

SEQUENTIAL TREATMENT AS A POSSIBLE WAY OF SLOWING AR

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Abstract:

The use of combination anthelmintics and the application of "SEQUENTIAL TREATMENT" is a controversial topic which I have studied and have been using with great success in practice, even on farms where resistance is found to all the older remedies, apart from the 2 newly launched actives (Monepantel and Derquantel).

In order to protect the new actives, I recommend that farmers still use the older drugs, but preferably in combination or in sequence. I also want to make it very clear that combinations are subjected to various tests to make sure that they are compatible, in contrast to home mixes or cocktails which are often made on the farm. PLEASE leave cocktails for a barman to make in a pub!

Sequential dosing CANNOT be recommended on its own! It has to be part of a holistic approach.

My recommendation to ALL my clients is to dose LESS, but to make sure that when they dose individual, or small portions of animals in a flock, to make absolutely sure that all, or nearly all, of the parasites in those animals are removed at dosing time, so that few or hopefully NO survivors are left to contribute to the next generation.

The fact that there are always worms with an inherent resistance in a population, forces us to then at least try and slow down the development of resistance by respecting REFUGIA and other management options, in order to keep the level of resistant worms in the population as small/as low as possible.

Introduction:

My interest in parasitology began in 1985 when I "discovered" *Haemonchus* in Riversdale. I collected a honey bottle full of worms from one anaemic lamb. I could not hide my excitement and the late Prof Reynecke, just to hear: "My son – where did I go wrong in my teaching? Did I not teach you that *Haemonchus* does NOT occur in the "Western Cape"! (Southern Cape would have been more correct). Later in the late 1990's when he did his research in the Overberg area, I referred him to this telephone call and he humbly apologised! What a teacher and mentor!

Next I found my first *Stilesiaglobipunctata* at Kweekkraal, belonging to Charles van Wyk at the time.

I found farmers complaining that remedies that always worked so well, were letting them down and started looking for solutions. It was during the latter part of the 80's that Theo Taljaardt and myself started doing "drench tests" – checking for parasite eggs 10-14 days post drenching. My biggest client was dosing his adult sheep between 8 and 10 times per year! I cannot explain to you how controversial I was when I recommended to him to dose less! When I left Riversdale in 2004 they (he and his sons) were down to one dosing every 8 months or 1.5 drenches per year.

I sent samples to the Regional Laboratory in Stellenbosch. Did several "METRED" or FECRT-tests.

The one thing that actually bothered or intrigued me was that a combination remedy – one containing Albendazole + Closantel- still seemed to work on farms where both single actives were letting us down!

I am a “collector” and kept these results for many years but unfortunately my vehicle was stolen in 2008 in Bloemfontein with my parasitology “mobile lab” and my box of information which I was putting on my laptop at the time. About 3 months later my laptop was permanently “removed without my permission” during the LHPG (now RUVASA) congress in Stellenbosch. With this years of work vanished from life in a matter of a few months...

During my time in Industry I worked in close collaboration with various parasitologists from across the world. Flip van Schalkwyk stands out as one from whom I have learnt a lot!

I was involved in the launch of STARTECT (Derquantel) and apart from the registration trial work; we also did a parasite resistance survey in which I did a fair amount of the field work.

Once again I could not understand why combination doses were nearly always doing better than the single actives on their own. That is when I started reading up on **combination drenches** and on **SEQUENTIAL dosing**, and found that this was, and still is, part of just about the “rest of the world’s” recommendations in the fight against anthelmintic resistance.

After many meetings with Helminthologists from across the world, Pfizer (now Zoetis) decided to bring derquantel out as a combination instead of as a single active as part of protecting the molecule against the development of anthelmintic resistance. It just did not sound right to me at first, but after studying the concept of combinations and of sequential dosing, I am now converted!

Sequential dosing cannot be recommended, or practised, on its own – it is part of a HOLISTIC APPROACH. Before even attempting to explain the concept, you need a thorough understanding/knowledge of:

- **How Resistance develops**
 - In all populations there are a few animals/individuals that carry genes for resistance to remedies.
 - Without treatments/drenching resistance genes are normally kept at very low levels
 - With drenching it is not a matter of if, but rather a matter of WHEN and HOW BAD...
 - Irresponsible dosing is the pivot around which drug resistance develops!
- **Understanding Drench Resistance**
 - Drench resistance is a change in the GENES in a worm population which allows certain worms to survive exposure to a drench or drenches
 - Drench resistance is a farm level problem
 - Whether resistance takes a few years or a few decades to develop, once a critical proportion of resistant worms is reached the rate of development/spread is very rapid!
- **What is Reproductive Advantage?**

This is the period of time drench-selected worms lay eggs without competition from non-selected worms.

- **REFUGIA** management determines the proportion of the total worm population exposed to drenching. It is explained in detail by other speakers.
- **Only THEN** can we look at the use of combination anthelmintics and/or Sequential treatment as a possible way of slowing AR

Using combination anthelmintics and/or Sequential treatment as a possible way of slowing AR

- The use of combinations as well as of “sequential dosing” is very often “mis-understood”
- There are two different types of combination drenches:
 - those designed to extend the spectrum of activity of a broad spectrum drench (for example adding triclabendazole to levamisole to kill liver fluke, or closantel to albendazole to extend its range of effectivity), and
 - those designed to overcome resistant worms, which is what we are focusing on here today
- Combinations of anthelmintics with different modes of action are recommended to delay development of resistance **in a susceptible parasite population**. The theoretical basis for this approach to parasite control is that if resistance to each anthelmintic is initially rare, dual- and triple-resistant parasites are extremely rare. For example, if 1 in 10,000 (10^4) parasites is resistant to benzimidazoles and 1 in 10,000 (10^4) is resistant to levamisole, then we would expect that only 1 in 100,000,000 (10^8) would be resistant to both.
- Using combination products or unrelated products in sequence removes all, or nearly all, of the resistance genes from the exposed population and keeps the resistance genes very rare. This is also referred to as **sequential dosing**. By contrast, when half the parasites are resistant to one anthelmintic and half are resistant to another, we can expect one quarter of the worms to be resistant to both.
- Combined treatment may then provide an improved clinical response for only a few years, if the combination is used carefully **AND in combination with other resistance control measures** (like respecting REFUGIA)!
- Ultimately, resistance to the combination drenches also develops, but modelling and practical experience has shown that the chemicals will remain effective longer if used together, than if used separately. **The end result of using the combinations is bi- or tri-resistant parasites; it just takes longer to get to this stage** (Sangster and Dobson, The Biology of Nematodes, 2002; Leathwick, 2009, NZ Vet J).
- This is thus not a “sales gimmick” by companies trying to sell more drugs, but a recommendation based on solid scientific principles and should in my opinion be applied more often in South Africa (and in the game industry where we are still in early days?).
- Keep in mind that the earlier you start applying this, BEFORE resistance develops or early on when there are still only **few resistance genes** on the farm, the better! BUT, in my opinion, even if there is resistance, the use of combinations is still a good option!
- Leathwick and Dobson have posted/published very good articles on this subject and were involved in the development of Derquantel, as well as in bringing it to market as a combination, rather than as a single “entity”. Once again, reasoning that this will postpone the development of resistance against this novel molecule – especially if used in combination with other management practices that combat development of resistance:

1. Do not blanket treat
 2. Do NOT dose and move – rather dose and leave, or move and then dose!
 3. Know your client's STATUS and work out a dosing MANAGEMENT program accordingly
 4. Monitor your recommendations regularly
 5. Apply good/sensible quarantine and bio-security measures
 6. REFUGIA, REFUGIA, REFUGIA...
- Ideally, anthelmintic combinations should be used when the individual chemicals are still fully effective (The new anthelmintic combination containing derquantel, for example, was shown to be >99% effective against a broad range of gastrointestinal and respiratory nematodes) and when worms' resistance genes are at very low frequencies.
 - Bringing a new active to market as a combination and using either combination drugs or using single actives in sequence, thus makes good scientific sense to me!
 - **Strive to deworm as seldom as possible**, BUT when you decide to deworm, why then play with a "small calibre rifle" when you have a BIG GUN available. In other words – if you decide to get rid of the worms, do a decent job and then apply basic principles:
 1. If all parasites are/were "removed", my "instinct" tells me that there won't be any females left, or very few then, that would/could "spread" the resistance...
 2. If a single animal e.g. a new ram is going to be released onto a new farm with an existing flock, it will soon pick up existing parasites which were hopefully not exposed to the same active ingredient recently " (refugia)

All I ask is that we do not just dose for the sake of dosing, but THINK the whole process through in a logical way BEFORE we make recommendations and/or commence treatment. Resistance to anthelmintics is a given but ... I believe in my heart that the solution does not lie in a bottle/can or a dose gun. We have to take a holistic approach and keep on monitoring the situation on a case to case or farm to farm basis. Unfortunately one shoe does not fit all! The idea is not to let the cat amongst the pigeons, but rather to let us realize that there are more sides to the coins than many of us might think or realize!

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