WHY TREATMENT FAILURE MAY OCCUR

When a treatment fails to clear up a problem with internal parasites, many might be tempted to believe that this failure is due to anthelmintic resistance. This is only one reason for treatment failure (often called "drench failure") which can occur for several different reasons:

USE OF THE WRONG ANTHELMINTIC

If an anthelmintic is used to treat a parasite for which it has no efficacy. A common example is the use of ivermectin to treat tapeworms.

FAILURE TO ADMINISTER AN ANTHELMINTIC PROPERLY

There are many reasons why an anthelmintic is administered in such a way that it will not work. It is the responsibility of the producer and veterinarian to make sure that the risk of this happening is minimized. The following is a list of how to prevent drench failure.

WEIGH THE ANIMALS TO BE TREATED

Use a calibrated livestock scale to prevent under-dosing (underestimating weight). If the animals are variable in weight, dose for the heaviest in the group.

USE ONLY DRUGS THAT HAVE A CANADIAN DRUG IDENTIFICATION NUMBER (DIN)

Drugs obtained through the internet (for example) may not contain what the label says it does as they may be manufactured in countries that do not have strict legislation on quality control. A DIN indicates that the drug was manufactured under Canadian regulations and rules.

SELECT THE CORRECT DOSE

Read the label for products approved for sheep. If not labelled for sheep or if using in goats, obtain the correct dose by veterinary prescription. Table 1 has some suggested dosages.

Proper Dosage for Goats

Goats often require a higher dosage than sheep and cattle, sometimes twice as much. This is because goats will metabolize (use up) anthelmintics faster than sheep and cattle, so the drug disappears faster from the body and doesn't get a chance to do its job. Table 1 has some suggested dosages for goats but before using get advice from your veterinarian. Additionally, withdrawal issues for meat and milk must be considered.

DOUBLING THE DOSE VERSUS TREATING TWICE

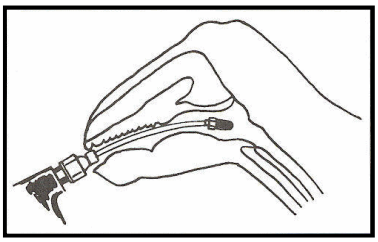
Doubling the dose provided in table 1 will not always double the efficacy of the drug. Some drugs can be toxic if the dose is doubled, particularly if the animal is ill with parasites. But if necessary because of anthelmintic resistance (see below), repeat the dose 12 hours apart with BZ and ML drugs as this will lengthen the time in the GI tract when an effective dose is present.

CALIBRATE YOUR DRENCH GUN FREQUENTLY

To assure delivery of the correct dose, it is important to frequently check the drench gun to make sure it is delivering the amount that is indicated. Drench guns frequently do not actually deliver the amount listed on the syringe so measure and compare. To calibrate your gun, draw up the drench and then "inject" 2 doses into a syringe (take out the plunger and put your finger over the end). This will accurately measure what you just delivered. Was it the amount it should have been?

DRENCH CORRECTLY

This is done by depositing the entire dose over the tongue, at the back of the throat. This will ensure that the drench is swallowed into the rumen and is more slowly released. If administered in the front of the mouth, loss may occur by spitting or having the drug swallowed directly into the abomasum where it will pass through the digestive tract quickly reducing its effectiveness. Do not lift the head too high as that will prevent proper swallowing.



IF INJECTION IS PERFORMED

Make sure that the automatic syringe is calibrated appropriately and that the entire dose is injected subcutaneously (not "intra-wool").

DON'T USE BY THE INCORRECT ROUTE OF ADMINISTRATION

Do not use a cattle pour-on product either as a pour-on or as a drench. Do not use an injectable product orally. Do not use pour-on products as a pour-on as they are not absorbed adequately to be effective and may contribute to development of anthelmintic resistance.

HOLD ANIMALS OFF FEED PRIOR TO TREATMENT

Holding the animals off-feed for 12 to 24 hours before treatment, will increase the length of time that the concentration of the anthelmintic is effective. This is only effective if using BZ drugs, and should not be done if the ewes/does are in late gestation because of the risk of pregnancy toxaemia.

REINFECTION AFTER TREATMENT – APPARENT TREATMENT FAILURE

If the pasture that the animals are turned out to graze after treatment is infested with high levels of L3, then there can be apparent treatment failure. Most anthelmintics have no persistency, which means that very soon after treatment; the lambs/kids are infected from the L3 on pasture. If the challenge is high, then clinically they may appear as if they have not responded to the treatment. Depending on when the faecal samples are re-examined (e.g. 2 weeks later), the FEC may be very low indicating that the parasites within the animals were killed - but that immature adults are numerous enough to cause disease. This is prevented by reducing the challenge after treatment through pasture management.

ANTHELMINTIC RESISTANCE (AR)

Around the world, AR is becoming very common - particularly in *Haemonchus* and *Teladorsagia*, and to all classes of anthelmintics. As a result, sheep and goat rearing is being threatened in many countries and regions. By the time AR is clinically apparent (i.e. failure of treatment to improve the health of the animals being dewormed), it is well-advanced in the flock. Prevention of development of AR is critical for the survival of the small ruminant industries. The following will explain how AR develops and strategies to avoid its development.

DEFINITION OF AR

Resistance or AR is the heritable ability of the parasite to survive a normally effective dose of an anthelmintic. Usually a parasite is considered resistant if it survives a normal dose of a single anthelmintic. Parasites often survive if the treatment is administered incorrectly - this is not AR but drench failure (see above). Because resistance is a genetic trait, the parasite may be homozygous resistant, i.e. having two copies of the genes for resistance (RR), or heterozygous resistant, i.e. having only one copy of the gene for resistance (Rr).

The homozygous resistant parasite is much more resistant to an anthelmintic than are heterozygous parasites. Heterozygous resistant parasites are still susceptible to the correct dosing of an anthelmintic, but will survive if the animal is under-dosed. However, a homozygous resistant parasite may not be affected at all, although repeated dosing at a high level, or dosing with two anthelmintics simultaneously, may be effective for a while. The homozygous resistant parasite is rare in an unselected population of parasites. But once the selection has occurred, parasites do not lose their resistance.

HOW DOES AR DEVELOP?

REFUGIA EXPLAINED

To understand the development of anthelmintic resistance, it is necessary to understand the concept of refugia. This term is applied to the free-living stages of GIN on pasture, i.e. L1, L2 and L3 stages of larvae as well as the parasitic GIN in the sheep/goats that are not exposed to an anthelmintic treatment. Traditionally a higher proportion of the total parasite load on a farm is on the pasture (80%) as eggs and free living larvae, compared to the parasite load in the animals (20%) which is comprised of L4, L5 and adult parasites. This is important when understanding how anthelmintic resistance develops on a farm. The refugia are the farm's source of susceptible parasites. Elimination or severe reduction of refugia will hasten the development of this resistance. However, this has to be balanced with the risk of having a high level of refugia which is a primary cause of sheep/goats developing clinical parasitism and perhaps even dying of its effects. It is important to learn how to ride the fine-line between too many parasites in refugia, and too few.

PRESSURE OF ANTHELMINTIC USE

Repeat dosing with an anthelmintic will often kill 95% or more of all GIN in an animal. But it is the surviving, genetically resistant population that will continue to lay eggs and contaminate the pasture. Repeat, frequent

dosing, particularly if under-dosing occurs, will hasten the development of a resistant refugia. While sheep/goats will clinically respond to a drench that is less than 95% effective, eventually the susceptible parasites are in the minority and the drench ceases to be clinically effective. This does not happen overnight, and may take years for a farm to get to this state.

SIDE RESISTANCE

Resistance is generally shared by all drugs in an anthelmintic class. E.g. if the parasite is resistant to fenbendazole, then it is also resistant to albendazole. This is less true with the avermectins and moxidectin, where moxidectin may still be effective in the face of avermectin resistance, but often resistance will develop to moxidectin in a year after it is first used in a flock with ivermectin resistance.

PARASITE FITNESS

It appears that AR can develop more quickly if the population of parasites is already resistant to one or more classes of anthelmintics. It may be that those parasites have the ability to more quickly metabolize drugs than those that are 100% susceptible. This may play a role in the development of multi-class resistance on a given farm. In an Ontario study conducted in the summers of 2010 and 2011, we have seen multiple drug class resistance more often than single drug resistance, even on farms that have not used one of those drugs for years.

CONSEQUENCES OF HAVING LOW LEVELS OF REFUGIA ON THE FARM IN THE FACE OF AN AGGRESSIVE DEWORMING PROGRAM

Having susceptible refugia on pasture allows the flock the opportunity to become infected again with susceptible parasites - thus lowering the risk of AR becoming a farm problem. However, it is also important to make sure that pastures are not heavily contaminated, so our parasite control practices include lowering the level of parasites in refugia (see later in the handbook for those methods). However, if an aggressive deworming program is also instituted in the face of low refugia - the development of AR is accelerated. Two examples of particularly risky methods of parasite control are:

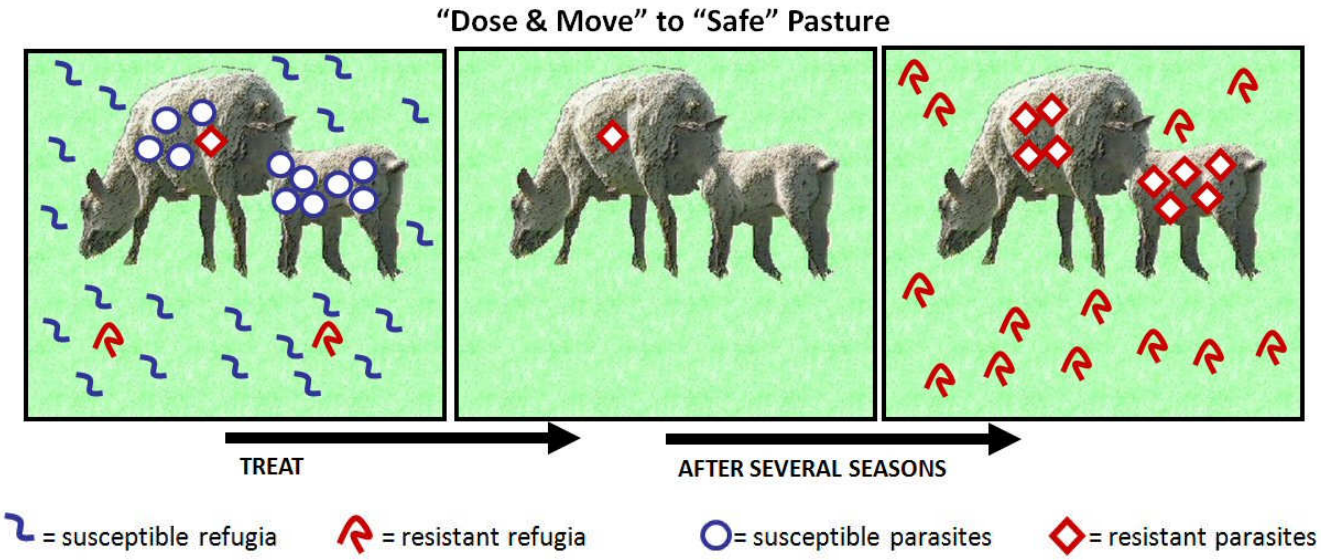
"Dose and Move" Pasture Rotation

The"dose and move" strategy was designed to prevent animals from"carrying" parasites into a clean pasture. If animals are treated and returned to a contaminated pasture, they will become reinfected with a population of susceptible parasites that were already on the pasture. But if they are treated and moved to a clean pasture, the only parasites to shed eggs into the new pasture are resistant strains. It might take several grazing seasons to build-up a resistant population, but when it happens, severe losses may occur. See figures 3- a, b, c & d for a more full explanation of this issue.

Figure 3 a. Deworming sheep and goats on a contaminated pasture and then moving them to a pasture with low levels of pasture contamination (i.e. a "safe" pasture) will allow animals to maintain a low infection status for longer. A "safe pasture" is one that has no or very few eggs and larvae on it. However, the parasites that have survived treatment and remain in the animals are those that are resistant to the deworming product that was used. The result is that these surviving parasites will go on to produce resistant eggs which will then contaminate the pasture with resistant L3. The build-up of resistant parasites on pasture and in the animals to

a level where the producer sees infection levels that cause disease, may take several grazing seasons – but when this happens, it is often too late to reverse the high level of anthelmintic resistance on the farm. For this reason, it is strongly recommended <u>not</u> to practice "dose and move" deworming strategy.

Figure 3 a



In figure 3 b, we can see what might happen if the sheep / goats are dewormed and either left on the same contaminated pasture or moved to another contaminated pastures. The development of anthelmintic resistance is slowed considerably as there are plenty of susceptible parasites in refugia. However the animals quickly become infected again and so must be dewormed more frequently over the season. Eventually, resistant parasites will build-up on pasture over several grazing seasons, and AR will develop as in 3 a, just more slowly.

Figure 3 b

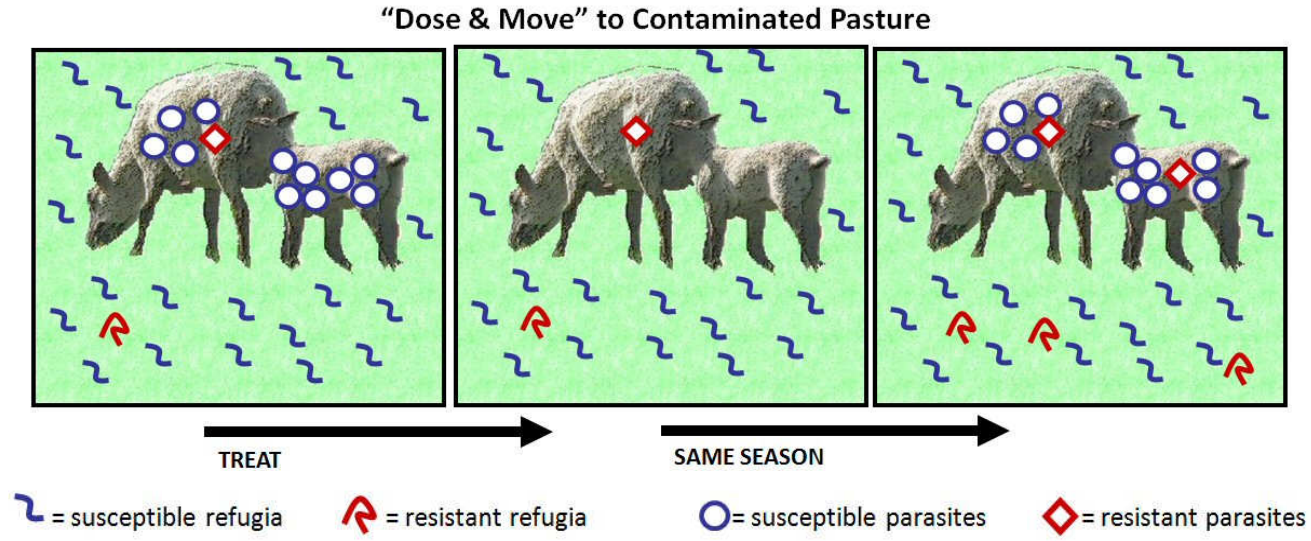
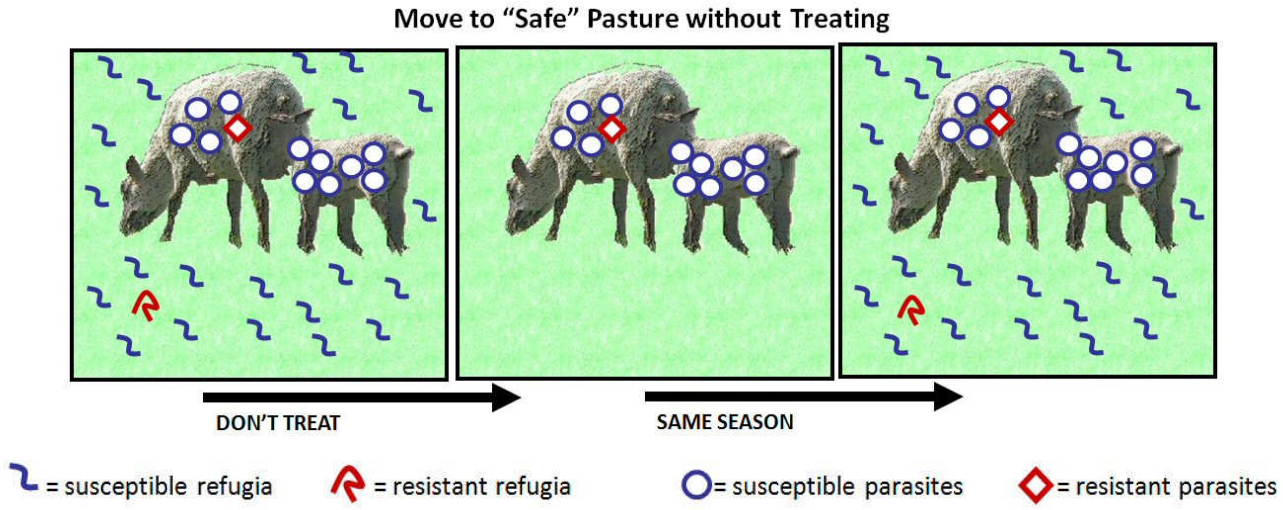


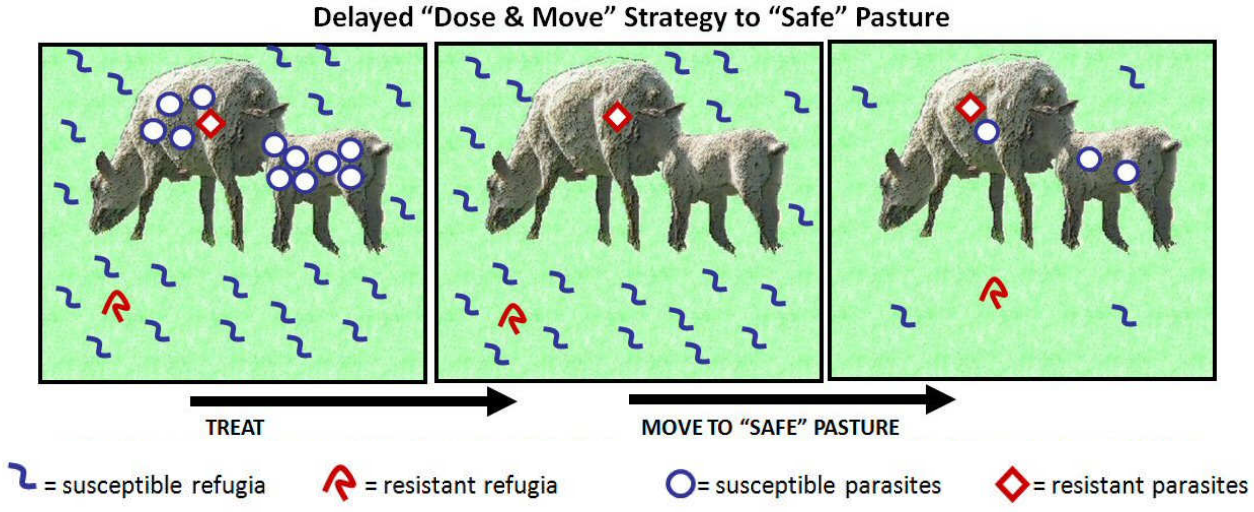
Figure 3 c



In figure 3 c, we can see what happens if sheep / goats are not dewormed but simply moved to a "safe" pasture instead, i.e. one with low levels of contamination with L3. For the short-term, they will not pick up more parasites and so the level of infection won't reach the stage where the parasites cause disease. If the farm has many safe pastures, it is possible to rotate the animals through the pastures quickly (e.g. < 2 weeks per pasture) and so keep the level of parasites low. But most farms don't have that many safe pastures and so eventually the animals must return, the pasture becomes increasingly contaminated and the parasite load in the animals may reach a level that requires deworming to prevent disease.

Figure 3 d shows the preferred approach. To prevent disease in the animals, they are dewormed when infection levels reach high enough levels. But to prevent the development of AR, the sheep / goats are left on the pasture for a <u>few days</u> to pick up susceptible larvae – enough so that they become mildly reinfected with parasites. This dilutes the resistant eggs being shed on pasture while still keeping low levels in the animals.

Figure 3 d



Dose at Lambing / Kidding

While *Teladorsagia* and *Trichostrongylus* L3 overwinter well on pasture in our climate, *Haemonchus* does not. This sounds like good news because spring pastures have very low levels of refugia of this parasite. However, if we deworm all adults prior to turnout (e.g. if we treat all ewes or does at lambing/kidding) we will eliminate all the *Haemonchus* on a farm – with the exception of *Haemonchus* in the animals that have resistance to the anthelmintic used. These resistant *Haemonchus* then infect lambs and kids. It may take a very short time for AR resistant *Haemonchus* to become predominant on a farm, even if the adults are rarely dewormed and may occur more quickly if they are dewormed while still in the barn.

In our AR study of 2010 and 2011, almost all the parasites we found on AR farms, were *Haemonchus* – suggesting that this is what may be happening here in Ontario sheep flocks.

INTRODUCTION OF RESISTANT PARASITES

Purchase of sheep or goats that contain large numbers of resistant parasites, may introduce AR to a farm - which when combined with improper parasite control measures, will hasten the development of AR on a farm. Goats are a particular risk as AR tends to develop more quickly with this species. This is because many anthelmintics are metabolized more quickly in goats than sheep (increasing the risk of sub-therapeutic dosing) and because adult goats do not develop immunity as well as sheep do, so they carry more severe infections. Quarantine of new introductions and proper deworming of new introductions is an important strategy to prevent introduction of AR. For details, see ★4 of the 5 STAR WORM PLAN.

IMPROPER TREATMENT

There are many ways to improperly administer a treatment (see above for prevention of treatment failure). By under dosing, heterozygous resistant parasites are more likely to survive, which will hasten the development of AR on a property.

THE CENTRAL CANADIAN SITUATION

Anthelmintic resistance to both avermectins and benzimidazoles appears to be widespread in Ontario sheep flocks and may also be present in some goat herds. If parasite control practices do not change, Ontario may become one of the areas of the world where it is difficult to raise small ruminants. Of course, we need to do whatever we can to prevent this from happening.

DETECTING THE PRESENCE OF AR IN A SHEEP FLOCK

If AR is suspected in a flock, it is important to review the treatment protocols to make sure that the drug is being administered properly. To confirm AR on a property the following methods can be used:

DRENCH RESPONSE TEST

This can be performed with only 1 faecal sample collection time but only suggests, rather than proves, that AR is present. The group is treated and faecal samples are collected from 10 randomly selected lambs or kids after a period of time (7 days for LV, 10-14 days for BZ, 14-16 days for ML). Failure to achieve low counts may indicate AR, or treatment failure from other causes.

FAECAL EGG COUNT REDUCTION TEST (FECRT)

The FECRT is often used as the "gold standard"for determining if AR is present on a farm. It is scientifically sound when done correctly and will give an accurate picture of how effective anthelmintics are on a given farm. However, as you can see - the process is labour intensive and expensive - but gives the best information. If you decide to perform a FECRT, the following protocol is followed:

- A minimum of 30 lambs/kids or young adults (first grazing season) with elevated faecal egg counts are required.
- Individual minimum FEC of 150 epg is required but 300 epg is preferred.
- Ten to 15 lambs/kids are randomly assigned to control and treatment groups. It is necessary to use these many animals per group because of the normal variation in egg output between animals.
- If three anthelmintics are being evaluated (e.g. ivermectin representing the macrocyclic lactones (ML), fenbendazole representing the benzimidazoles (BZ) and levamisole (LV)), then four groups (60 animals) are needed (e.g. control group (no treatment), ML group, BZ group and LV group).
- Individual faecal samples are obtained per rectum on day 0 (treatment day).
- The lambs/kids are weighed using a scale and treated appropriately by drenching.
- The control animals are not treated but are sampled.
- All of the animals are returned to the same pasture to graze.
- All the animals are sampled again later (7 days for LV, 14 days for BZ and ML).
- The post-treatment faecal egg counts are compared to the control.
- Failure to reduce by 95% or greater compared to the control indicates resistance.
- Confidence intervals (CI) are also calculated and AR is present if the lower CI is < 90%.

LARVAL DEVELOPMENT ASSAYS (IN VITRO TEST)

Larval development assays can be used to detect AR in the laboratory but have some drawbacks. They cannot be used to detect ML resistance, are expensive, and require a specialized laboratory to work properly. Eggs are hatched and developed to the L3 stage while exposed to an anthelmintic. The level of successful hatching, development or feeding is then measured. The positive aspects of the assays are that they require less labour on farm and don't require treatment or handling of animals. At this point, LDA's are mostly used as a research tool.