Impact of VMPs on resistance development

What is the impact of using multiple active products with overlapping activity to prevent or delay the development of resistance?

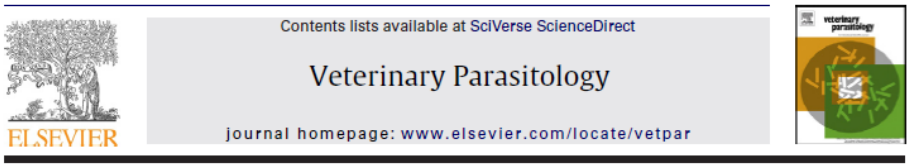
IFAH-Europe

Thomas Geurden (DVM, PhD, Dipl EVPC)

AR management

Options for management of AR

- Maintaining adequate refugia of susceptible worms, mainly on pasture
- Treatment when needed → targeted treatment principle
- Treatment with effective drugs = minimise the opportunity for resistance genes to be selected in a population
- Combinations of two or more active molecules.


Contents lists available at SciVerse ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Announcement

World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) Guideline: Anthelmintic combination products targeting nematode infections of ruminants and horses

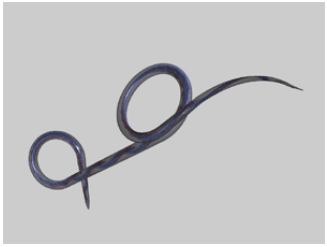
et al., 1995; Leathwick, 2012). Fixed-dose combination anthelmintic products appear to slow the development of resistance because they afford the highest possible kill of nematodes (Bartram et al., 2012). Parasites that survive one

Combination therapy

Europe IFAH
Representing the European Animal Health Industry

Combination therapy is already used for the control of nematodes in livestock

- Use in sheep and later cattle nematode control was initially for **the control** of drug-resistant parasites
  1. 2-way (*e.g.* benzimidazole + levamisole; macrocyclic lactone + levamisole; macrocyclic lactone + spiroindole)
  2. 3-way (*e.g.* benzimidazole + levamisole + macrocyclic lactone)
  3. 4-way (*e.g.* benzimidazole + levamisole + macrocyclic lactone + salicylanilide).



Benefits of combination therapy

Benefits of combination products:

1. Increase potency of the chemotherapeutic product.
2. Increase the spectrum of activity.
3. **Delay or prevent the emergence of drug resistance.**

- Early modelling around use of **insecticides** suggested combinations are far superior to rotations or sequential use.
- Some disagreement, principally because of assumptions made (*e.g.* half-doses, treatment of whole population).
- General agreement that if the **right conditions are met**, combinations will greatly delay the development of resistance.
- Combinations are extensively used in treatment and/or control of malaria, HIV, tuberculosis, weeds, insect pests, cancer.

Rationale of combination therapy

Combination of two molecules efficacious against the same intestinal nematodes, but through a **different mechanism of action**

< *molecule 1* >

< *molecule 2* >

<u>Complementary action (key factor 1)</u>

The parasite strains least sensitive to molecule 1 will be eliminated by the combined molecule 2 (and vice-versa).

Benefits of combination therapy

Combinations slow resistance because

- fewer resistance genotypes survive treatment
- thereby increasing efficacy and the diluting effect with unexposed parasites

- *i.e.* maximise the benefit of 'refugia'
- The presence of '**refugia**' is essential to realise the full benefit from combinations **(key factor 2)**
- In the complete absence of refugia a combination treatment has no advantage.

Benefits of combination therapy

Europe IFAH
Representing the European Animal Health Industry

Combination therapy for the prevention of AR development in nematodes in livestock

- Four (five) nematode models built independently of each other:
  - Barnes, Dobson & Barger ('Worm World'; Australia) – mono-specific but built into a multi-species model for monepantel experiments.
  - Leathwick (New Zealand) – general nematode disease.
  - Learmount & Taylor (UK) – multi-species.
  - Smith (USA) – mono-specific; general nematode disease.
  - Dobson & Hosking (AUS) – Risk Management Model for Nematodes™ multi-species/cost-benefit.
- Leathwick has undertaken empirical studies to validate his model.

Benefits of combination therapy

- Key outputs from these models are consistent:
  - Combination anthelmintics will select for drug resistance **more slowly** than any single drug strategy.
  - Combinations are of most benefit when the (initial) frequency of resistance alleles is low.
  - Drugs affected by resistance still provide valuable efficacy when used in combination (and with appropriate refugia).

Benefits of combination therapy

The model and experimental results support the use of combination anthelmintics as a tool to **delay the development of resistance**, ideally before resistance to their constituent actives is well developed.

Reversal to susceptibility?

Annual rotation of drench classes will slow the development of resistance: if resistant worms are less fit than susceptible worms then reversion toward susceptibility will occur in the years when an alternate drench class is used.

Reversal to sucseptibility

International Journal for Parasitology: Drugs and Drug Resistance 5 (2015) 9–15

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

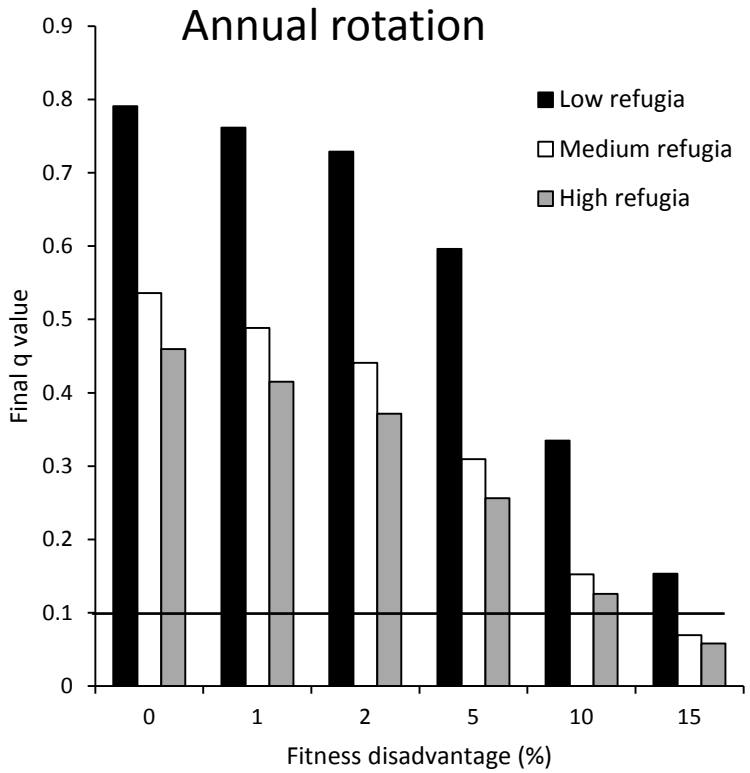
Evidence for reversion towards anthelmintic susceptibility in *Teladorsagia circumcincta* in response to resistance management programmes

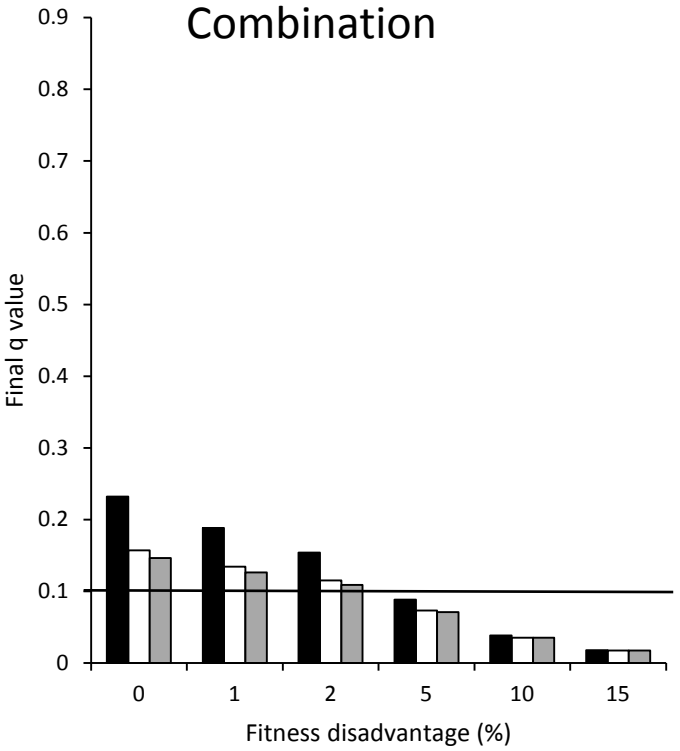
Dave M. Leathwick, Siva Ganesh, Tania S. Waghorn *

AgResearch Grasslands, private Bag 11008, Palmerston North, New Zealand

- Reversion towards susceptibility occurred **with both rotation and combination** but was more pronounced and occurred at lower fitness costs when a combination was used
- i.e. the combination appeared to be ‘better’ at achieving reversion than the rotation

Reversal to susceptibility





Benefits of combination therapy

Europe IFAH
Representing the European Animal Health Industry

Conclusions

- The models and experimental results support the use of combination anthelmintics as a tool to manage and delay the development of resistance, in conjunction with appropriate resistance management strategies (refugia).
- Reversion towards susceptibility was 'better' achieved by combination treatment reversion than by rotation treatment

IFAH AR Task Force

Thomas Geurden	**Zoetis**
Barry Hosking	**Elanco**
Steffen Rehbein	**Merial**
Cornelia Schleunter	**MSD**
Gertraut Altreuther	**Bayer**
David John	**IFAH-Europe**

Dave Leathwick (AgResearch New Zealand) is acknowledged for providing some graphics from his work on reversion.

Thank you

Europe IFAH
Representing the European Animal Health Industry

THANK YOU