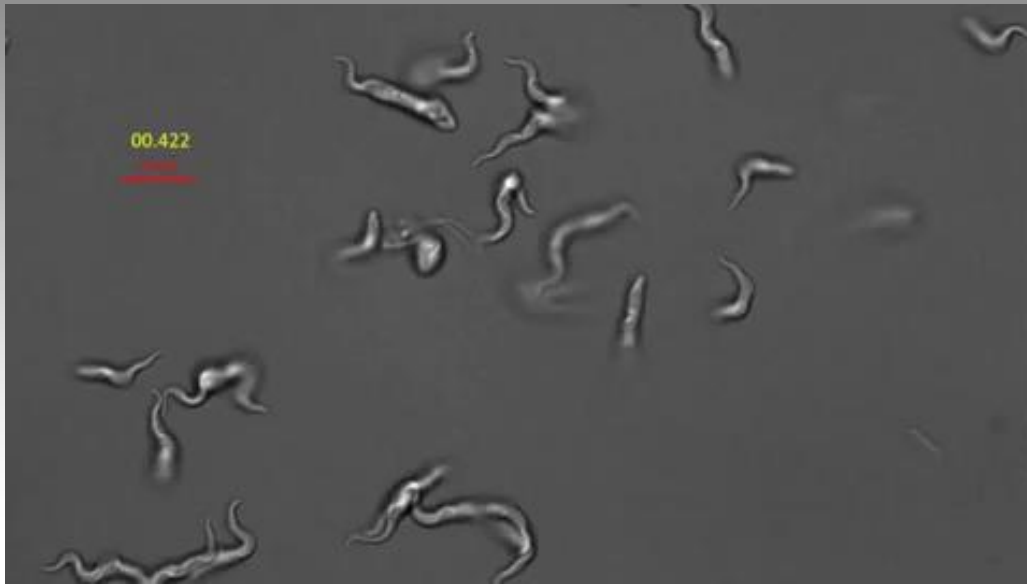




# Les trypanosomes et la résistance aux produits - Un défi majeur en Afrique



Liam Morrison, Roslin Institute, University of Edinburgh

Mike Barrett, University of Glasgow

Harriet Auty, University of Glasgow



THE UNIVERSITY of EDINBURGH



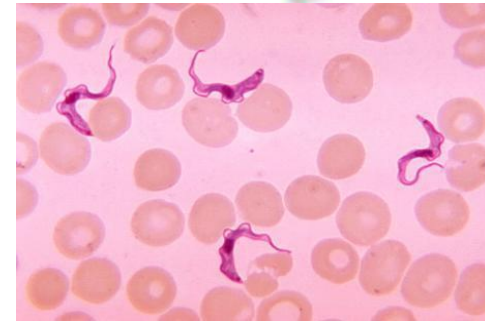
# African trypanosomes

Three major species affecting human and animal health

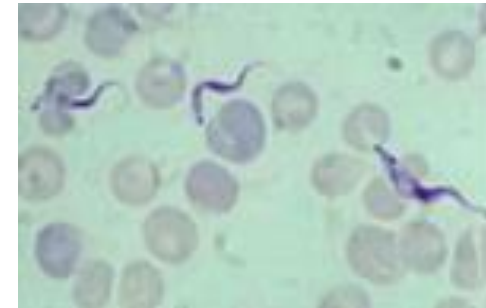
*Trypanosoma congolense*

*Trypanosoma vivax*

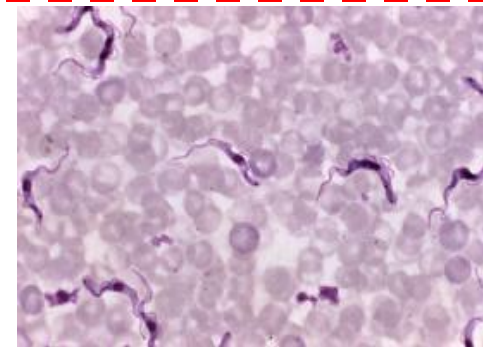
*Trypanosoma brucei*



*T. congolense*



*T. vivax*



*T. brucei*

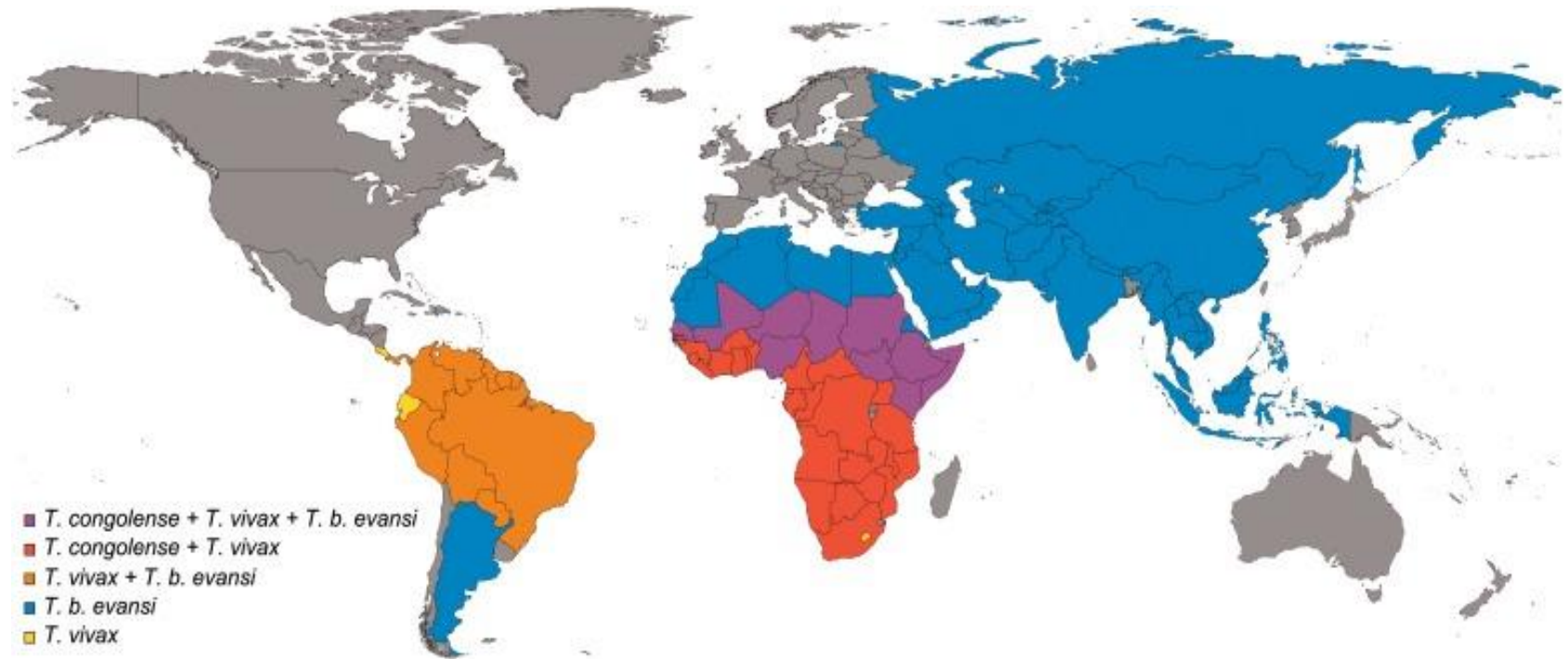
# African trypanosomes & disease



799 human cases in 2022

~**55 million** cattle infected, ~3 million deaths

~**120 million** cattle at risk



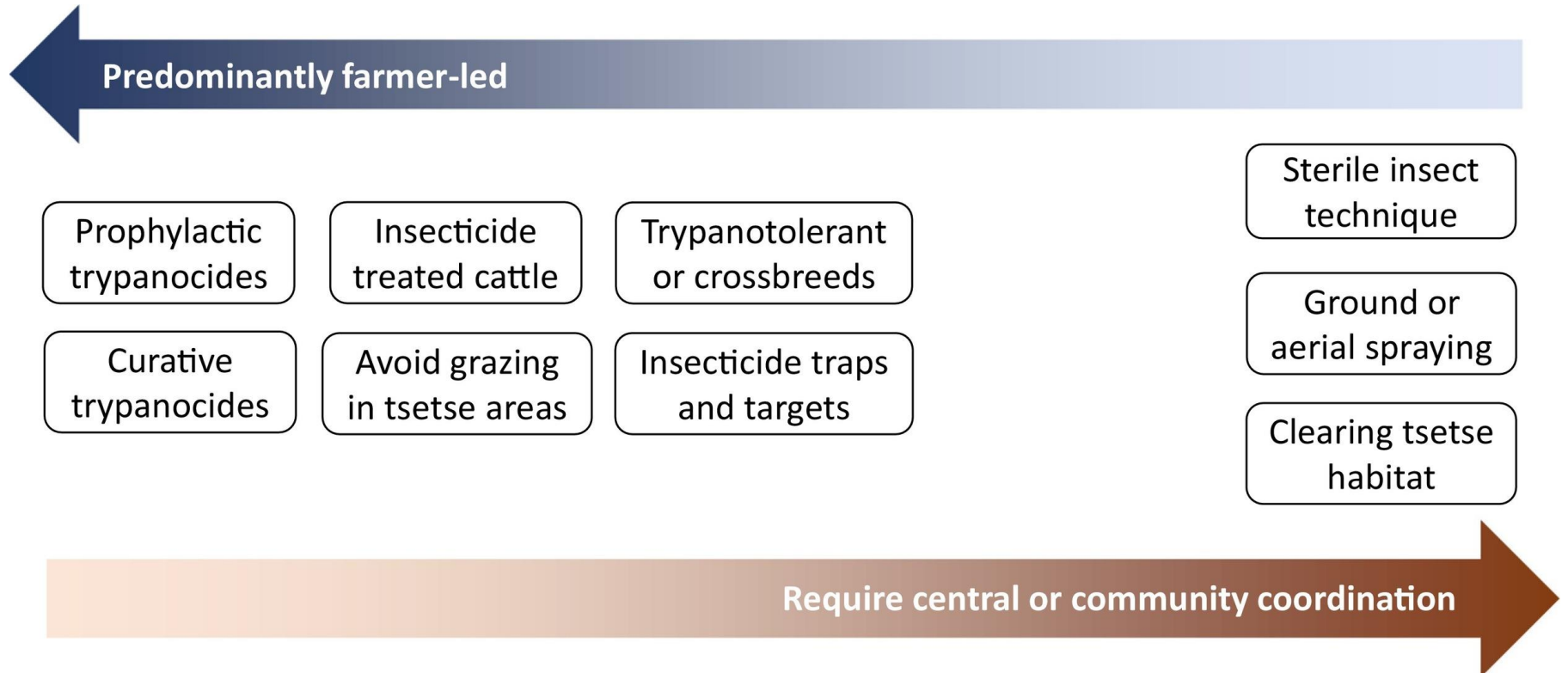
Cause huge economic losses to agriculture, estimated to be **\$2.5 billion/annum** for cattle production in East Africa alone (e.g. **70 million doses of trypanocide** sold each year)



# Current methods of control

***Almost all control is farmer-led***

Veterinary health is considered a private good



**Trends in Parasitology**

# Current methods of control

- There is no vaccine for AAT
- Vector control includes tsetse traps and insecticides
  - Requires maintenance & infrastructure
  - Tick resistance is an increasing problem for insecticide use





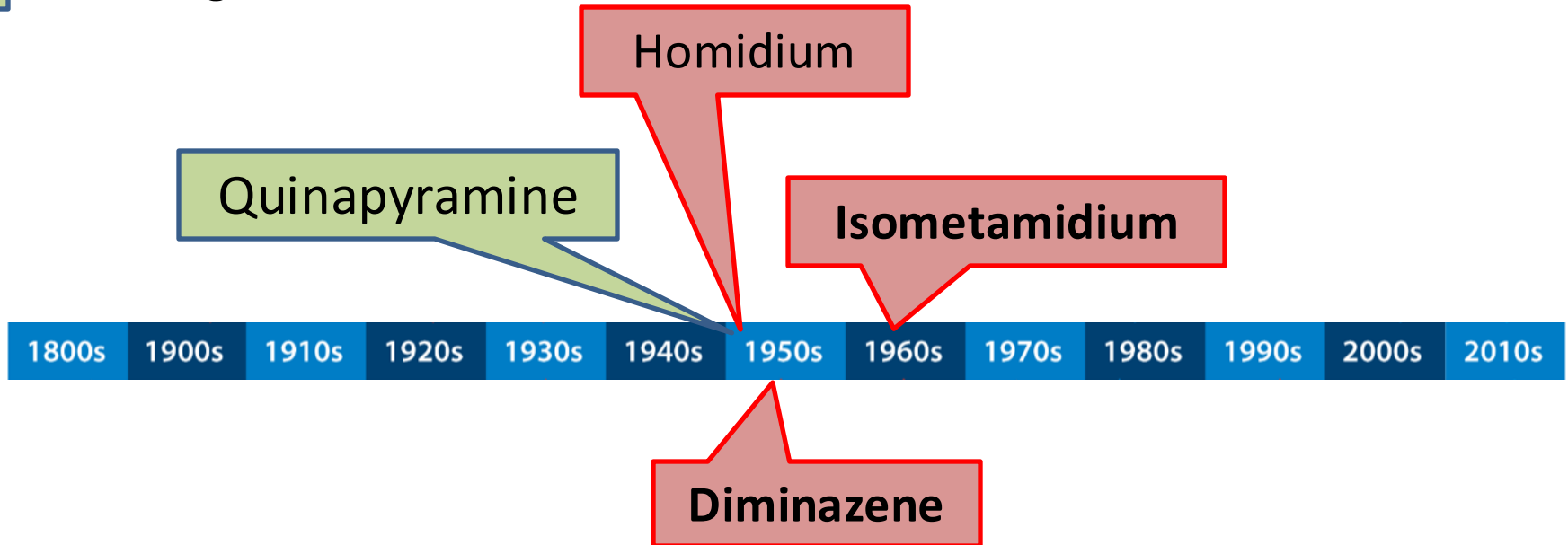
LSTM Tsetse project



YouTube

# Veterinary trypanocides

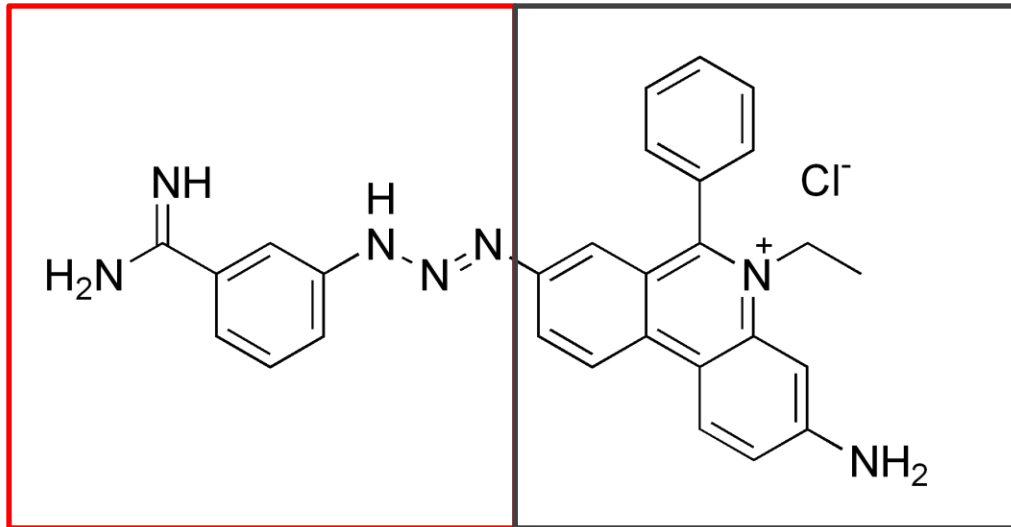
-  = related compounds
-  = No longer in use



- Resistance to all drugs has been reported since the 1970s
- Current effort (GALVmed/BMGF) has identified candidate therapeutic that may result in the first new trypanocide for <60 years

# Veterinary trypanocides

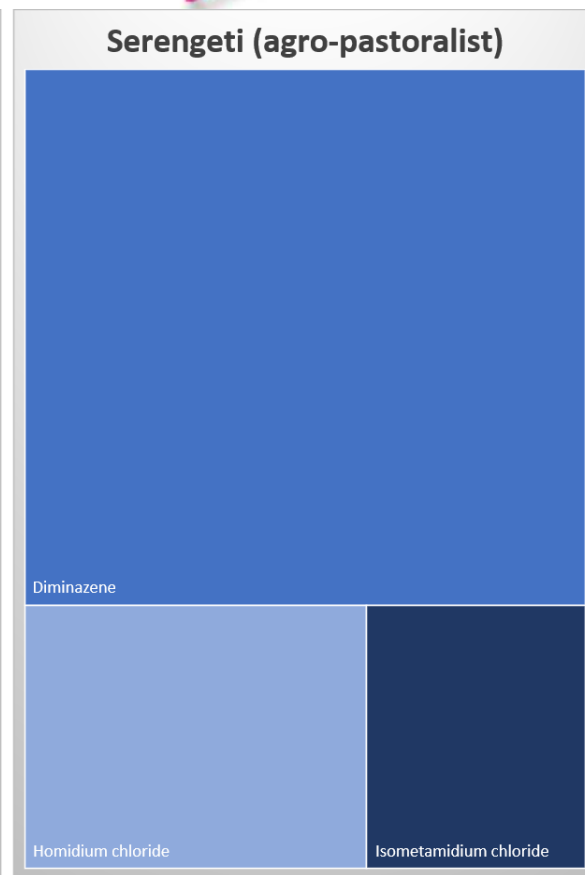
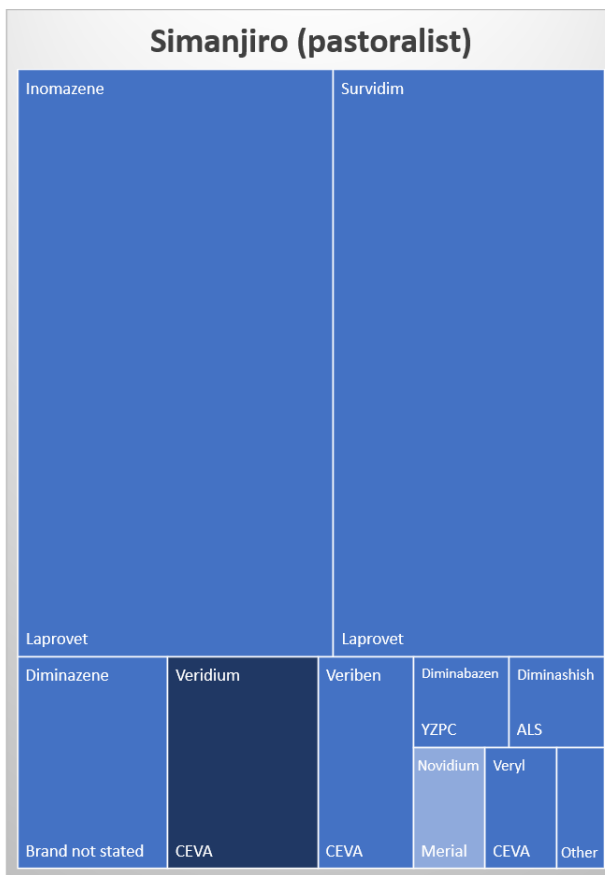
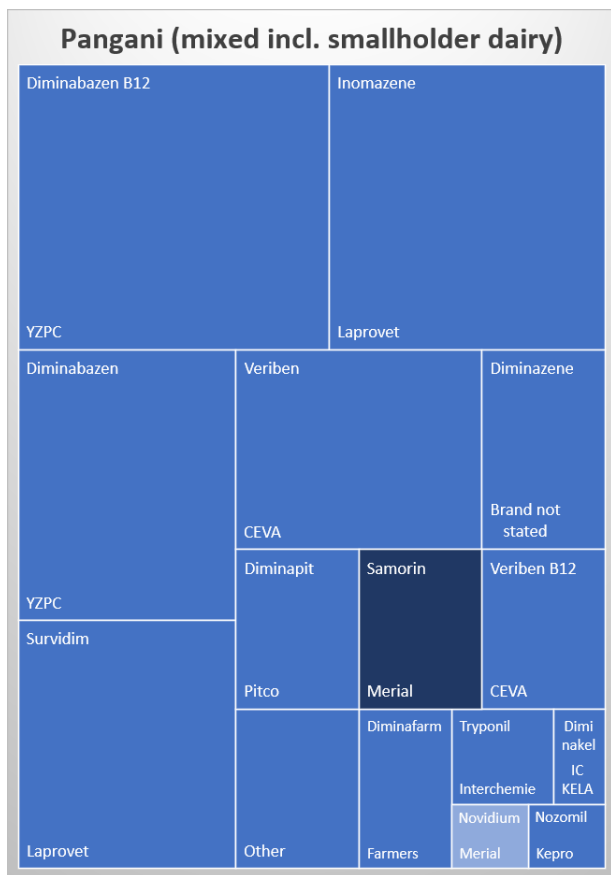
- Isometamidium (ISM) is a phenanthridine compound generated by fusing parts of homidium (ethidium bromide) and diminazene
- Diminazene & Homidium both used as therapeutic drugs
- Isometamidium is currently the only available drug for prophylaxis
- Drug target is mitochondrial (accumulate in kinetoplast – the trypanosome mitochondrion)



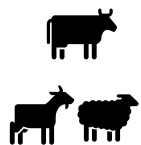
Diminazene

Homidium

# Farmers use trypanocides frequently



■ Diminazene     
 ■ Isometamidium Chloride     
 ■ Homidium Chloride



100%

35%

100%

89%

100%


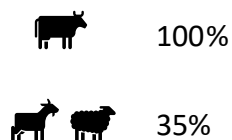
32%



# Farmers use trypanocides frequently


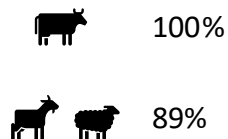


Pangani District – mixed incl. smallholder dairy

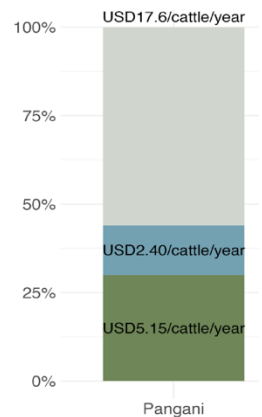



median 10 treatments/animal/yr

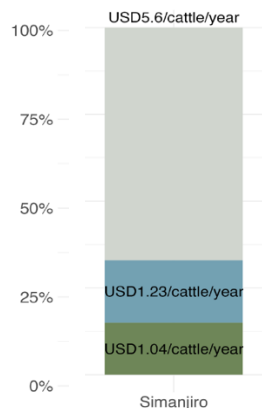
Simanjiro District – pastoralist

median 4 treatments/animal/yr



**7.5% of cattle-derived income is used to tackle AAT**

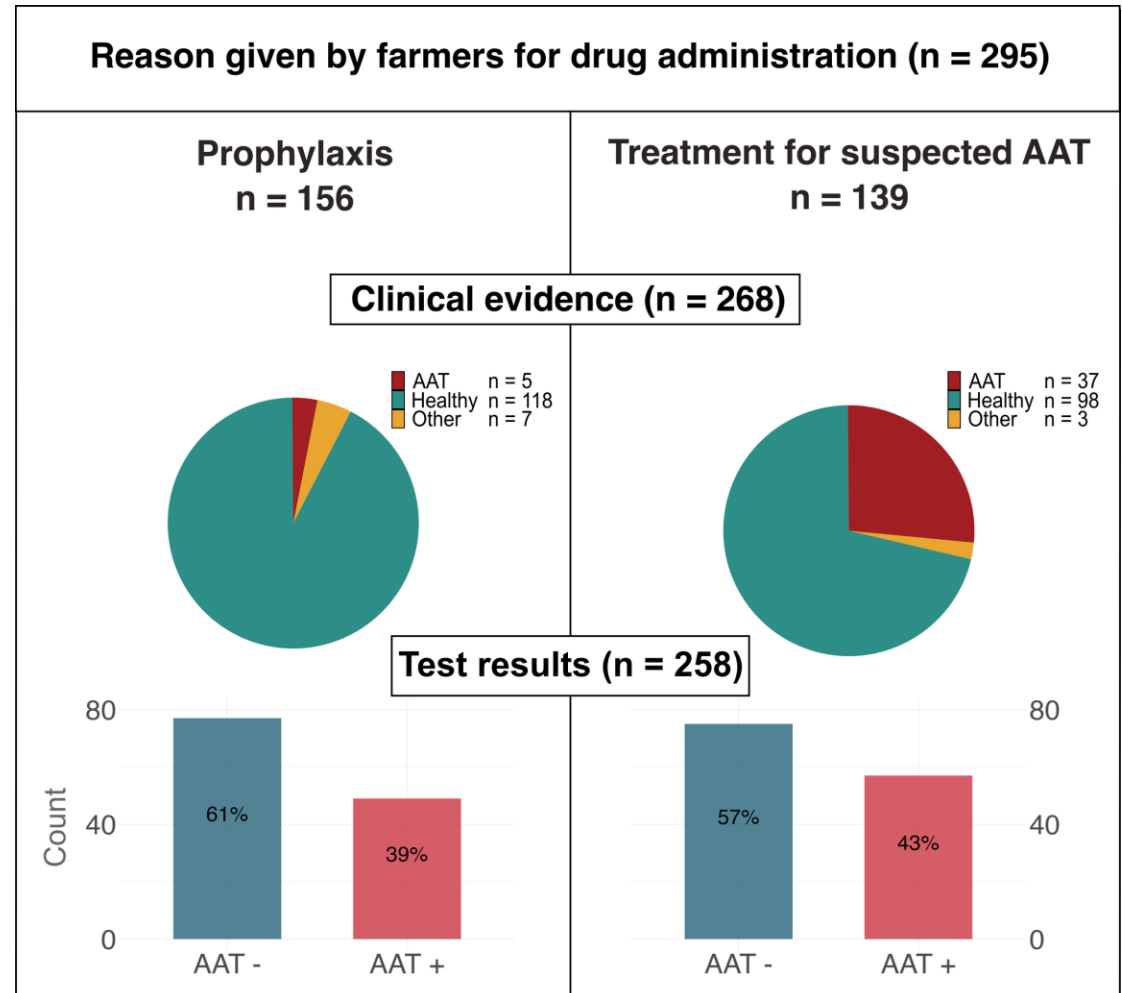


**10.5% of cattle-derived income is used to tackle AAT**

# Farmers use trypanocides frequently



- Farmers use drugs for both prophylaxis and treatment
- Farmers mostly treat on basis of clinical signs
- lack of pen-side diagnostic test means that treatment accuracy is variable



# Farmers use trypanocides frequently



## Farmer questionnaires



## Stakeholder workshops



## Frequent farmer comments:

- Drug quality is variable
- Sometimes drugs don't work – quality or resistance issues?
- Drugs don't work as well as used to
- Some think needing to use more frequently than used to (3 monthly cf 6 monthly)

**Treatment failure with trypanocides is often reported – what is driving this?**

Treatment failure can result from:

- Drug resistance
- Inappropriate use of drugs
- Poor quality/counterfeit drugs

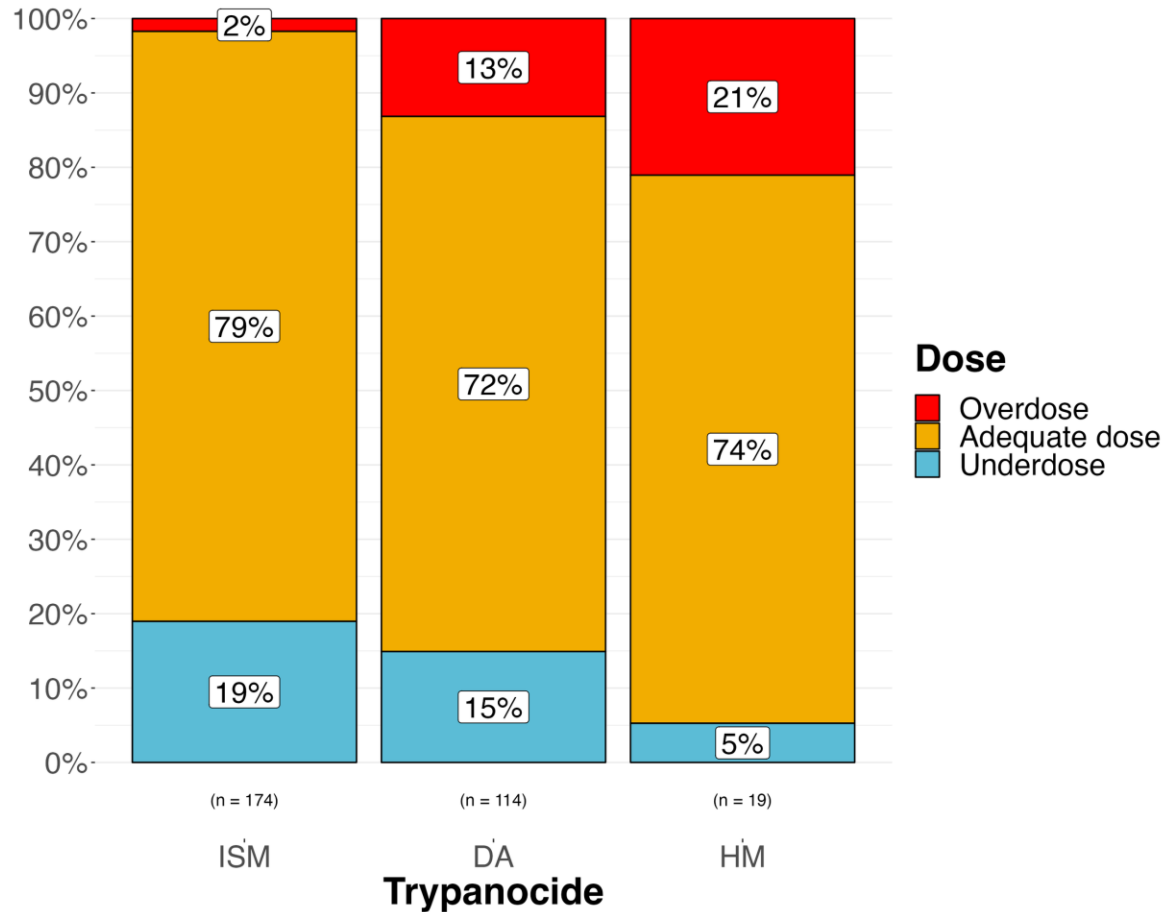
Identifying which of these is the reason(s) driving treatment failure in a particular scenario is not straightforward

# Inappropriate drug use

Drug efficacy will be affected by:

- Administering the wrong dose
- Administering via the wrong route
- Administering drugs formulated incorrectly (e.g. wrong diluent)

All of these happen, but we know little about the extent.



# Poor quality/counterfeit drugs



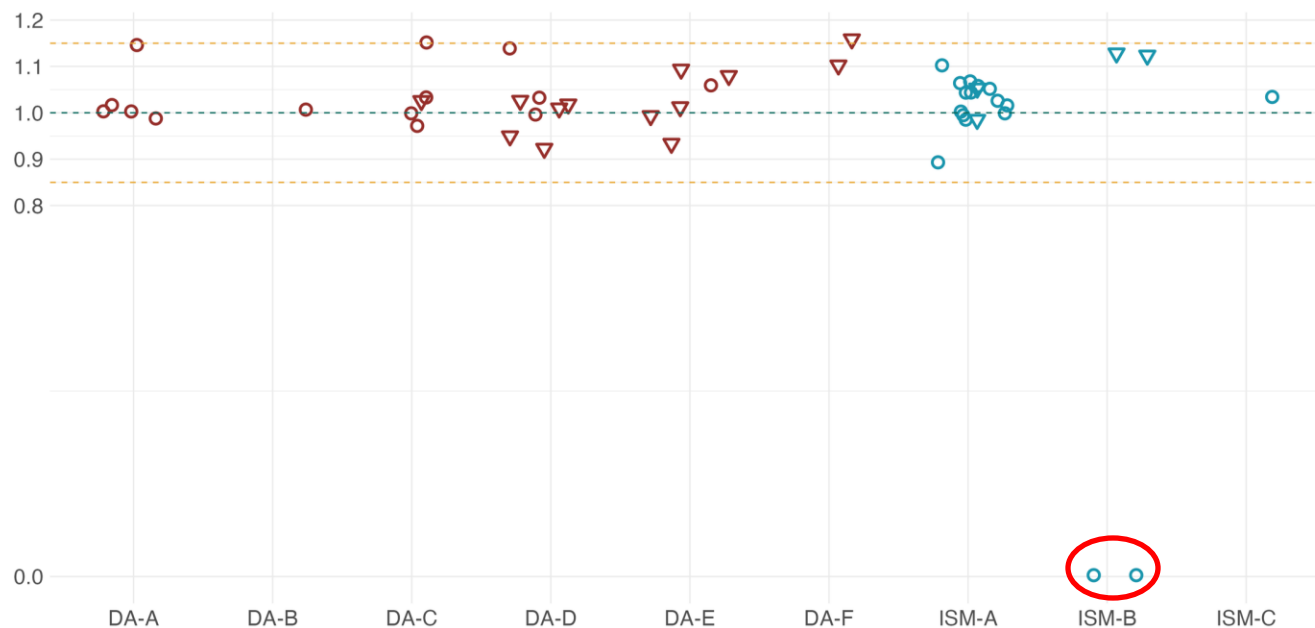
Counterfeit drugs are anecdotally widely reported – **few robust data**

West African study analysed drugs purchased from official and non-official sources

- 51.9% of products were non-compliant (>10% divergence in stated content)
- Figure was higher in drugs bought from non-official sources
- Non-compliance was higher for ISM (73.91%) than DA (50%)

Recent study from Tanzania reported higher compliance (for ISM)

- However, counterfeits were readily detected and available



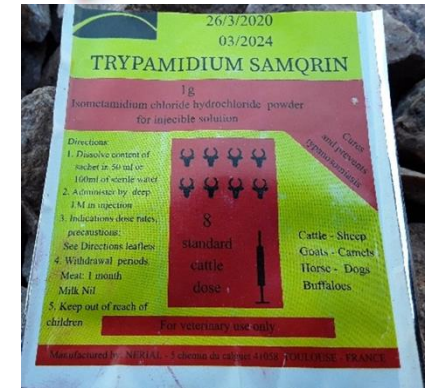
# Poor quality/counterfeit drugs

Counterfeit drugs clearly occur, but other factors can also impact upon drug quality

- Drug storage
- Drug formulation (diluent)

Multiple issues contribute to the difficulty in maintaining drug quality

- Formal versus informal market
- Lack of regulation for veterinary products
- Difficulty in easily assessing drug quality in the field
- Literacy/instructions on packaging not in local language



- Sustained reporting (E & W Africa) of treatment failure
- Very little knowledge on mechanisms of resistance and no markers, particularly for *T. congolense* & *T. vivax*
- Very little (no) understanding of the dynamics of and the drivers of drug resistance emergence and spread



# Validated drug resistance?



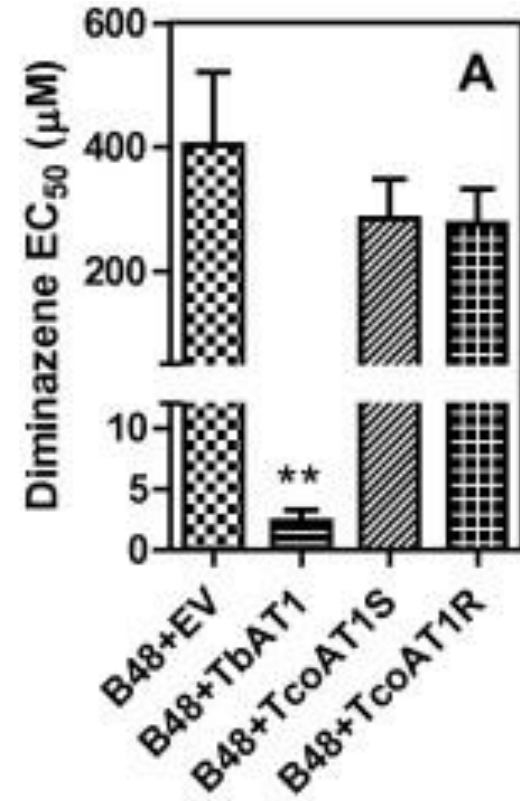
Resistance has been validated in the field

- Intervention trials (treatment & follow up)
- Single & double resistance (isometamidium & diminazene) has been identified
- Isolated parasites validated as resistant (*in vivo* tests by experimentally infecting and treating mice or cattle)
- Expensive & resource intensive
- Markers for resistance would enable testing & screening

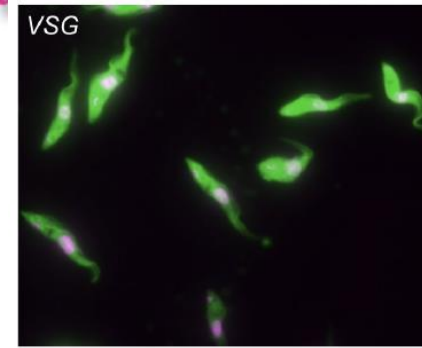
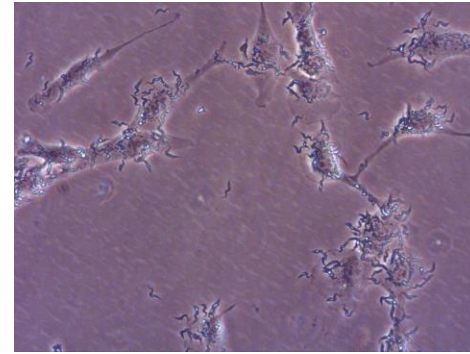
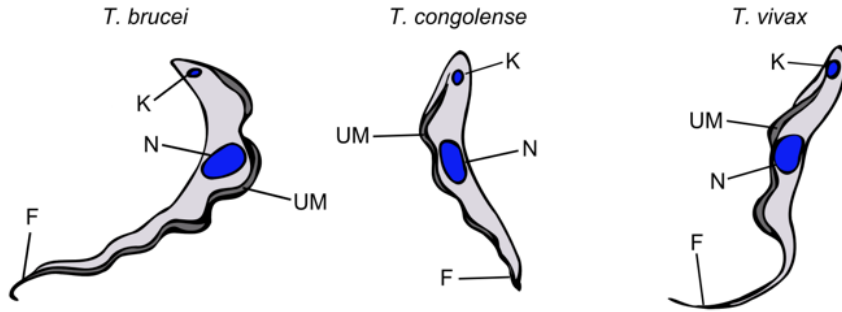


# Drug resistance marker?

- Diminazene resistance in *T. brucei* has been shown to occur due to loss of a key transporter, TbAT1
- Orthologue was identified in *T. congolense* (TcoAT1) and proposed to contain drug resistance related polymorphisms
- However, there is no TbAT1 orthologue in *T. congolense*
- ***This gene is therefore not a marker for resistance and should not be used***



# Almost all knowledge & resources are from *T. brucei*



99% of knowledge and resources come from *T. brucei*  
Assumption has been that this will be directly translatable to *T. congolense* & *T. vivax* – *not the case*

*Efforts underway to improve ability to work with T. congolense and T. vivax in vitro*

- will improve ability to identify mechanisms and markers of resistance
- identified mechanism of resistance to ISM

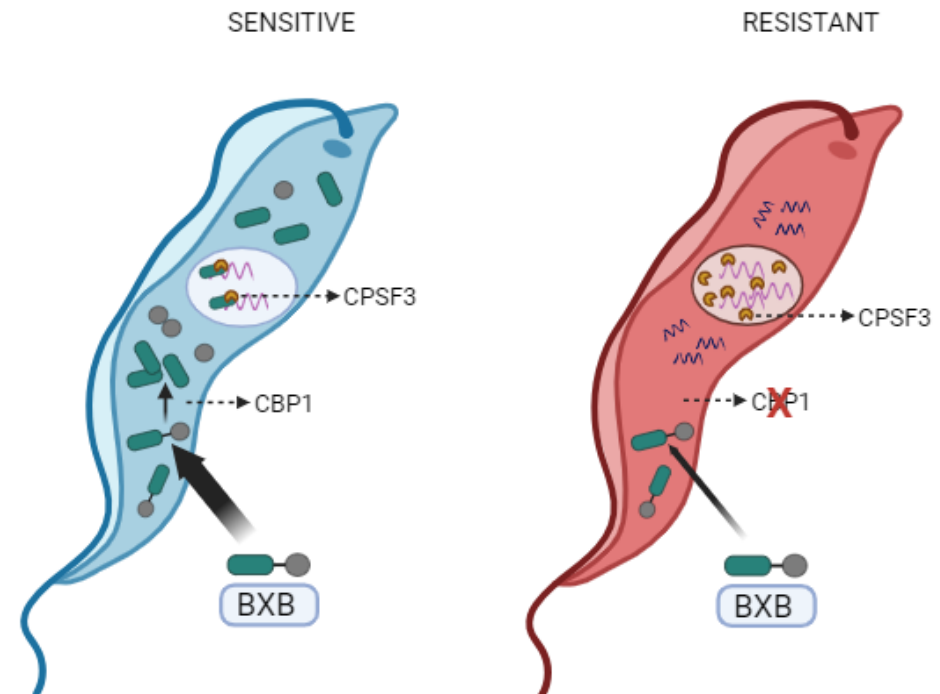


# New drug hope - Benzoxaboroles



- Class of compound chemically distinct to existing drugs
  - acoziborole in clinical development for Human African Trypanosomiasis
  - benzoxaborole in clinical development for animal trypanosomiasis
- Relevant class of benzoxaboroles are prodrugs
- Drug target defined (genome wide screen) as CPSF3 - (Cleavage and Polyadenylation Factor 3)

- Enzyme (Carboxypeptidase; CBP1) identified that converts prodrug to active drug
- Mutation in CBP1 results in resistance (shown to occur in *T. brucei*, *T. congolense* & *T. vivax*)
- **Potential marker for resistance**



# Summary - where we are at



- Improving understanding of
  - Mechanisms (markers?) of resistance beyond *T. brucei*
  - Epidemiology of drug resistance in the field
  - Causes of treatment failure
- Improving laboratory capabilities
  - Improved culture for *T. congolense*
  - Genetic toolkit for *T. congolense*
  - Progress with *T. vivax*
- Stakeholder & funder engagement with problem
  - meeting with >140 attendees in Tanzania, 2023 (<https://sulsa.ac.uk/salt-tz/>)
  - EU COMBAT project (<https://www.combat-project.eu/>)
- *Prospect of first new drug in >60 years*



# Summary - what is needed going forward?



- Increased laboratory efforts
  - Improved capabilities to work with relevant species/strains
  - Drug discovery & development pipeline
- Better understanding of drug use, and drug resistance & treatment failure in field
  - Market scale, details and quality
  - Socioeconomics; what are farmers using and why?
  - Markers of resistance would enhance efforts
  - How do we integrate with insecticide use?
  - How do we best integrate a new drug into existing setting?
- Increase/improve communication & harmonization across trypanosome research & control stakeholders



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