



Regional Seminar for OIE National Focal Points for Veterinary Products – 4 th Cycle Entebbe, Republic of Uganda , 1 – 3 December 2015



Anthelmintic Resistance

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"Anthelmintic resistance:

Heritable genetic change in a population of worms that enables some individual worms to survive drug treatments that are generally effective against the same species and stage of infection at the same dose rate."

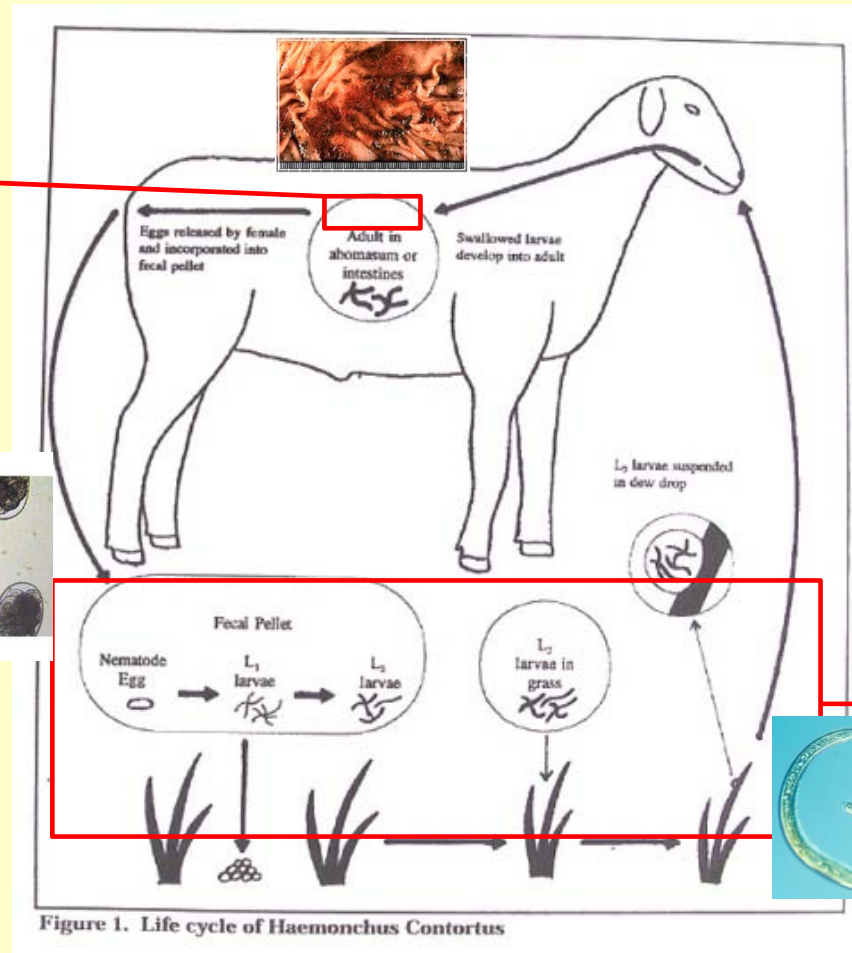
Kaplan

<90% worm egg reduction following use of a specific dewormer = resistance



Parasites have complex life cycle

Hypobiotic
Or
Active



Direct
Or
Indirect

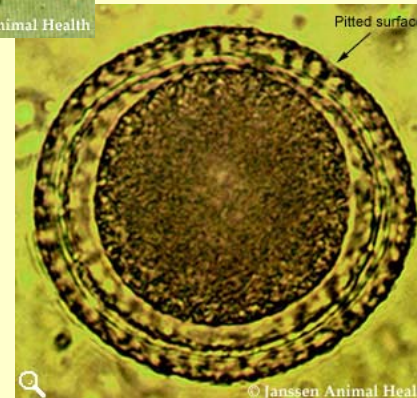
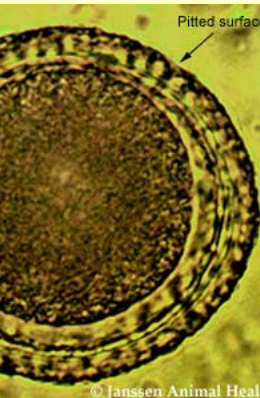
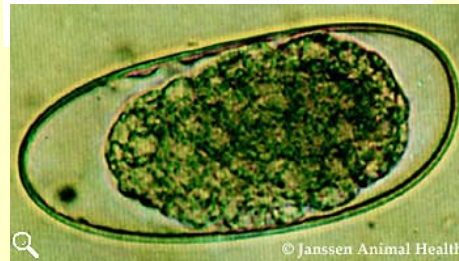
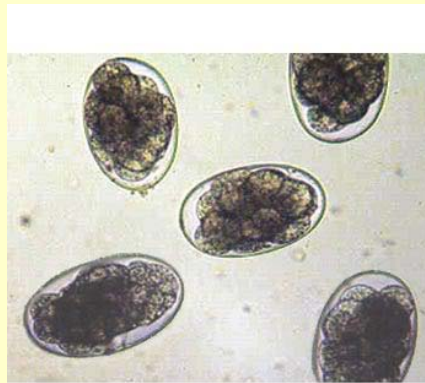
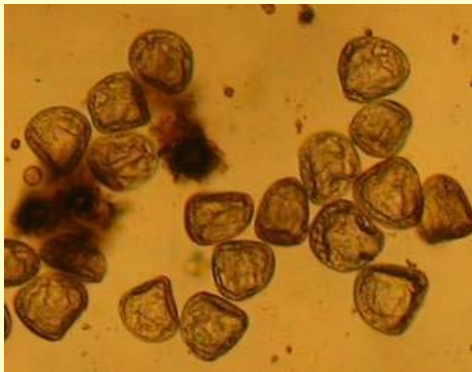
Figure 1. Life cycle of *Haemonchus Contortus*



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Parasites have different egg shapes, size and diagnostic tech.





Major Anthelmintic Families

- **Group 1: Benzimidazoles (BZ)**
fenbendazole, oxfendazole and albendazole
attack parasite's metabolic system through binding
beta-tubulin & inhibit microtubules
- **Group 2: Imidazoles (levamisole, LEV) and
hydropyrimidines (pyrantel/morantel)**
selective nematode nicotinic agonists – selectively
cause contraction of nematode muscle
- **Group 3: Endectocides, macrocyclic lactones**
ivermectin, doramectin, eprinomectin
attack parasite's nervous system, cause nematode
paralysis and immobilization



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Resistance Mechanisms

- Target changes molecularly
- Metabolism
- Access
- Amplification of genes



Mechanism of resistance

Anthelmintic family	Mechanism of resistance
Benzimidazoles	β -tubulin isotype 1 mutations: F200Y, F167Y
	β -tubulin isotype 2 mutations: F200Y, F167Y, deletion. Altered metabolism and/or uptake.
Avermectins & milbemycins	Mutations in GluCl and/or GABA-R genes
	Overexpression of P-glycoproteins
Levamisole	Changes in nicotinic acetylcholine receptors



□ Three phases of accumulation of resistance:

- Establishment
- Development
- Emergence

13 treatments: **1/1,000,000**; 1/500,000; 1/250,000;
1/125,000; 1/62,500; 1/31,250; 1/16,000; 1/8,000; 1/4,000; 1/2,000;
1/1,000; 1/500; 1/250; 1/125.

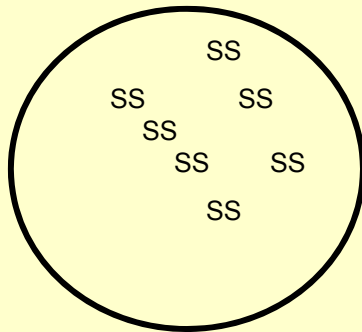
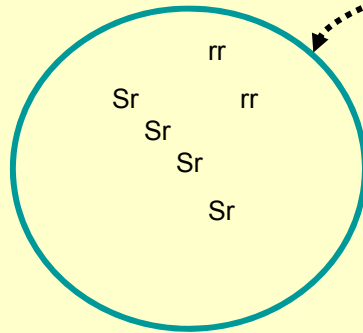
6 more treatments to reach complete treatment failure
(1/125; 1/62; 1/31, 1/15; 1/8; 1/4, 1/2).



Kinetics of spread of resistance

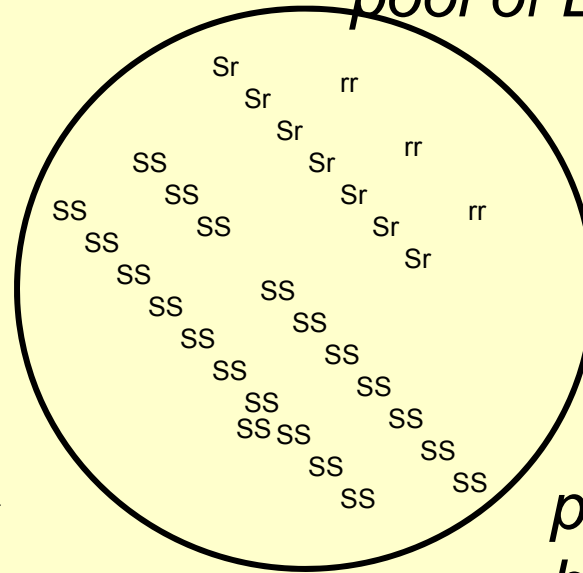
pool of animals releasing resistant L_3

releasing resistant L_3

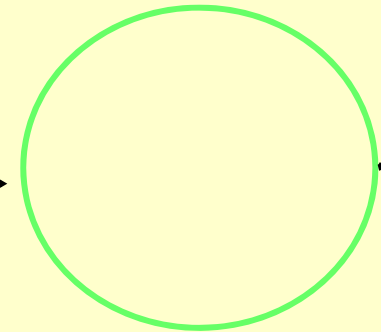


pool of animals releasing sensitive L_3

pool of L_3 on the pasture



pool of animals infected by L_3





Factors affecting selection pressure

Parasite genetics

- Recessive or dominant genes
- Number of genes – fewer faster
- Genetic diversity of parasites
- Fitness of resistant parasites

• Parasite Biology

- Generation time *Haemonchus*
- Direct life cycles
- Movement of hosts
- REFUGIA



Identification of Anthelmintic Resistance

1. Fecal Egg Count Reduction Tests (FECR)

Advantage:

- Easy to perform with training
- Good for services studies
- Can be done on the farm level.

Disadvantage:

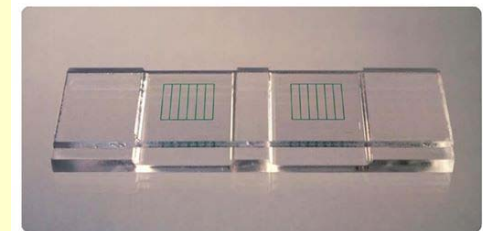
- Dose not Always reflect the actual parasitic load an animal with 100 EPG can harbor up to 100,000 luminal worms
- Can not be used for all parasitic infection
- Samples preservation issues.

2. Egg Hatch Assays

3. Larval Development Tests -

4. Adult Development Tests -

5. DNA Probes





The extent of the problem

- **Small ruminants (sheep, goats)**

Haemonchus contortus, *Trichostrongylus*
spp. and *Ostertagia*, *Nematodirus*

- **Cattle relatively few studies**

Cooperia spp., *Ostertagia*,
Oesophagostomum spp.

- **Horses**

Cyathostomins and *Parascaris equorum* to a
lesser extent: *Oxuris equi* and *Habronema/Draschia*



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Countries with highest record of Resistance

- **United State**
- **Africa: South Africa, Kenya, Other ???**
- **Australia and New Zealand**
- **Brazil**
- **Europe lesser extent**
- **Asia**
- **Middle East ??? Turkey**



Managing selection pressure

- Rate of appearance of resistance varies between anthelmintics
- Slow release anthelmintic worse
- Avoid under-dosing: dose per weight, goat/sheep dose, proper delivery
- Maintain refugia: maintaining population of susceptible parasites in the environment
- Planned treatments – reduce survival of resistant I_3
- Combinations of anthelmintics or complementary methods



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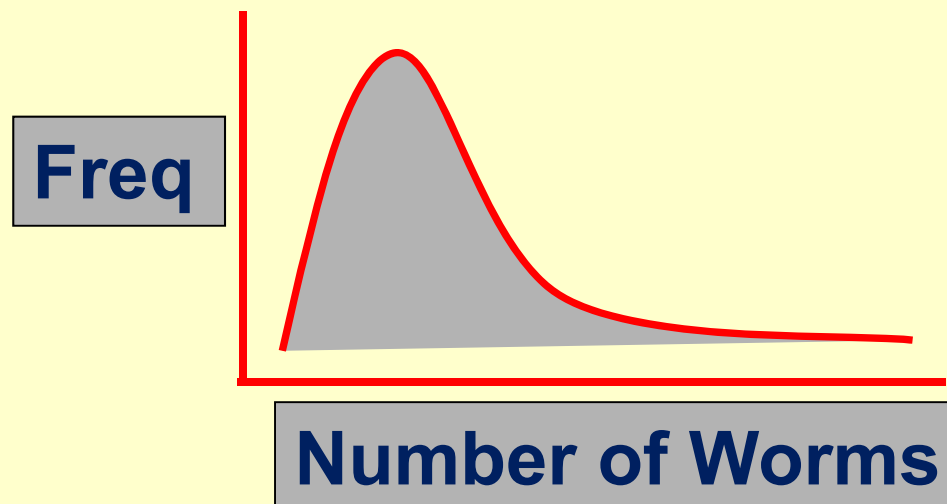
How to deal with anthelmintic resistance

- **No reversion**
- **Pasture management to reduce treatments**
- **Vaccines?**
- **Reduce practices that increase emergence and spread.**
- **New Compounds from drug companies--now some found to be resistant.**



Selective Treatment

- Parasites are not equally distributed in groups of animals
 - ~20 % of animals harbor most of the worms responsible for most of egg output





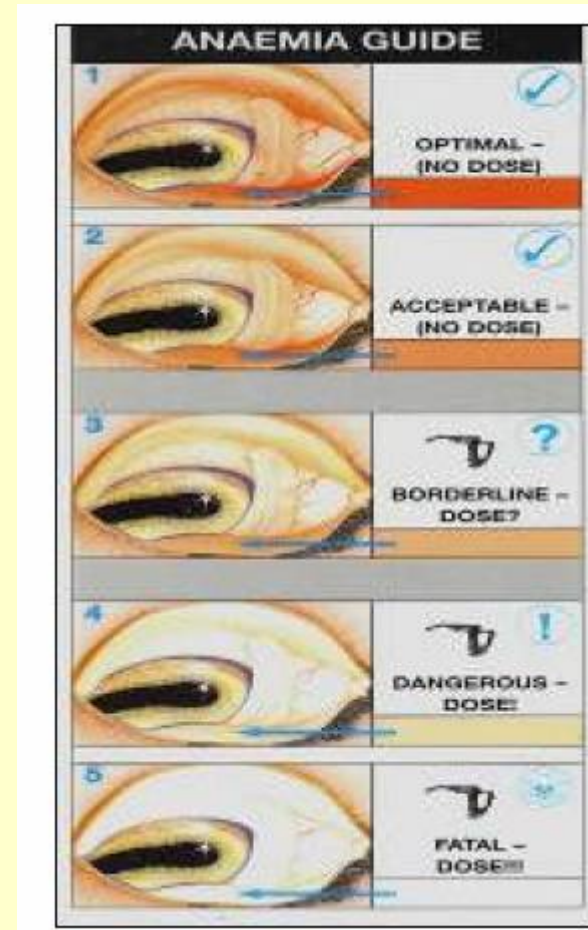
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Management in endemic areas.

FAMACHA

- Management in endemic areas
 - Sustainability, treat pathogenic species when clinically required.





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How to deal with anthelmintic resistance

- **Combinations**

Combining anthelmintic with different mode of action might delay resistance

- **Quarantine:**

- New animals

- Animals harboring resistant parasites



Non-chemical methods

- Protein and energy supplements
- Alternate grazing
- Rotation of pastures in hot areas – allowing L3 to die
- Removal of feces – horses
- Host selection –sheep and cattle may be resistant
- Nematophagous fungi





The Australian Model for Over coming Resistance in Small Ruminant

- **Using effective anthelmintics**

 - New drug monepantel

 - Combination anthelmintic derquantel + abamectin

- **Combination chemotherapy**

- **Diagnosis**

Rapid and accurate diagnosis..... PCR for resistance gene

- **Refugia...**mix animals of different age, treat only infected with high parasitic load



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Recommendation

- Surveillance studies to determine the extent of AnR
- Capacity Building for lab worker for better diagnosis and resistance measurement.
- Selection for resistant animal breeds.
- Education program for farmer and veterinarian for dealing with parasitic resistance issue
- Building a health program in each area based on data obtained specifically for that area including anthelmintic resistance information.
- Establishing reference laboratory for parasite ID and detection of anthelmintic resistance

Acknowledgment

