The current state of anthelmintic resistance in the UK and simple messages to slow the progression

5th July 2013

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Periparturient (Spring) Rise - PPR

Source: Veterinary Parasitology, 1998. GM Urquhart et al.
Structure

• Anthelmintic resistance
  – Prevalence in UK and Ireland
  – Principles for sustainable use of anthelmintics

• Why combine anthelmintics?
  – Additive effects
  – Criteria to maximise ability of multiple active formulations to delay resistance

• STARTECT Dual Active
# Anthelmintic classes

2-LV, 4-AD and 5-SI operate at different nicotinic acetylcholine receptor (nAChR) subtypes

<table>
<thead>
<tr>
<th>Class</th>
<th>Class name</th>
<th>Mode of action</th>
<th>Actives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – BZ</td>
<td>Benzimidazoles</td>
<td>tubulin binding</td>
<td>albendazole, fenbendazole, oxfendazole, mebendazole, ricobendazole</td>
</tr>
<tr>
<td>2 – LV</td>
<td>Imidazothiazoles</td>
<td>nAChR agonist</td>
<td>levamisole</td>
</tr>
<tr>
<td>3 – ML</td>
<td>Macrocyclic lactones</td>
<td>modulate glutamate-gated chloride channels</td>
<td>ivermectin, abamectin, doramectin, moxidectin</td>
</tr>
<tr>
<td>4 – AD</td>
<td>Amino acetonitrile derivatives</td>
<td>modulate ion channels associated with nAChRs</td>
<td>monepantel</td>
</tr>
<tr>
<td>5 – SI</td>
<td>Spiroindole</td>
<td>nAChR antagonist</td>
<td>derquantel</td>
</tr>
</tbody>
</table>
How common is wormer resistance in the UK?
The prevalence of resistance in the UK and Ireland

Wales

Anthelmintic resistance was detected on:
- 82% of 122 farms
- Resistance to BZ only = 46%
- Resistance to LV only = 5%
- Resistance to both BZ and LV = 31%

Scotland

- Lowland farms
  - Resistance to BZ only = 80%
  - Resistance to IVM only = 30%
  - Resistance to BZ, LV, IVM = 8%

England and Wales

- Resistance to BZ only
  - Lowland farms = nearly 100%
  - Upland/hill farms = 83%
- Resistance to LV and BZ
  - Lowland farms = 47%
  - Upland/hill farms = 17%
- Suspected resistance to IVM or MOX
  - Herefordshire/Powys farms = 55%

Ireland

Anthelmintic resistance was detected on:
- 91% of 11 farms
- Resistance to BZ only = 64%
- Resistance to LV only = 27%
- Resistance to BZ and LV = 27%

Coop, R & Jackson, F (2007) Presentation at BVA Congress
History of resistance to modern broad-spectrum wormers

Adapted from Waller 2006

1950

1955

1960

1965

1970

1975

1980

1985

1990

1995

2000

1-BZ = benzimidazole; 2-LV = levamisole; 3-ML = macrocyclic lactone; R = resistance
Is this the point to change strategy?
Mechanisms of resistance

• Development of resistance may be inevitable once use of anthelmintic commences, but it can be delayed.
• Three main selection pressures exist for the development of AR:
  – Overuse of anthelmintics
  – Under-dosing with anthelmintics
  – The influence of the *refugia* population
Mechanisms of resistance

Overuse of anthelmintics

– Frequent use of same family
– Use of products as endectocides

→ Gives worms with resistance alleles a selective advantage
Mechanisms of resistance

Under-dosing with anthelmintics

• Poor calibration of drenching guns
• Poor estimation of body weights
• Poor dosing/injection technique
• Poor storage and misuse of products

→ Gives worms with resistance alleles a selective advantage
Mechanisms of resistance

Exposure of large proportion of the total worm population to given anthelmintic
• The concept of the worm population *in refugia*
• The free-living population of parasites, which is not exposed to a given anthelmintic
In refugia population

Exposed population

Exposed population

In-refugia population

Eggs
L1
L2
L3
on pasture,
and
worms
in untreated
sheep

Worms in
treated sheep

Susceptible
Resistant

Susceptible
Resistant

Acme Sheep Drench
Refugia population at smallest

A particularly large proportion of total parasite population exposed to any anthelmintic treatment

– On “safe” / “clean” grazing
– During dry hot periods
– At the end of the winter

→ Selective advantage applied to larger population making emergence of AR more likely
SCOPS

- **Sustainable Control Of Parasites in Sheep**
- Industry-wide initiative including representation from: NSA, NOAH, RUMA, CSL, SVS, SAC VS, NFUS, Scottish Government, AHDA, Defra
- Reducing the selection pressure towards anthelmintic resistance
The eight SCOPS Recommendations for farmers

1. Work out a control strategy with your veterinarian or advisor.
2. Use effective quarantine strategies to prevent the importation of resistant worms in introduced sheep and goats.
3. Test for anthelmintic resistance on your farm.
4. Administer anthelmintics effectively.
5. Use anthelmintics only when necessary.
6. Select the appropriate anthelmintic for the task.
7. Adopt strategies to preserve susceptible worms on the farm.
8. Reduce dependence on anthelmintics.

Scops Owl
Treatment of ewes pre-tipping

• Very few adult ewes will have significant burdens or FECs at this time
• Prolonged advantage to AR worms, particularly in hot dry summers
• No routine drenching of fit adult ewes pre-tipping
• Drench immature or lean ewes only
Treatment of ewes at lambing

• Treatment at this point has less serious AR implications
• Evidence of advantages for lambs
  – in reducing pasture contamination due to PPR
  – further reduction in pasture contamination through “hoover effect”
How are you doing on your farm?

Adapted from SCOPS, ‘Stay out of the red!’
## Drench Checks

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichostrongyle-type eggs (per gram) [P1]</td>
<td>1750</td>
</tr>
<tr>
<td>Nematodirus spp. eggs (per gram)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Nematodirus battus eggs (per gram)</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Consistency (†)</td>
<td>Soft</td>
</tr>
<tr>
<td>Trichostrongyle-type eggs (per gram) [P1]</td>
<td>600</td>
</tr>
<tr>
<td>Nematodirus battus eggs (per gram)</td>
<td>50</td>
</tr>
</tbody>
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<td>Sample Consistency (†)</td>
<td>Soft</td>
</tr>
<tr>
<td>Trichostrongyle-type eggs (per gram) [P1]</td>
<td>300</td>
</tr>
<tr>
<td>Nematodirus spp. eggs (per gram)</td>
<td>&lt;50</td>
</tr>
</tbody>
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<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Consistency (†)</td>
<td>Liquid</td>
</tr>
<tr>
<td>Trichostrongyle-type eggs (per gram) [P1]</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>
Drench Checks

DON'T LET HIDDEN WORMER RESISTANCE TAKE YOU INTO THE LOST ZONE!

Undetected wormer resistance can cost thousands of pounds, even if there are no obvious clinical signs. The FREE STARTECT Drench Test is the first step to avoid the drift into the Lost Zone.

To arrange your FREE STARTECT Drench Test, please call 0800 XXXXXX or email booking@startectdrenchtest.info

Further information please contact: Zoetis, Wilson Vale, Dunking Road, Watson-on-the-hill, Surrey KT20 3UX. Information is subject to change. Zoetis recommends that you seek veterinary advice prior to any medication prescription. Zoetis does not sell products for use in food-producing animals. Zoetis can be contacted at zoetis.com. Zoetis is an equal opportunity employer. Date of preparation: January 2013.
Why is resistance management important?

• Production losses occur even when the parasitism caused by anthelmintic resistance is subclinical

• Growth performance is increased by the use of an anthelmintic which is fully effective

• Performance benefits can greatly exceed the cost of using an effective anthelmintic

Leathwick et al 2008 NZ Vet J. 56, 184-195
Macchi et al 2001 NZ Vet J. 49, 48-53
Sutherland et al 2010 Vet Parasitol. 171, 300-304
Why is roundworm control important?

Stomach worm infections decrease growth rates in lambs
As the level of challenge increases, the growth rate decreases

Coop et al 1982 J Agric Sci 98, 247-255
Why combine anthelmintics?

• Broaden spectrum of action
  – fluke and roundworm
  – roundworm and tapeworm

• Management of anthelmintic resistance
  – combinations of different chemical classes with similar spectrum of action

‘COMBINATION’

‘MULTIPLE ACTIVE’
Why use multiple active formulations?

1. To enable the effective control of roundworms in the presence of single or multiple drug resistance

2. To delay the development of resistance to the component anthelmintic classes

Leathwick et al 2009 NZ Vet J 57, 181-192
## Additive effect

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of worms</td>
<td>100</td>
</tr>
<tr>
<td>First treatment</td>
<td>80% efficay</td>
</tr>
<tr>
<td>Number of worms remaining</td>
<td>20</td>
</tr>
<tr>
<td>Second treatment</td>
<td>90% efficay</td>
</tr>
<tr>
<td>Number of worms remaining</td>
<td>2</td>
</tr>
<tr>
<td>Additive effect</td>
<td>98%</td>
</tr>
</tbody>
</table>

Assumes resistance to both components does not arise in the same individual worms.
How does this delay resistance?

- Roundworms that survive one wormer are removed by the other

- Fewer resistant genotypes survive treatment because worms must be resistant to all of component anthelmintic classes for survival

- Diluted by unselected parasites in refugia

- Reduced proportion of resistant worms available to reproduce with other resistant survivors

Anderson et al 1988 Aust Vet J 65, 62-64
Anderson et al 1991 Aust Vet J 68, 133-136
Entrocasso et al 2008 Vet Parasitol 155, 249-256
Le Jambre et al 2010 Animal Production Science 50, 946-952
McKenna 1990 NZ Vet J 38, 45-49
Time to detectable reduction in field efficacy due to resistance (0.25 resistance allele frequency) for DQL (initial resistance allele frequency - 0.0001) and ABA (ML initial resistance allele frequency - 0.165) formulated as single actives and used sequentially or in annual rotation under a SCOPS and non-SCOPS management strategy. ML resistance allele frequency of 0.165 = initial efficacy of ABA 95%; 0.8 = initial efficacy of ABA 50%
Martin et al 1989 Aust Vet J 66, 236-240
Time to reduction in field efficacy
Dual active sequential

Time to detectable reduction in field efficacy due to resistance (0.25 resistance allele frequency) for DQL-ABA (DQL initial resistance allele frequency - 0.0001; ML initial resistance allele frequency - 0.165 or 0.8) formulated as a dual active with sequential use under a SCOPS and non-SCOPS management strategy. ML resistance allele frequency of 0.165 ≡ initial efficacy of ABA 95%; 0.8 ≡ initial efficacy of ABA 50%
Martin et al 1989 Aust Vet J 66, 236-240
FECRT: UK farms, 2011

Comparative efficacy of STARTECT on 4 UK farms with identified anthelmintic resistance

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Farm A</th>
<th>Farm B</th>
<th>Farm C</th>
<th>Farm D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control – epg</td>
<td>678.4</td>
<td>1153.6</td>
<td>296.2</td>
<td>1696.7</td>
</tr>
<tr>
<td>STARTECT</td>
<td>99.5</td>
<td>99.1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>moxidectin</td>
<td>100</td>
<td>98.6</td>
<td>100</td>
<td>98.2</td>
</tr>
<tr>
<td>fenbendazole</td>
<td>84.4</td>
<td>52.9</td>
<td>0</td>
<td>36.4</td>
</tr>
<tr>
<td>levamisole*</td>
<td>86.8</td>
<td>55.2</td>
<td>26.7</td>
<td>75.4</td>
</tr>
<tr>
<td>ivermectin</td>
<td>94.6</td>
<td>77.5</td>
<td>60.1</td>
<td>91.2</td>
</tr>
</tbody>
</table>

Based on reduction in arithmetic mean worm egg count 14 days (*7 days) post treatment n=11 to 15 per group. 100% efficacy of STARTECT against *Nematodirus battus* on all farms. Mixed nematode infections on all farms prior to treatment. *T. circumcincta* was the predominant nematode species post treatment regardless of whether it was the predominant species before treatment.

Study number: 5243R-03-10-181

The farms were in Oxfordshire, Carmarthenshire, Gloucestershire and Devon. The study used commercially available orally-administered formulations.
Production Cost Of Resistance

Using less effective wormers (white drench with known resistance) compared to using STARTECT (99% effective), led to:

• Reduction in lamb weight

• 10% reduction in carcass value

• Additional days needed to bring up lambs to target weight

The production cost of anthelmintic resistance
A New Zealand study examined the economic impact of resistance by comparing production parameters in lambs treated either with STARTECT (>99% effective) or a white drench (1-BZ) to which resistance was known to be present (40-50% effective) over a 5 month period.¹

Using the less effective wormer led to:
1) A reduction in lamb live weight by 9kg = 4.7kg dead weight
2) 10.4% reduction in carcass value
3) Additional 17 days needed to get 50% of lambs to target weight

The production losses due to resistance greatly exceeded the cost of STARTECT
<table>
<thead>
<tr>
<th>Product Choice</th>
<th>White drench</th>
<th>Ivermectin</th>
<th>STARTECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost of drench per dose 25kg</strong></td>
<td>5p</td>
<td>5p</td>
<td>30p</td>
</tr>
<tr>
<td><strong>Drench cost per farm over 5 months</strong></td>
<td>£121.75</td>
<td>£121.75</td>
<td>£730.50</td>
</tr>
<tr>
<td><strong>Drench efficacy %</strong></td>
<td>50%</td>
<td>80%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td><strong>Estimated cost of lost performance for average holding</strong></td>
<td>-£8,897</td>
<td>-£3,560</td>
<td>£0</td>
</tr>
</tbody>
</table>

**STARTECT® Return on investment £’s**

|                | £8,288 | £2,951 | **STARTECT** |

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5. Estimated cost assumes 5 doses at one month intervals and UK average number of lambs per holding. Dec 2011: 487
6. Drench efficacy is based on results of UK STARTECT FECRT studies (see ‘STARTECT, The future of worming starts here’, p.8)
Dosing Guidelines?
Dosing guideline

**Option 1:** at the start of the lamb production cycle

Lambing

Other drenches

Lambs sold

*Dosing frequency depends on worm challenge and wormer persistency*

**Lamb production treatments using STARTECT**

**Option 2:** at the end of the lamb production cycle

Lambing

Other drenches

Lambs sold

*Dosing frequency depends on worm challenge and wormer persistency*
Safety

- Meat withdrawal period: 14 days
- Not for use in dairy sheep
- Can be used in pregnant, lactating and breeding animals
- Mild transient coughing is very commonly reported following drenching.
- Doses 4.5 x the recommended dose and higher have been associated with signs of toxicity
- Safety not established in sheep <6 weeks old or <10Kg
Unique Dual Active Wormer

A NEW Class of Wormer
- derquantel 5-SI

And a Potent ML
- abamectin 3-ML

Effective Against
Resistant Worms¹

Helps to Delay
Resistance Development²,³

Enhanced Wormer Efficacy Can Improve Growth Rates
Is this the point to alter your strategy?