VOLGENAU SCHOOL OF ENGINEERING

GEORGE MASON UNIVERSITY

A Discrete-Event Simulation Study of the Re-emergence of *S. vulgaris* in Horse Farms Adopting Selective Therapy

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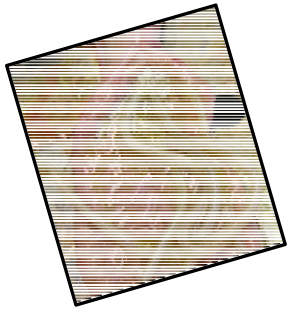
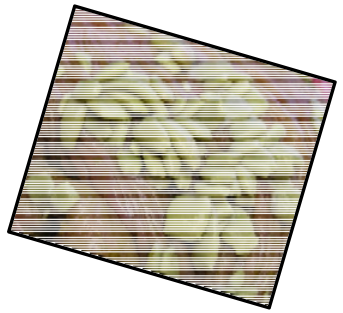
Outline

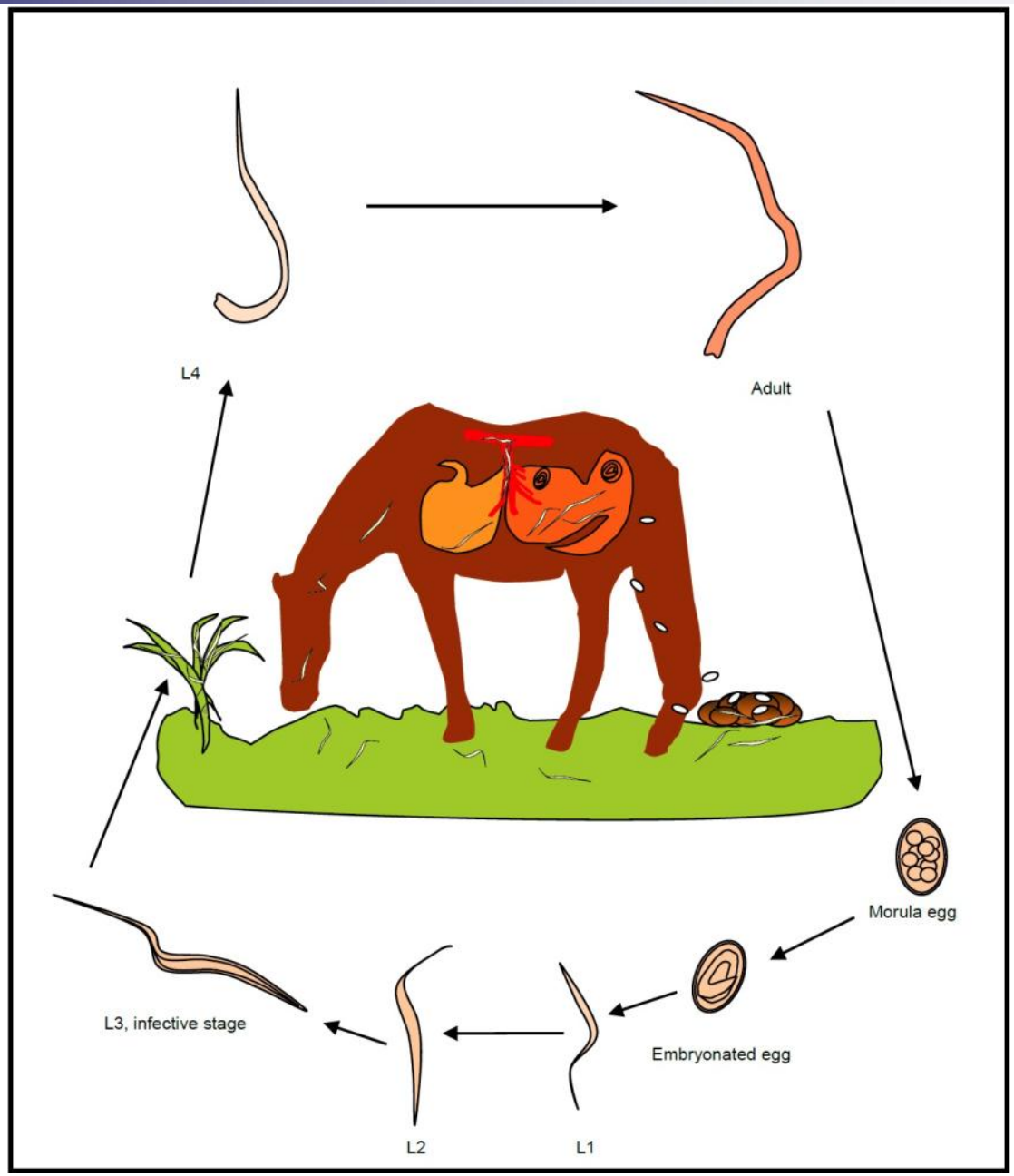
- Equine parasites and anthelmintic drug efficacy
- Selective therapy and the re-emergence of *S. vulgaris*
- A discrete-event simulation model for the equine anthelmintic treatment process
- Simulation results and discussion

Equine parasites

- About 100 different parasite species
- Ubiquitous
- Health-related problems
  - Weight-loss, retarded growth rates
  - Poor performance
  - Colic
  - Diarrhea
  - Death






L4
Adult
Morula egg
Embryonated egg
L1
L2
L3, infective stage

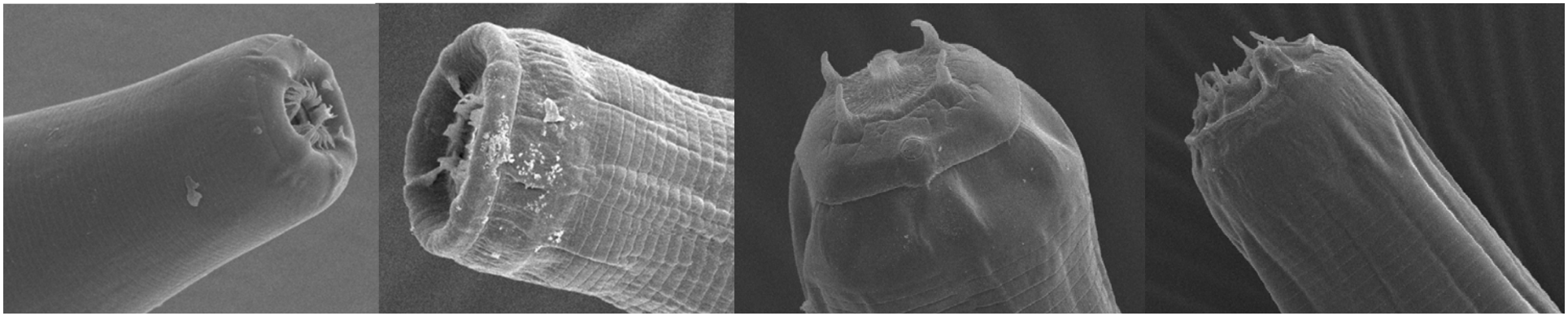
Equine parasites

- Anthelmintic treatments (dewormers) applied typically every six month, one in spring and the other in fall

Drug resistance

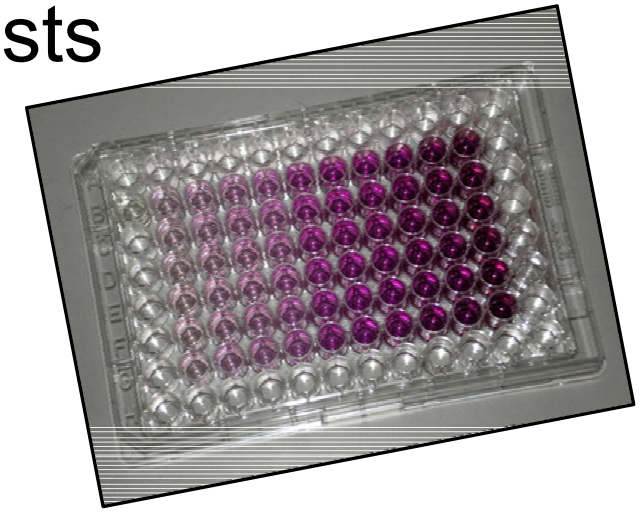
Drug	Cyathostomins (small strongyles)	Large strongyles	Ascarids
Ivermectin	Emerging resistance	Full efficacy	Resistance
Moxidectin	Emerging resistance	Full efficacy	Resistance
Oxibendazole	Widespread resistance	Full efficacy	Full efficacy*
Fenbendazole	Widespread resistance	Full efficacy	Full efficacy*
Pyrantel	Resistance	Full efficacy	Full efficacy*

* Cases in USA and Scotland



How to measure resistance?

- "True" resistance is not measurable
  - A genetic change
- Critical controlled efficacy tests
  - "Kill them – count them"
- In vitro assays
  - None validated for horses
- Molecular assays
  - None available
- Fecal Egg Count Reduction Test (FECRT)
  - Parasite eggs in feces before and after treatment



Fecal Egg Count Reduction

$$\%\boldsymbol{FECR} = \left(\frac{\boldsymbol{FECpre - FECpost}}{\boldsymbol{FECpre}}\right)\boldsymbol{X\ 100}$$

- Typically 6-10 horses tested per farm
- Each horse acts as its own control
- Mean FECR calculated for each farm

- No established cut-off values for determining resistance

FECRT examples

38	200	0	100
39	240	0	100
40	320	20	93.75
41	200	0	100
42	260	0	100
43	280	20	92.85714
44	1800	400	77.77778
45			94.91213
46	2440	580	76.22951
47	1000	320	68
48	1900	400	78.94737
49	1820	160	91.20879
50	200	40	80
51	3260	60	98.15951
52	300	40	86.66667
53	660	120	81.81818
54			82.62875

Selective Therapy

- European countries introduced selective therapy to slow down the development of drug resistance in cyathostomins
- A horse is treated if the fecal egg count > cutoff value (typically 200 EPG) and prescription is required
- Anthelmintic drugs are still over-the-counter in U.S.

Re-emergence of *S. vulgaris*

- The most pathogenic strongyles
- No drug resistance detected yet among *S. vulgaris*
- A statistical study links selective therapy with re-emergence of *S. vulgaris* on Danish horse farms

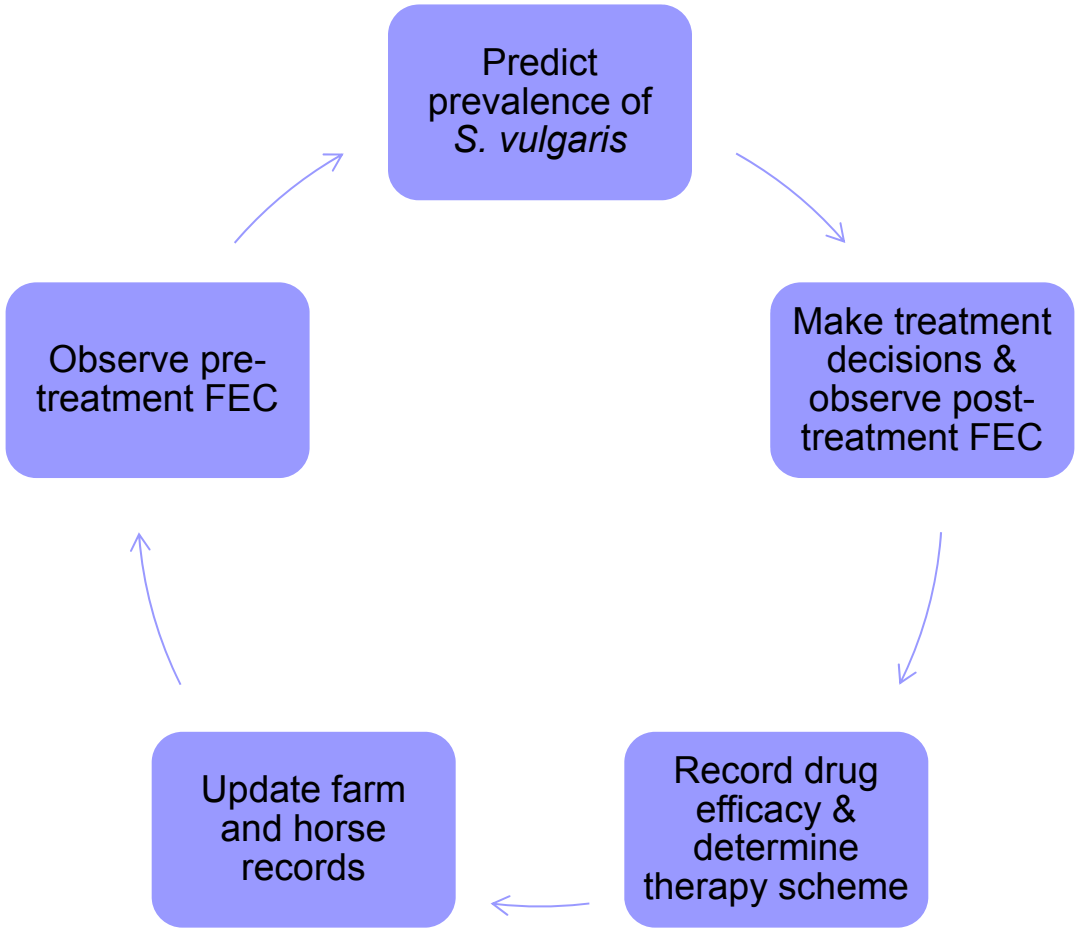
Problem statement

- What is the dynamic relationship between selective therapy and the re-emergence of *S. vulgaris*?
  - The fundamental question on the balance between drug resistance and pathogenic effects
- How does the cut-off FEC value affect the re-emergence of *S. vulgaris*?

Discrete-event simulation study

- No valid biological model for reduced drug efficacy and re-emergence of parasites
- Statistical models for drug efficacy and re-emergence provide “snapshots” of a complex dynamic process
- A statistical model driven discrete-event simulation approach to quantitatively study the relationship between selective therapy and re-emergence

Simulation cycle



Pre-treatment FEC model

- Negative binomial distribution has been the default choice for *static* statistical study
- A time-series model required for discrete-event simulation
- Negative binomial integer-valued GARCH model (NBINGARCH)
  - $FEC_{pre}(t) \sim NBin(r, p_{nb}(t))$
  - $(1-p_{nb}(t))/p_{nb}(t) = \lambda(t) = \alpha_0+\alpha_1 FEC_{pre}(t-1)+\theta_1\lambda(t-1)$

S. vulgaris prevalence model

- No valid biological model
- Past study used random effect logistic regression models to associate selective therapy with re-emergence of *S. vulgaris*
- We propose a dynamic random effect logistic regression model
  - $\text{Log}(p_s(t)/(1-p_s(t))) = \gamma_0 - \gamma_1 n_s(t) + H_s(t)$
    - $n_s(t)$: number of continuous treatment prior to cycle t
    - $H_s(t)$: horse random effect

Efficacy model

- $\text{Log}(p_{ij}(t) /(1- p_{ij}(t)))= \beta_0 + \beta_1 FEC_{pre} + \beta_2 age + S.\ vulgaris$ + gender + horse + farm - $\delta_0 t - \delta_1 n_s(t)$
  - β0: overall mean efficacy
  - β_1: slope for pretreatment egg count effect
  - β_2: slope for age effect
  - δ_0 (≥0): reduction in efficacy over time
  - δ_1 (≥0): reduction in efficacy due to continuous treatment
  - Random effects:
    - farm
    - horse

Observed efficacy and therapy

- Under selective therapy, treat if FEC_{pre} > cut-off (200 e.g.)
- $FEC_{post} \sim Bin(FEC_{pre}, p_{ij}(t))$
- Observed horse-level efficacy = $(FEC_{pre} - FEC_{post}) / FEC_{pre}$
  - Average horse-level efficacy gives observed farm-level efficacy
- Switch to selective therapy
  - If observed farm efficacy < threshold (92% e.g.), adopt selective therapy for next treatment cycle
  - If observed farm efficacy >= threshold (92% e.g.), keep treating all horses in the next cycle

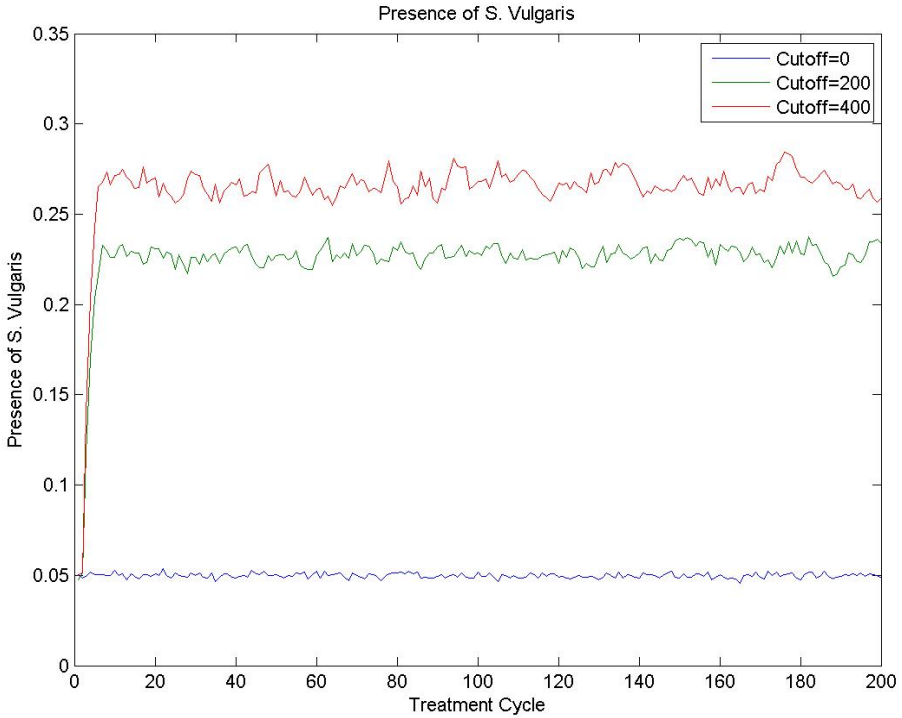
Farms and horses information

- Data taken from a Danish horse farm study in 2008
- Number of farms and horses in each farm
- Horse age and gender information
- Prevalence of *S. Vulgaris*
- Distribution of pre-treatment FEC
- Observed efficacy
  - Used to fit a static efficacy model
- Horse movement between farms not modeled yet
  - Horse replacement only happens due to aging

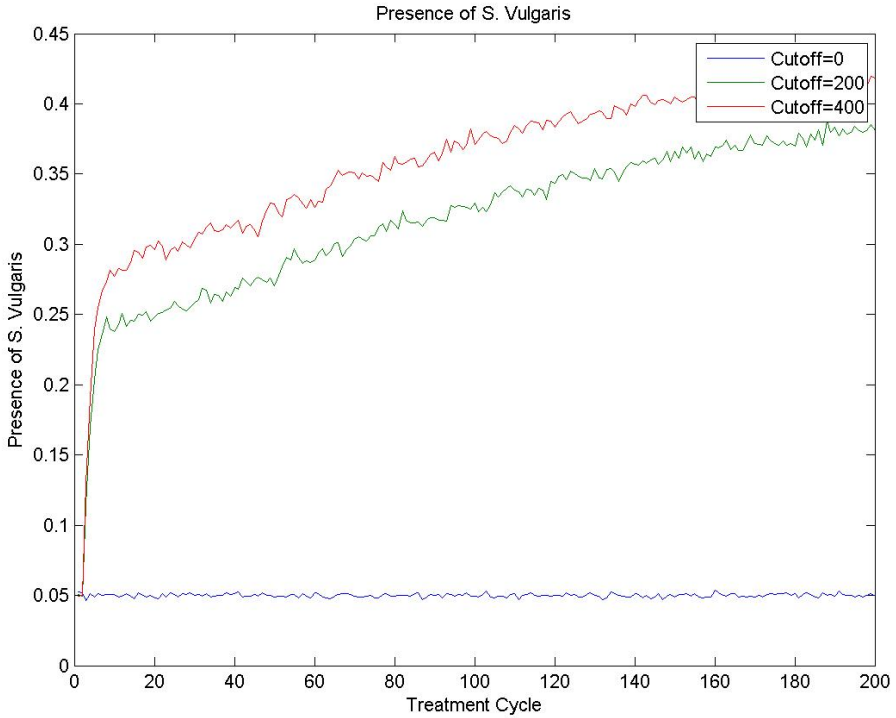
Simulation experiment setup

- Simulation model built in Matlab
- 25 replications, each with 100 cycles (50 years)
- Plots show the average across 25 replications
- Experimented with different patterns of temproal reduction in drug efficacy

Re-emergence of *S. vulgaris*



$\delta_1 = 10^{-5}, \delta_2 = 10^{-2}$

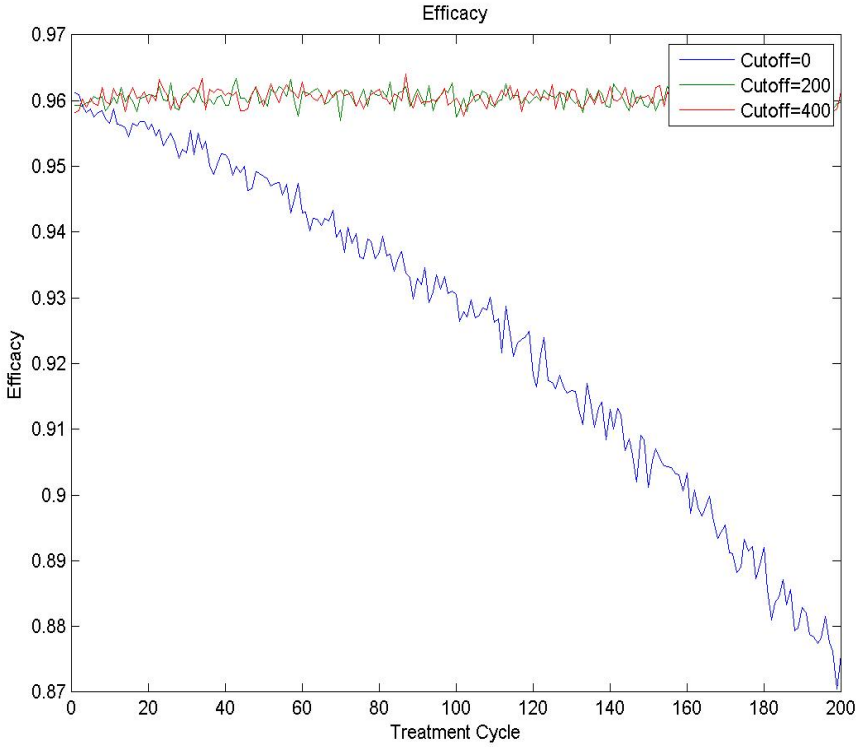


$\delta_1 = 10^{-2}, \delta_2 = 10^{-2}$

Findings

- The introduction of selective therapy leads to increased prevalence of *S. vulgaris*
- A higher cut-off value leads to increased *S. vulgaris* prevalence
  - No surprise…
  - Quantitatively link different cut-off values to different prevalence levels of *S. vulgaris*

Efficacy



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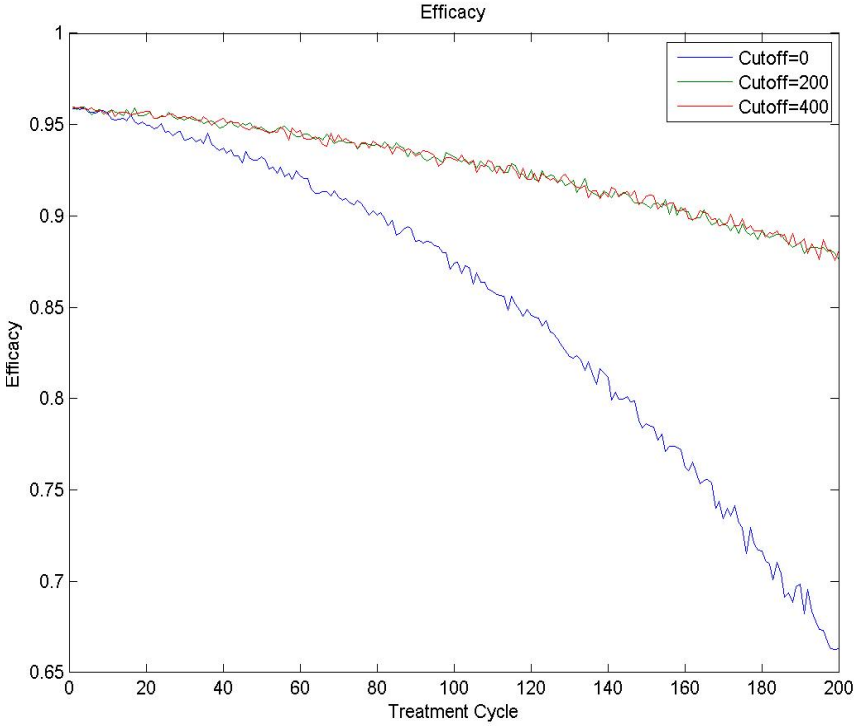

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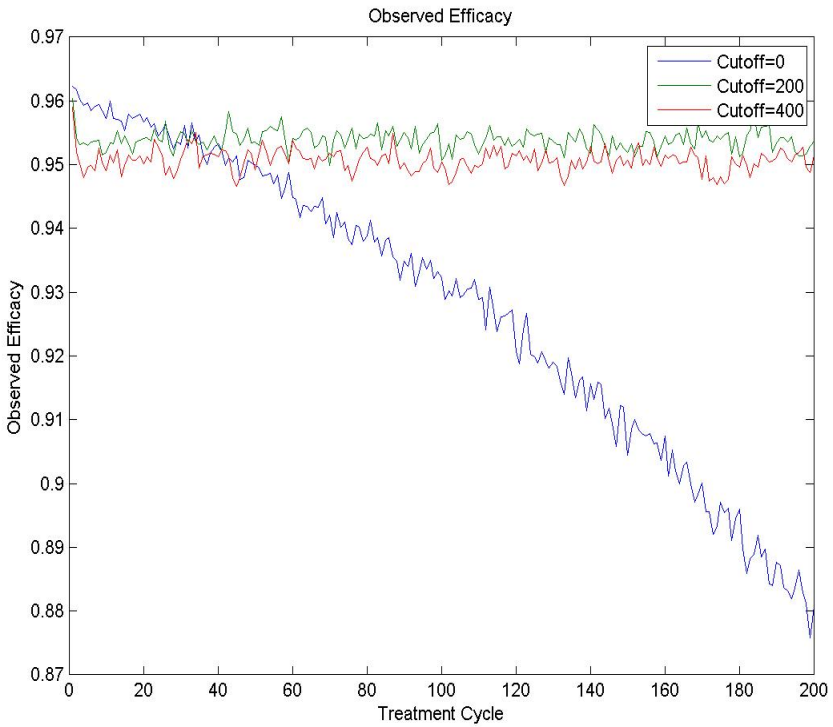
Observed Efficacy



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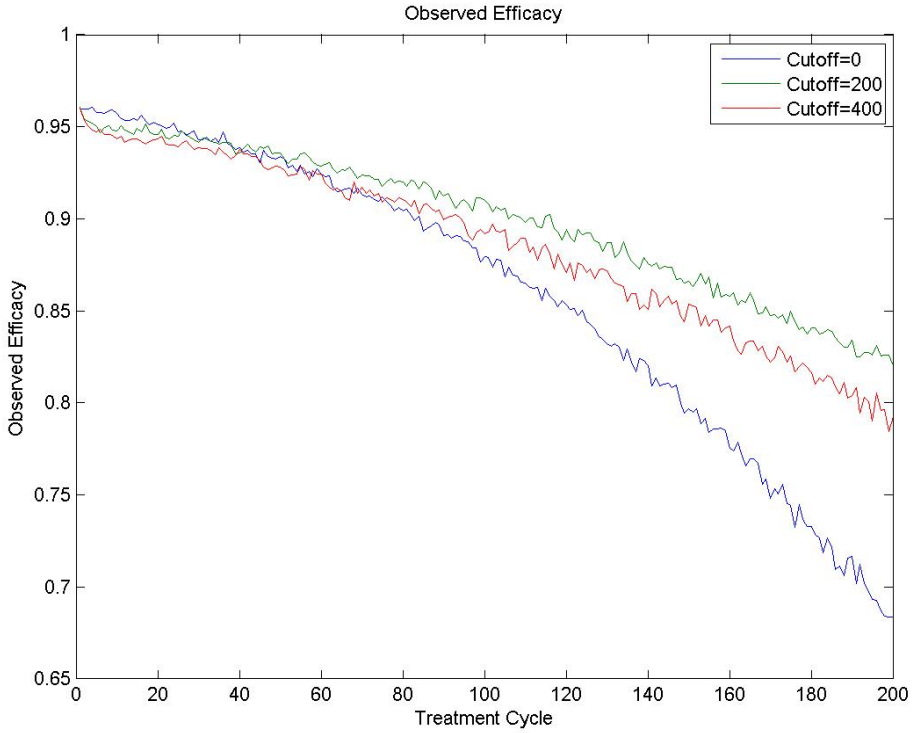
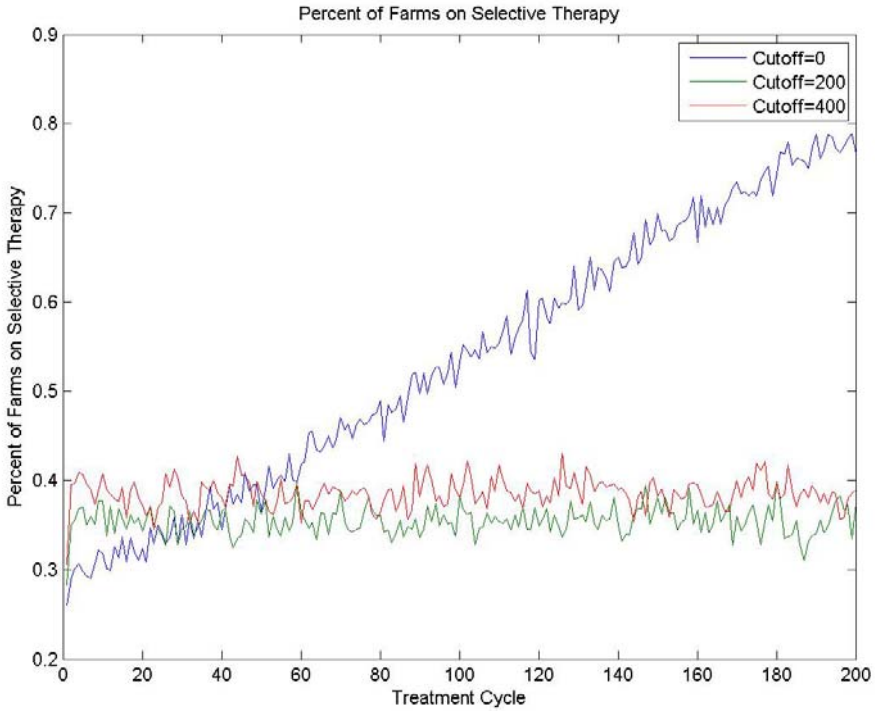


$\delta_1 = 10^{-2}, \delta_2 = 10^{-2}$

Findings

- Selective therapy is effective in maintaining drug efficacy *if the drug efficacy model is correctly specified*
- Different cut-off values do not impact efficacy
- Larger cut-off values lead to lower observed efficacy because of model construction
  - Findings from static statistical models
  - Efficacies observed on horses with small pretreatment FECs tend to be overestimated

Percent of farms on selective therapy



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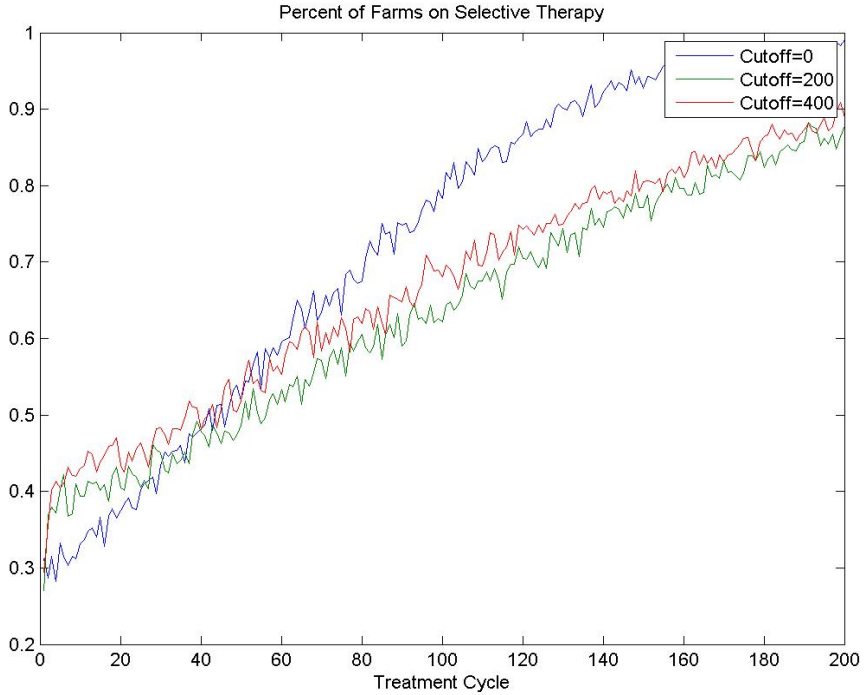
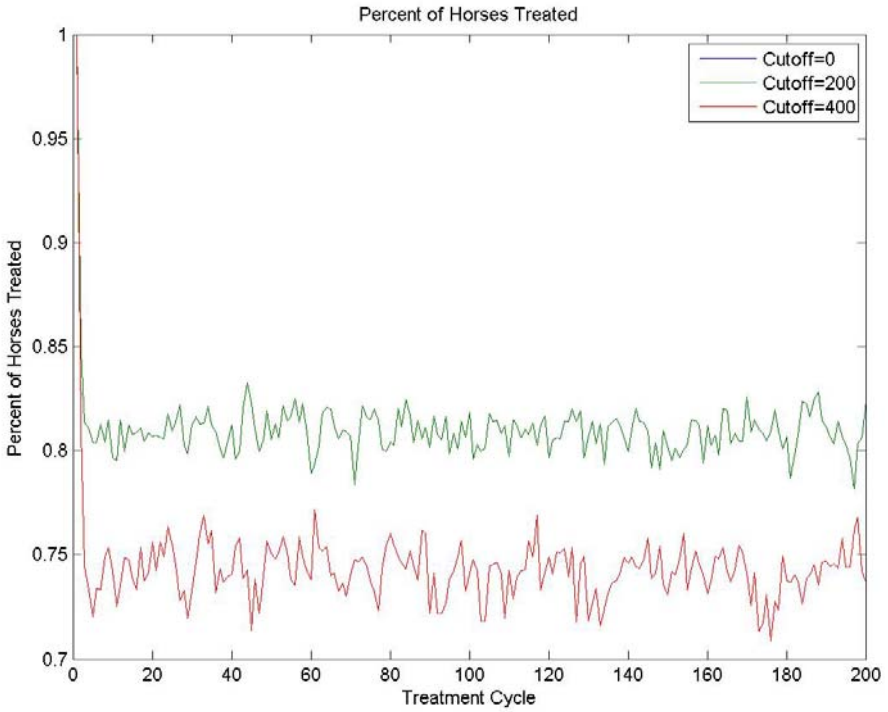


$\delta_1 = 10^{-2}, \delta_2 = 10^{-2}$

Percent of horses treated



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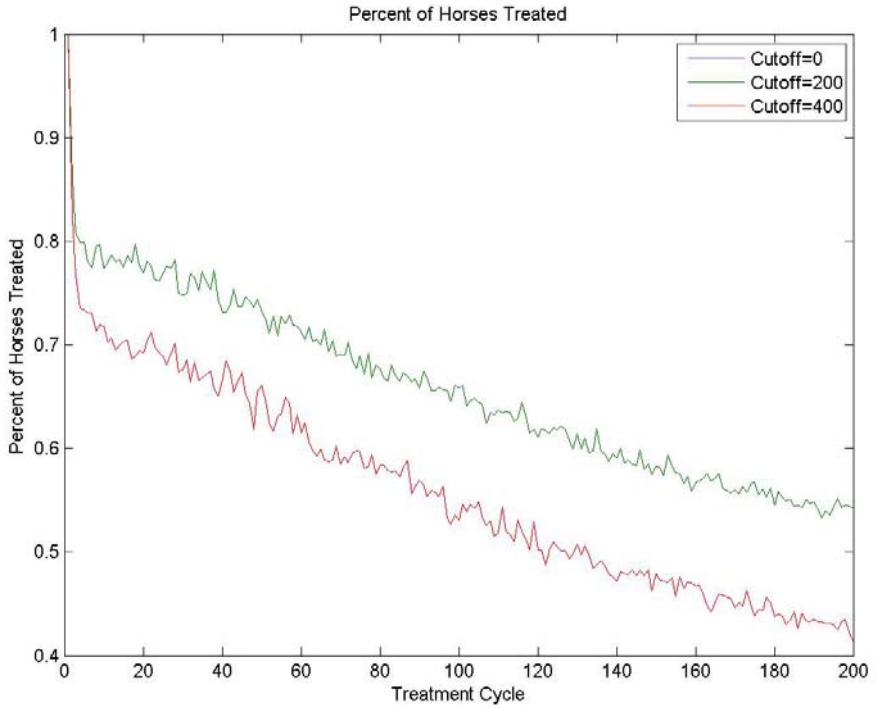

$\delta_1 = 10^{-2}, \delta_2 = 10^{-2}$

Findings

- A larger cut-off value leads to more farms on selective therapy because of lower observed efficacies when selective therapy is effective in maintaining drug efficacy
- Fewer horses treated with a larger cut-off value
  - Cause of higher *S. vulgaris* prevalence

Discussion

- The first study on the dynamics of selective therapy and re-emergence of *S. vulgaris*
- Provide simulation evidence on the re-emergence of *S. vulgaris* when selective therapy is adopted in response to observed decrease in drug efficacy
- Show that a smaller treatment cut-off value (200) is as effective as a large cut-off value (400) in maintaining drug efficacy

Discussion – continue

- A larger treatment cut-off value (400) leads to lower observed efficacy, more farms on selective therapy, fewer horses treated, and a higher level of prevalence of *S. vulgaris*
- Future research on optimizing selective therapy treatment cut-off parameter via our simulation framework

Next steps

- Sensitive tests
  - Lack of data to fit models for temproal development of reduced drug efficacy and re-emergence of *S. vulgaris*
  - Lack of data to fit the NBINGARCH model for pre-treatment fecal egg count
  - Robust simulations of biological/ecological systems?
- Model horse exchanges between farms, which happen very frequently at a large scale and introduce a lot of variability in the process