory response'. Levels of antibodies in saliva and serum together with eosinophils are used to measure the extent of this immune response. Understanding the factors involved in the establishment and maintenance of this acquired immunity is vital with respect to its role as a tool in sustainable worm control. This includes the need for a 'regulatory' population of worms within the immune sheep which acts as a continual focus to sustain the immune response, but it also acts as a restraint on the host response to incoming larvae.

There are three ways that the adaptive immune system deals with incoming helminths:

- **Disable** – restrict worm growth, development and fecundity, reducing overall fitness and the ability to reproduce (reach egg laying maturity). For example, worm length has been used in research as an indicator of immune response.
- **Degrade** – cumulative damage to the integrity of the worms e.g. calcification, affecting worm survival.
- **Dislodge** – expulsion of the worms by the intestinal response to attempts to attach to the gut wall, affecting the ability of the worms to establish in the host.

Factors that affect the immune response:

Age / exposure to larvae
It is generally accepted that lambs develop levels of acquired immunity (to *Teladorsagia* and *Trichostrongylus spp*.)strong enough to regulate worm populations between the ages of 6 and 12 months following exposure to infective larvae on pasture, though it has been shown that 4.5 month old lambs previously exposed to larvae can demonstrate an immune response. This was not as positive as in older lambs. In 5month old lambs it has been shown that the first indication of immunity, (disabling of worm development) was present after exposure to larvae for 4 weeks with resistance to the establishment (dislodging) of incoming larvae present after 4-8 weeks. By 12 weeks post exposure they were almost completely immune to incoming larvae. There is some evidence that female lambs have lower FECs compared with wether lambs of the same age. This has been linked to testosterone levels but may also be due to higher intakes of pasture (and hence larval ingestion) in the faster growing wethers, rather than any specific gender effect on immunity.

Nematodirus – assuming there is exposure to larvae, acquired immunity to *N. battus* occurs much earlier, at around eight weeks of age, with the first indication that adult worms are being expelled 3-4 weeks after infection.

Physiological state / Stage of production
The physiological state of sheep determines the immune response.
Dry, healthy, adult ewes have a good immune response to incoming larvae providing they have had sufficient historical exposure to establish immunological memory (acquired immunity). It is generally accepted that ewes experience a relaxation in immunity in late pregnancy and lactation. This is the foundation of the historic recommendation that ewes should be de-wormed using an anthelmintic at or around lambing. More recent evidence shows that the demands of lactation have the greatest influence, rather than late pregnancy. Weaning lambs at 2 days of age for example has an immediate effect with ewes regaining their immune response very quickly and FEC levels falling rapidly. The effect of nutritional status in the peri-parturient ewe is discussed below.

There does not appear to be any effect of nutrition (within the limits of reasonable energy and protein supply and absence of trace element deficiencies) on the rate at which lambs develop acquired immunity.

Continued exposure
If sheep are removed from infected pasture to a worm free environment, or dosed with anthelmintics continuously or at high frequency, the acquired immunity wanes. Even adult sheep my become susceptible again if the 'regulatory' worm population they normally maintain is removed. Currently there is no evidence regarding the effect of a persistent product on the development of acquired immunity. SCOPS advice is to use persistent products carefully, acknowledging that prolonged exposure may have an effect on acquired immunity and taking this into account, planning grazing to avoid high challenges and monitoring FECs carefully.

Resistance and Resilience

<u>Resistance</u> to parasites refers to the strength of the acquired immune response following exposure to helminths. This corresponds to the ability of sheep to limit the rate of establishment, growth, fecundity and survival of worm parasites. *This is not to be confused with anthelmintic resistance in the parasites themselves.* Most research has been directed at ways to enhance resistance through nutrition and selective breeding because there is considerable variation in the strength of resistance between sheep with genetics being a significant factor. The heritability of resistance (h^2) to helminths is considered to be high enough to support schemes which aim to breed for higher levels of resistance. In practical terms, the value of resistance in sheep is the reduced egg output from resistant sheep and hence reduced pasture contamination. A reduction in egg output is most likely to have greatest benefit for breeding females, particularly when applied to the peri-parturient rise.

<u>Resilience</u> is the ability of sheep to continue to grow, maintain condition, lactate and/or reproduce despite being parasitised. Sheep with a high degree of resilience have FECs that are comparable to others in the flock, but they maintain higher levels of performance at the same level of parasite challenge. These are the animals that can be left untreated based on liveweight gain. Such targeting of anthelmintic use is a vital tool in strategies which aim to reduce anthelmintic use and protect the larval population *in refugia.* The heritability of resilience is considered to be lower than for resistance, but there is still evidence that breeding for resilience has positive effect in terms of growth rates in finishing lambs.

Development of vaccines

The availability of vaccines to enhance the acquired immune response would be a major step towards reducing reliance on anthelmintics. In recent years, there has been significant progress with a focus on vaccines against both *H. contortus and T. circumcincta.*

There are currently no vaccines for Haemonchus licensed in the UK. A commercially available vaccine * licensed in parts of Australia and South Africa induces high serum antibody levels to 'hidden' gut antigens of Haemonchus and manufacture of the vaccine involves harvesting extracts of the parasite's gut. Vaccination results in a reduction in egg shedding and disease in lambs, yearlings and ewes. This vaccine is being used successfully to help in the control of *H. contortus* in parts of Australia and, S. Africa. Sheep require three priming doses of vaccine, followed by boosters every six weeks to six months depending on level of challenge.

**(Barbervax TM) is commercially available in some countries but is not currently authorised in the UK. The use of the vaccine has not been evaluated in control programmes in the UK.*

References

Susceptibility and immunity to helminth parasites. Maizels R. M *et al.* Current Opinion in Immunology. (2012) 24: 459-466

Immunity to *Haemonchus contortus* and Vaccine Development. In Advances in Parasitology (2016). 93(8): 353-396.