U.S. FOOD & DRUG ADMINISTRATION

Antiparasitic Resistance:

Challenges, Awareness, Change

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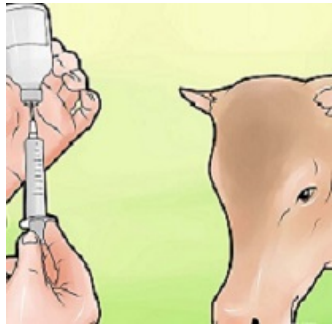
FDA-CVM

- Within the Food & Drug Administration (FDA), the Center for Veterinary Medicine (CVM) regulates animal drugs (including antiparasitics), animal feed, and veterinary devices—*not* vaccines (USDA)
- We make sure an animal drug is safe and effective before approving it
- We monitor the safety and effectiveness of animal drugs on the market



Overview

Antiparasitic resistance is a global issue for grazing livestock

- What is antiparasitic resistance
- How to test for it
- Global scope
- How to manage it
- Challenges
- Awareness/collaboration

Common gastrointestinal nematodes (roundworms) of grazing livestock

- *Haemonchus**
- *Trichostrongylus**
- *Ostertagia**
- *Strongylus vulgaris**
- *Cooperia*
- *Cyathostomes*
- *Parascaris equorum*

*most pathogenic

The Usual Tools

Antiparasitic Drug Class	Examples
Benzimidazoles	Thiabendazole, albendazole, fenbendazole, oxfendazole, oxibendazole
Imidazothiazoles	Levamisole
Macrocyclic lactones	Ivermectin, doramectin, eprinomectin, moxidectin, abamectin**
Sprinoindoles	Derquantel **
Tetrahydropyrimidines	Morantel tartate, pyrantel
Piperazines	Piperazine
Isoquinolones	Praziquantel*
Amino-acitonitrile derivatives (AADs)	Monepantel **

Effects of parasitism

Internal parasitism has a negative impact on livestock, which affects livestock owners

- Results in:
  - Weight loss
  - Decreased milk production
  - Decreased fertility
  - Increased susceptibility to other diseases
  - Death

Net effect: negative impact on food supply (meat and milk)

Defining Antiparasitic Resistance

"Ability of a p ment with an antiparasit y effective against the s t the same dose and ag infection."

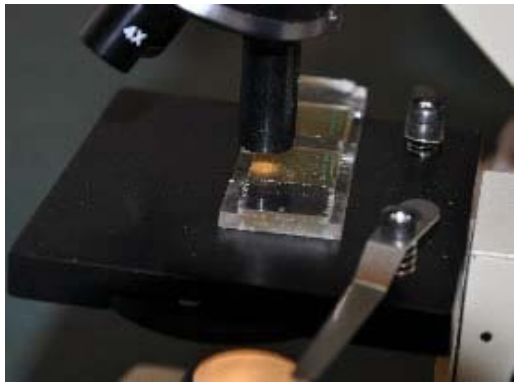
– *Due mostly parasite which are passed s of parasites*

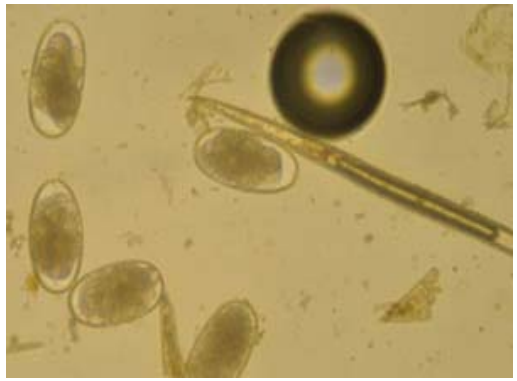
Measuring Antiparasitic Resistance

Fecal egg count reduction test:

$$\frac{\text{(Pre-tx egg count} - \text{post-tx egg count)}}{\text{(Pre-tx egg count)}} \times 100$$

Egg reduction < 90% post-treatment *generally* indicates antiparasitic resistance





First global reports of antiparasitic resistance (Kaplan 2004)

Drug	Host	Year of initial drug approval *not necessarily in US	First published report of resistance
Benzimidazoles			
Thiabendazole	Sheep	1961	1964
	Horse	1962	1965
Imidothiazoles-tetrahydropyrimidines			
Levamisole	Sheep	1970	1979
Pyrantel	Horse	1974	1996
Macrocyclic lactones			
Ivermectin	Sheep	1981	1988
	Horse	1983	2002
Moxidectin	Sheep	1991	1995
	Horse	1995	2003

What was happening?

- Ivermectin and other macrocyclic lactones (MLs) were highly effective when first approved in 1980s/1990s
  - Wide safety margin
  - Easy to use
- Producers became heavily dependent on drugs for control/eradication of parasites, resistance has developed

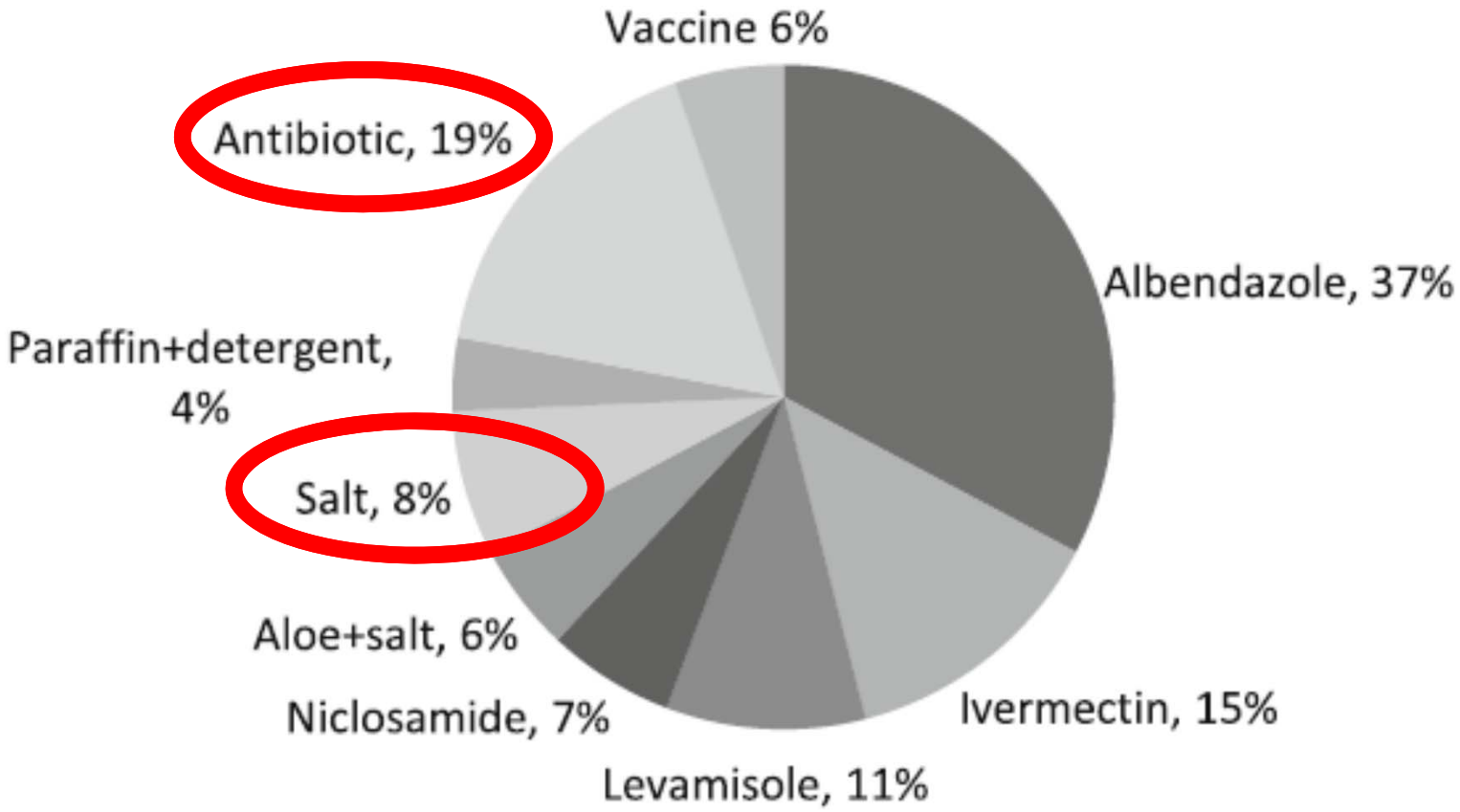
Antiparasitic Resistance: Global scope - Africa

- First case of ivermectin resistance in sheep reported by Van Wyk in South Africa in 1987
- Reports of antiparasitic resistance from other African countries:
  - Primarily from Kenya and South Africa
  - Mainly sheep, *Haemonchus contortus*
  - South African commercial sheep industry reported as the worst affected in the world with regard to antiparasitic resistance (Vatta and Lindberg 2006)

Africa (Tsotetsi, et al 2013)

Description of variable	Percentage (%)
Farmers with communally grazing livestock	56
Farmers already making profit out of their livestock	22
Farmers who have livestock, but do not make a profit, still trying to decide as to what form of profit making they can venture into with their livestock	63
Farmers who keep livestock for other reasons than profit making	16
Farmers providing nutritional supplements	83
Farmers aware of animal helminthosis	88
Farmers who treat their animals for worm infections	67
Farmers who use targeted selection methods for worm treatment	72
Farmers who require more information on animal health and production matters	89

Products used for deworming in South Africa (Tsotetsi, et al 2013)



Uncertainty!

Parasitologists are uncertain of the current prevalence and distribution of resistant parasites in the US and other areas of the globe

You only find resistance when you look. Many countries lack personnel, infrastructure, funding, and tools for diagnostic testing and research

Responsible Use

There is a need for a change in the way veterinarians and producers view parasites:

From parasite elimination to parasite control

Responsible management

- Weigh/weight tape animals to ensure proper dosing
- Follow label directions for adequate administration
- Quarantine new livestock, if possible
- Reduce grazing density on pastures, if possible
- Cull chronic poor-doers, if possible
- Sheep and goats: use FAMACHA evaluation
- Avoid deworming the entire herd: Use Targeted Selective Treatment (TST)

Targeted Selective Treatment (TST) – a success story

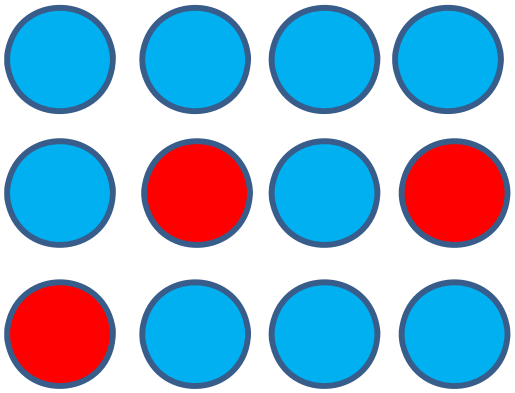
- Study in Botswana (Walker, et al, 2015) demonstrated viability of TST of individual animals in small farms in low-income economies
  - Farmers taught to evaluate health of goats and only treat when needed based on:
    - FAMACHA, bottle jaw, body weight, diarrhea scores
  - Results showed that farms that used TST did not suffer losses at a higher rate than farms treating all animals
    - TST is feasible and effective for resource-poor farmers
    - TST helps reduce use of antiparasitics

Refugia

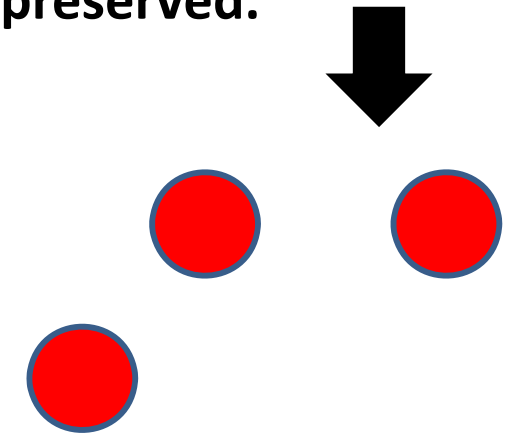
The proportion of the total parasite population that is not selected for antiparasitic treatment

- **Those parasites that are in "refuge" from the drug**
- **Therefore have no selection pressure to develop resistance**
- **A benefit of refugia is to maintain a proportion of susceptible parasites on the farm**

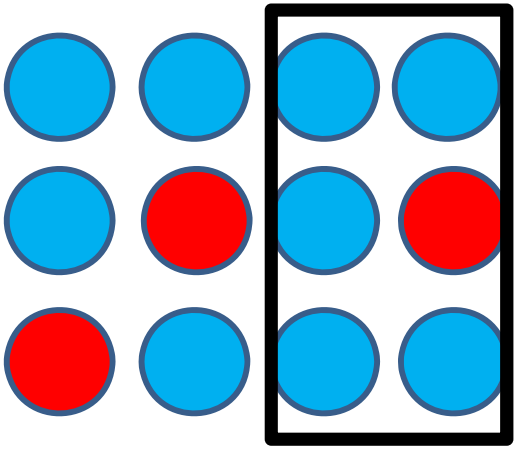
Parasite population within the herd:



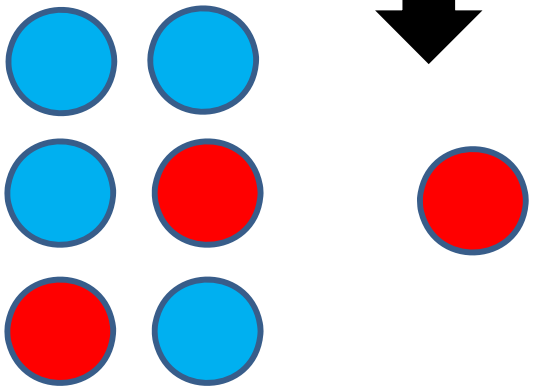
Treat entire herd, so no refugia is preserved.



Parasite population within the herd:



Treat only 50% of herd, so some refugia is preserved.

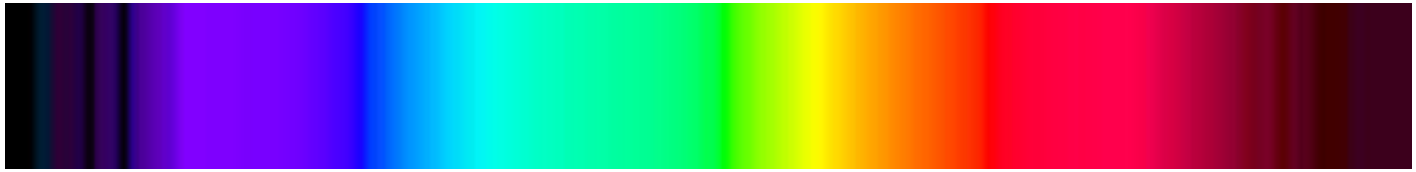


Key:

- Susceptible parasite
- Resistant parasite

Global Challenges

Combating antiparasitic resistance globally faces a spectrum of challenges:



- Counterfeit drugs
- Total anthelmintic failure in some livestock species
- Combinations for 3 or 4 active ingredients
- Challenges of maintaining refugia

Role of education

- In the U.S., many veterinary schools are starting to emphasize parasite management and veterinarians are becoming more aware of the emergence of resistance
- This is where collaboration and communication play a vital role
  - Both locally and globally!

Global efforts to increase awareness

- Europe: **Parasol/GloWorm**
  - EU project 2006 – 2009, demonstrated Targeted Selective Treatment was feasible
  - GloWorm project 2012 – 2014, investigated sustainable control options

Global efforts to increase awareness

- United Kingdom: **SCOPS (Sustainable Control of Parasites in Sheep)**
  - "Industry-led group that represents the interests of the sheep industry"

Global efforts to increase awareness

- New Zealand: **WormWise**
  - Developed by national government, agricultural industry representatives, and the national veterinary association
- Australia: **WormBoss** – "Australia's sheep and goat worm control resource"
  - Developed by the Australian Sheep Industry Cooperative Research Centre and Australian Wool Innovation with the support of Animal Health Alliance, in 2005

Global efforts to increase awareness

FDA-CVM's Initiative: Antiparasitic Resistance Management Strategy (ARMS)

- An initiative to promote sustainable use of antiparasitic drugs in grazing livestock species
- Launched in September 2012
- 3-pronged approach:
  - Education
  - Research
  - Regulation

Final Thoughts

- **Ultimately, we want to ensure that approved antiparasitics remain effective for as long as possible**
- **This should be a shared goal throughout the world for the benefit of animal and public health**

Final Thoughts

- **Global antiparasitic resistance has a large impact on animal welfare and economies, both locally and nationally.**
- **Education is key in spreading the word about responsible use of antiparasitic drugs.**

Resources

- CVM website: http://www.fda.gov/animalveterinary/safetyhealth/ucm350360.htm
- Docket for public meeting: http://www.fda.gov/animalveterinary/resourcesforyou/ucm318015.htm
- Public meeting overview: http://www.fda.gov/downloads/AnimalVeterinary/ResourcesforYou/UCM344299.pdf
- Brochure: http://www.fda.gov/downloads/animalveterinary/resourcesforyou/ucm347442.pdf
- *Antiparasitic Resistance and Grazing Livestock in the United States* J Am Vet Med Assoc 2014 May 1;244(9):1020-2.
- Veterinary Parasitology Special Issue Vol 204, Issues 1-2, Pages 1-80 (30 July 2014)
- Video: https://www.youtube.com/watch?v=kn1NE-vmhr4

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