Worm Control in Grazing Livestock and Anthelmintic Resistance

By

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INTRODUCTION

- In the 20\textsuperscript{th} and 21\textsuperscript{st} centuries, control of worms in grazing livestock worldwide has relied mainly on use of anthelmintics.

- Contributing factors to over-reliance on anthelmintics:
  - Ease of application.
  - False assumption that worm control is easy and can be accomplished with drugs without an epidemiological database.

- Consequence = **Resistance** to all groups of anthelmintics in all the economically important roundworms of sheep and goats.

- Reports of resistance in cattle, pigs and horses.
What is resistance?

- The ability of worms in a population to survive drug treatments that are generally effective against the same species and stage of infection at the same dose rate.

- Clinical definition:

  When normal therapeutic dose is no longer fully effective.
How does resistance develop?

- Natural biological consequence of drug treatment.
- Resistance genes exist in a worm population before drug is used.
- Use of the drug removes susceptible parasites and selects for those with “resistance” genes.
- Multiplication of selected worms increases frequency of “resistant” alleles in the population.
- *Haemonchus* - large population sizes and multiplies fast.
Changes in Allele Frequency in Response to Drug Selection

- Clinical detection level
- Diagnostic detection level

Generations – Number of Treatments

Resistance is Forever
First reports a few years after release of drugs.
Mainly involves *Haemonchus contortus*.
Other round worms: *Trichostrongylus, Oesophagostomum, Cyathostomes* and *Parascaris*
Flukes: *Fasciola*

<table>
<thead>
<tr>
<th>DRUG</th>
<th>No. OF REPORTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Benzimidazoles</td>
<td>26</td>
</tr>
<tr>
<td>2. Levamisole</td>
<td>23</td>
</tr>
<tr>
<td>3. Ivermectin</td>
<td>3</td>
</tr>
<tr>
<td>4. Thiophanate</td>
<td>1</td>
</tr>
<tr>
<td>5. Closantel</td>
<td>1</td>
</tr>
<tr>
<td>6. Rafoxanide</td>
<td>1</td>
</tr>
<tr>
<td>7. Multiple resistance</td>
<td>7</td>
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- Large-scale, government and institution farms.
- *Haemonchus contortus* most commonly involved.
- Deaths due to treatment failure reported on some farms.
CONTRIBUTING FACTORS

- Prolonged use of drugs with the same mode of action e.g. BZs, LEV and Mls.
- Frequent and suppressive mass treatments.
- Under-dosing and use of sub-standard products.
- Buying in of resistant worms into a farm.
- Dose and move.
- Treatments when free-living component of the parasite population (refugia) is small.
Refugia and resistance

- The proportion of worm population that is not exposed to drug treatment.
  - “In Refuge” from drug
    - Worms in untreated animals.
    - Eggs and larvae on pasture.

- Provides a pool of “sensitive” genes.
- Dilutes frequency of resistant genes.

- Currently recognized as the most important component in reducing selection for drug resistance.
DIAGNOSIS OF RESISTANCE

- In vivo methods: Only real tools available
  1. Faecal Egg Count Reduction Test (FECRT)
     - Most practical test under field conditions.
     - Based on ability of the drug to reduce faecal egg counts in treated animals by more than 95%.
     - Labour intensive.
  2. Controlled Anthelmintic Efficacy Test (CAET)
     - Compares the number of worms in treated and non-treated animals.
     - Labour intensive and Expensive - animals have to be slaughtered.

- In vitro methods (e.g.s):
  1. Egg Hatch Assay (EHA)
  2. Larval Development Assay (LDA)
     - Require specialised equipment and skilled labour.
PROTOCOL FOR THE FECRT

- **Prerequisite:**
  - Groups of 10 – 15 animals per anthelmintic to be tested and a non-treated control group.
  - Pre-treatment EPG higher than 150.
  - Animals not treated in the previous 8 to 12 weeks.

- **Treatment and sampling:**
  - Use recommended dose of drug and weight of the heaviest animal in the group.
  - Post-treatment EPG 10 – 14 days.
  - Culture and identify larvae.
DATA ANALYSIS — Excel Program available
sydney.edu.au/vetscience/sheepwormcontrol/software/FECR4.xls

Number in group \( n \) (\( N = \sum n_j \))
Arithmetic mean \( X_i = \sum X_{ij}/n_i \)

Variance of counts:
\[ S^2_i = (\sum X_{ij}^2 / (\sum X_{ij})^2 / n_i)(n_i-1) \]

Percent reduction \( R = 100 \left( 1 - \frac{X_t}{X_c} \right) \)

Variance of reduction (on log scale)
\[ V = \left[ \left( \frac{S^2_i}{n_t X_t^2} \right) \right] + \left[ \left( \frac{S^2_c}{n_c X_c^2} \right) \right] \]

Approximate 95% Confidence Interval for \( R \)
Upper confidence limit 100 \[ 1 - \left( \frac{X_t}{X_c} \right) \text{expt} (-2.1 \sqrt{v}) \]
Upper confidence limit 100 \[ 1 - \left( \frac{X_t}{X_c} \right) \text{expt} (+2.1 \sqrt{v}) \]

Where:
- \( i \) denotes either treated \((t)\) or control \((c)\) groups
- \( J \) denotes each sheep in the group
- \( S^2_i \) denotes variance on the arithmetic scale
INTERPRETATION OF RESULTS

Resistance is considered present if:

1. Percentage reduction is less than 95%
2. The lower 95% Confidence limit is less than 90%
3. If only one of these criteria is met, resistance is suspected.
Example of FECR% Calculation

See attached Excel printout of calculations in your notes
DETECTION OF RESISTANCE IN FASCIOLA

- Use the FECRT
- Groups of 6 – 10 animals per treatment and a non-treated control group.
- Use recommended dose and weight of heaviest animal in the group.
- Post-treatment samples 7 – 21 days after treatment and determine EPG.
- Percent efficacy (PE) = \([MC – MT)/MC\] x 100
  - MC = mean counts at day 0
  - MT = mean counts after treatment.
  - Use geometric mean egg counts.
  - Resistance present if PE is below 90%
OPTIONS FOR CONTROL- ROUNDWORMS

- AR is a major problem that is not fully understood.
- Once AR develops it stays – no evidence of reversion to susceptibility even after withdrawal of a drug.

- There is no effective alternative to chemical control of worms where livestock are grazed:
  - Pasture management can reduce number of treatments but not replace anthelmintics entirely.
  - Effective vaccines, biological agents and novel products are all a distance in the future.
  - We have what we have!

- It's therefore important to maintain efficacy of current anthelmintics:
  - Regularly test for efficacy of drugs on a property.
  - Reduce practices that encourage emergence and spread of resistance.
AVAILABLE ANTHELMINTICS

- **Broad spectrum:**
  - Group 1: BZs and pro-BZs e.g. Albendazole, Fenbendazoles
  - Group II: Imidazothiazoles / Tetrahydropyrimidines e.g. Levamisole and Pyrantel
  - Group III: Macrocyclic lactones (MLs) e.g. Ivermectin, Moxidectin, Doramectin

- **Narrow-spectrum:**
  - Salicylanilides and substituted nitrophenols e.g. Closantel (Flukiver), Rafoxanide (Ranide or Ranox) and Nitroxynil
    - Combinations e.g. Flukazole or Multidose
SMART ROUNDWORM CONTROL PRACTICES

1. **No frequent and suppressive treatments:**
   Avoid regular treatment of all animals (e.g. every 3 months) with no regard to epidemiology of the parasites.
   - Selects inexorably for resistance
   - Not cost effective

2. **Alternating drugs** from different action groups on a yearly basis.

Drug companies need to colour code their products according to action groups.
3. Curative anthelmintic treatments

- Animals are dewormed based on clinical diagnosis of infection.
  - Levels of EPG in groups of monitored animals.
  - Clinical signs such as anaemia.
- Minimises the use of drugs as treatments are only given when necessary.
- Can increase **REFUGIA** through selective treatments.
- Regular monitoring of infections is needed.

- The FAMACHA system is based on colour of mucus membranes of the eye in sheep and goats, due to anaemia caused by *Haemonchus contortus*.
The FAMACHA Anaemia Guide
4. Strategic anthelmintic treatments

- Based on epidemiology of the parasites.

- Treat animals when levels of infection are likely to be highest or just before that.

- Moisture and temperature most important factors in determining levels of pasture infectivity.

- Greatest challenge is therefore a few weeks after onset of rains.

- Increase **REFUGIA** by **NOT** treating during dry periods.
Strategy 1: Treat at times of peak infections

- Treat animals 3 – 4 weeks after onset of rains.
- If rains are prolonged, a second treatment 4 – 6 weeks later.
- Monitor infections during the dry spells and treat individual animals only when necessary.
- In humid areas, factors always favourable for development of larvae. Monitor infections regularly and treat when necessary.
Strategy 2: Treat against inhibited larvae & peri-parturient rise

- In arid and semi-arid areas *Haemonchus* larvae undergo hypobiosis.
  - Treat before rains to reduce pasture contamination.
- Immune and well-fed animals suppress larval establishment and development and adult worms’ egg production.
  - Treat female sheep or goats 3-4 weeks before lambing/kidding and mid lactation.
5. Integrated roundworm control

Where possible integrate use of drugs with non-chemical methods:

1. **Pasture and breeding management:**
   - Rotational and alternate grazing.
     - Limited by scarce resources such as land and communal grazing/common watering points.
   - True zero-grazing reduces worm infections.
   - Proper stocking densities.
   - Timing of reproductive events (parturition, weaning).

2. **Proper nutrition:** supresses establishment and development of larvae and egg production in adult worms.
OTHER USEFUL PRACTICES

1. Use the recommended dose of the drug and dose based according to heaviest animal in the group (lambs, ewes and rams classified as different groups).

2. Reduce feed intake before drenching or drench in the morning to reduce flow of gut contents.

3. Buy products from reputable companies.

4. Animals bought into a farm should always be dewormed with an effective anthelmintic before release to pastures.
SEASONAL TREATMENTS AGAINST FLUKES

- Purpose is to remove fluke burdens in the animals and reduce contamination.

- Treat during times of peak infection (after rains) and when snails are not active (dry months and during floods).

- Treatments not effective if farmer is not in control of both the grazing and watercourse.

- In such cases, all farmers sharing the resources need to act together.

- Challenge of combination products.
FUTURE CONTROL OPTIONS

1. BIOLOGICAL CONTROL
Nematode-trapping fungi

*Duddingtonia flagrans*
- Chlamydospores fed to animals.
- Grow in fresh dung, trap and destroy larvae on pastures.
- Effective in cattle, horses, pigs, sheep and goats.

Limitations:
- Not commercially available.
- Lack of a suitable application system.
- Need to be combined with other methods.
2. VACCINATION

Available vaccine: *Dictyocaulus viviparus* (lungworm)

Research vaccines (Gut associated synthetic or recombinant *H. contortus* antigens):

- >90% protection in lambs for 23 days.
- 98% reduction in egg output in ewes.
- Protection in lambs through colostrum.

- Not commercially available.
FUTURE CONTROL OPTIONS

3. USE OF HERBAL DEWORMERS

- Many communities in Kenya use indigenous plants as livestock dewormers.
- Most common is *Albezia anthelmintica*.
  - A bark preparation shown to have 34% efficacy using FECRT in sheep.
  - A water extract shown to inhibit hatching of nematode eggs and development of larvae in vitro.
- Pyrethrum marc also shown to have effect on roundworms in sheep.

- Validation of efficacy still ongoing.
- No commercially available product.
4. BREEDING FOR HOST RESISTANCE

• **Resistant lines** of Merino & Romney established using FEC.

• **Resistant breeds** e.g. Red Maasai sheep and Small East African goats exist.

• **Limitations:**
  - Resistant lines susceptible to non-target parasites.
  - Inferior characteristics in resistant breeds.
  - Breeds not suitable for all geographical areas.
  - Resistant breeds succumb under stress e.g. poor nutrition.