Dealing with anthelmintic resistance in sheep

Theo de Waal - UCD
Outline

- Parasite epidemiology
- How AR develop
- Survey of AR in Irish sheep flocks
- Strategies to minimize development of AR
Parasites of importance

- Gastrointestinal nematodes
  - *Teladorsagia circumcincta* (Brown stomach worm)
    - abomasum
  - *Nematodirus battus* (Thread-necked worm)
    - small intestine
  - to lesser extend *Trichostrongylus* spp & *Cooperia curtecei* (Hairworm/Black scour worm)
    - Abomasum/small intestine depending on species
The epidemiology of nematode parasitism in sheep at pasture
Resistance

*Ability of worms in a population to survive drug treatments that generally are effective against the same species/stage at same dose rate*

- Genetic changes in
  - Drug target
  - Drug transport (ABC transporters)
  - Drug metabolism
Development of resistance

- Heritable trait
- Inevitable consequence of good nematode control
- Why?
  - Drug eliminate the susceptible genotypes
  - Resistant parasite survive → reproductive advantage and pass on their “resistant” alleles
  - Gradual build-up of resistant genotypes
Resistance clinically evident
Contributing factors associated with AR

- High treatment frequency
- Under dosing
  - Incorrect calibration of equipment
  - Underestimate live weight
  - Improper technique
- Treatment strategies that minimize in refugia population
  - Treat all animals
  - Treat when few larvae are on pasture
    - Early in grazing season
    - Treatment at ecological critical times
  - Treat & move to “clean” pasture
- Lack of quarantine treatments
  - Animal movement disperses resistant worms
- Worm/fluke combinations & ML for ectoparasites at inappropriate times

**Refugia** = The helminth population not under selection pressure of drug treatments
Background to the problem

- Modern anthelmintics
  - Broad spectrum, very effective, relatively cheap, safe

- Advice
  - Preventative treatment encouraged
    - Resistance issues ignored
  - Conflicting advice
    - Dose & move to “clean” grazing

- Over-dependence on anthelmintics
  - Common sense approaches lost
  - Effective drugs always available
## Drug life cycle

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drench Colour</th>
<th>Release</th>
<th>Years until resistance first detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazoles (BZ)</td>
<td>White</td>
<td>1961</td>
<td>3</td>
</tr>
<tr>
<td>Levamisoles (LM)</td>
<td>Yellow</td>
<td>1970</td>
<td>9</td>
</tr>
<tr>
<td>Macrocyclic lactones (ML)</td>
<td>Clear</td>
<td>1980</td>
<td>7</td>
</tr>
<tr>
<td>Amino acetonitrile derivatives (AD)</td>
<td>Orange</td>
<td>2009</td>
<td>4</td>
</tr>
<tr>
<td>Spiriondoles (SI)</td>
<td>Purple</td>
<td>2010</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Monepantel resistance

Lack of efficacy of monepantel against *Teladorsagia circumcincta* and *Trichostrongylus colubriformis*

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First report of monepantel *Haemonchus contortus* resistance on sheep farms in Uruguay

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*Haemonchus contortus* resistance to monepantel in sheep

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Anthelmintic resistance survey
Survey AR in Ireland

- **Summer 2012**
  - 20 sheep farms in counties Sligo & Leitrim
  - Treat with BZ, LV or ML

- **Summer 2013 & 2014**
  - Sheep Technology Adoption Program (STAP)
  - Established by DAFM in 2013 to increase productivity on Irish Sheep Farms by encouraging the adoption of best management practices
  - Criteria include attendance at 4 discussion group meetings and the completion of 2 technical tasks
  - 1 of the technical tasks involved testing anthelmintic treatment efficacy (STAP Task 3)
    - Drug routinely used in flock
FECRT - Resistance

Ability of worms in a population to survive drug treatments that generally are effective against the same species/stage at same dose rate.

Resistance is present if:

1. the percentage reduction in egg count is less than 95% and
2. the lower 95% confidence level is less than 90%.

If only one of the two criteria is met resistance is suspected.
Results: 2012 AR - Nematodes

FECRT Sligo-Leitrim Study group (2012)
Popularity of the various drug groups in Sheep Technology Adoption Program
Results

Efficacy of BZ, LEV and ML

- BZ (n = 207): 29% Efficacy ≤ 94, 71% Efficacy 95 - 100
- LEV (n = 105): 56% Efficacy ≤ 94, 29% Efficacy 95 - 100
- ML (n = 212): 71% Efficacy ≤ 94, 29% Efficacy 95 - 100

Efficacy: 95 - 100  Efficacy: ≤94
Results
Prevalence of resistance/treatment failure

Efficacy test

% failure/resistance of treatment

STAP
FECRT
MALDT
Drenchrite
FECRT NI

BZ
LM
ML

Efficacy test
Anthelmintic resistance in European

Worrying trends
Flocks reduced efficacy to different anthelmintic drug classes: Sligo & Leitrim

Fig. 1. Model simulation outputs for scenarios 1–3 (initial resistance allele frequency DQL = 0.0001 and ML = 0.165). Resistance allele frequencies for a new anthelmintic class (DQL) administered to lambs twice per season under a SCOPS management strategy as a single active sequentially (---) or by annual rotation (----------) and as a multiple active (DQL–ABA) product (---).
Fig. 2. Model simulation outputs for scenarios 4–6 (initial resistance allele frequency DQL = 0.0001 and ML = 0.165). Resistance allele frequencies for a new anthelmintic class (DQL) administered to ewes at turnout and lambs five times per season under a non-SCOPS management strategy as a single active sequentially (---) or by annual rotation (.........) and as a multiple active (DQL–ABA) product (———).
Example of additive effect of a multiple active product

- Drug 1 - 90% efficacy
- Drug 2 - 95% efficacy
- Worm population = 1000
- Drug 1 kills 90% of worms
  - Remaining worm population = 100
- Drug 2 kills 95% of worms
  - Number of worms surviving both drug treatments = 5
- Overall efficacy = 99.5%
Example of additive effect of a multiple active product

- Drug 1 - 90% efficacy
- Drug 2 - 95% efficacy

Overall efficacy = 99.5%
Delaying anthelmintic resistance
Best practice

- Maintain large *in refugia* helminth population
- Reduce dependence on anthelmintics
- Targeted (selective) treatment
- Genetic Selection
- Pasture Management
Targeted (selective) treatment

- Level of parasite control not the same for all animals
  - Parasites over dispersed
    - 80:20
  - Resilience & resistance
    - Breed variation
  - Targeted (selective) treatment(*)
    - Old idea rediscovered
    - Treat only when required
    - Whole flock: based on knowledge of the risk/parameters that quantify the severity of infection
    - Individual animals within the grazing group

Targeted (selective) treatment

► Treatment indicators

► Pathophysiological indicators - faecal consistency (dag scores), anaemia (FAMACHA)

► Faecal egg count, weight gain, milk yield and body condition score

► Significant diagnostic needs!
Genetic selection

- Data suggesting breed differences in natural resistance to nematode infection
  - Heritable

- Research in Ireland
  - Greater level of resistance in Texel breed over Suffolk
Texel : Suffolk

- Texel a consistently lower faecal egg count and higher serum nematode-specific antibody responses compared to co-grazed Suffolk

Genetic selection

- Benefit
  - Lower worm burdens
  - Decrease pasture contamination
  - Fewer anthelmintic treatments
Grazing management
“Safe” pastures

Spring
- New leys / seeds or forage crops
- Pasture grazed by cattle only previous season
- Grassland used for conservation previous year
- Pastures grazed by adult non-lactating sheep previous year

After late June
- Aftermath not grazed by sheep earlier in the year
- Pastures grazed by cattle in 1st half grazing season
- Pastures that was clean at start of season and grazed by adult non-lactating sheep only in spring

Reduce parasite burden
Managing multiple-active resistance

- Challenging - no single, simple one-stop solution*
- Resistance irreversible
- Combination anthelmintics & leaving some lambs untreated
  - Resistance develop slower than under annual rotation
  - Efficacy of both actives <70%, ability to slow development of resistance is largely lost
- “Exit drench”
  - Single treatment - new anthelmintic class - in late summer
    - remove resistant genotypes
  - Maintain *refugia* - minimise treatment of adult sheep
- Maximise integrated grazing
  - Alternate graze cattle/sheep
  - Bioactive forages#
    - high in condensed tannins

Conclusions

- Anthelmintic resistance becoming serious concern in Ireland
- Some farms already triple-resistant
- Encourage sheep farmers to test for AR
- Important to know efficacy of drugs used on the farm
  - Without this knowledge
    - Adequate worm control may not occur
    - Sensible drug rotation cannot be planned
- Follow best practice
Helminth control: Best Practice

- Quarantine treatment on arrival
  - 48 hours
  - Turned onto contaminated pasture
- Correct drench technique & right dose
- Test for resistance
- Examine control strategy
  - reduce treatments
- Reduce dependence on anthelmintics
  - Grazing management, use resistant rams
- Only treat when necessary
  - Pathophysiological markers, FEC, Performance indicators
- Use most appropriate anthelmintic
  - Preserve new generation anthelmintics
- Preserve susceptible worms
  - Leave some (10-15%) sheep untreated
  - Treat few days before moving

http://www.nationalsheep.org.uk/
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