



The Perfect Storm:

Factors that lead to increased transmission and resistance emergence of heartworm in the United States

Paige Miller¹, A.W. Park²

1. Gustavus Adolphus College; 2. Odum School of Ecology, University of Georgia



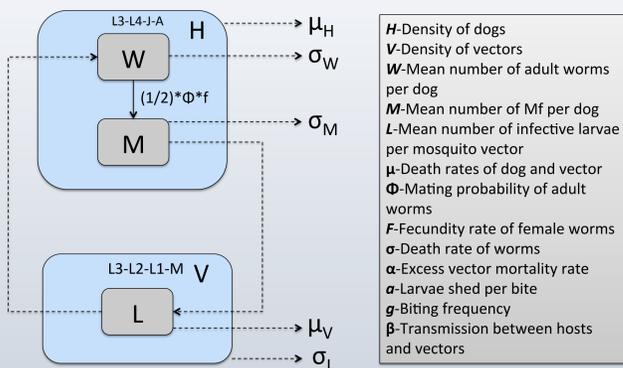
Overview

Macroparasites cause devastating human and animal diseases yet there is limited research concerning basic parasite biology, testing procedures, and disease transmission. Knowledge in these areas could lead to novel worm control treatments and possibly disease eradication. Heartworm disease, caused by *Dirofilaria immitis*, is observed globally but distributed heterogeneously. Distribution is thought to be affected by factors such as climate, pet and owner demographics, and mosquito habitat. Recent concerning evidence has suggested the establishment of drug resistant worms. Because only one class of drugs exists to treat heartworm, resistance would present a large problem. Two of the first models for heartworm disease dynamics and drug resistance emergence were developed in order to identify factors that could lead to higher rates of transmission and increased rates of resistance emergence.

Questions

- Can we model a vector-borne macroparasite population?
- Which factors lead to faster rate of resistance emergence?
- Will drug resistance ever become a problem in heartworm populations?
- What areas are most at risk for the emergence of drug resistance?
- Would drug alternation reduce the level of resistance allele fixation?

Model



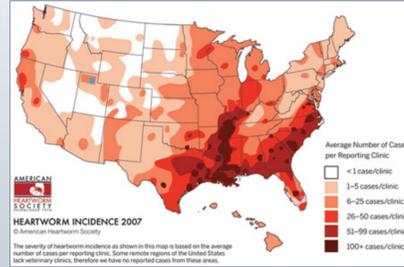
$$\frac{dW}{dt} = \left(\frac{V}{H}\right) \beta \delta_H L - W(\sigma_W + \mu_H)$$

$$\frac{dM}{dt} = \left(\frac{1}{2}\right) \phi F W - M(\sigma_M + \mu_H)$$

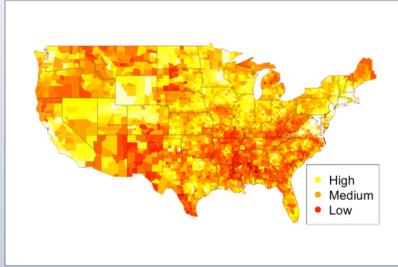
$$\frac{dL}{dt} = \beta \delta_V e^{(-LM)} M - L\left(\sigma_L + \mu_V + \alpha M + \frac{a}{g}\right)$$

Motivational Data

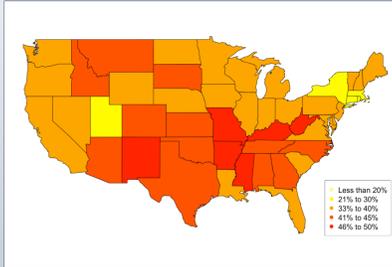
Heartworm incidence is high around the Mississippi delta



Median salary is lower in the South



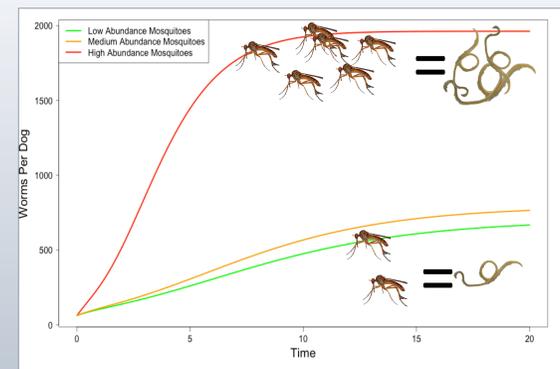
Higher Percentage of Dog Owners are in the South



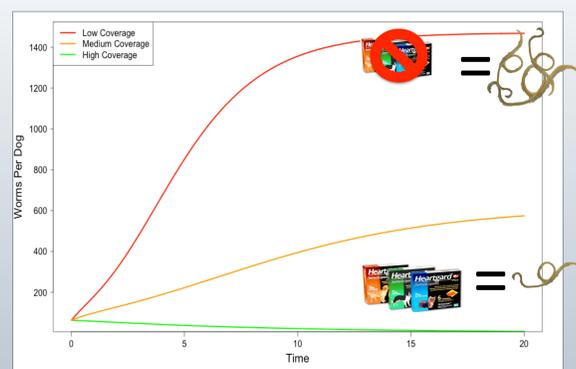
- Preliminary data suggests drug resistance establishment in heartworm populations in some areas (e.g. Mississippi delta region)
- Areas with low annual income and high dog populations (e.g. southern US) may have lower levels of compliance
- Areas with high year round temperature (e.g. southern US) are more conducive for mosquito development and heartworm transmission

Model Results

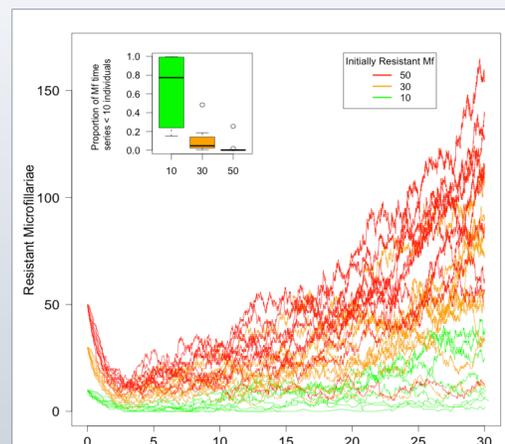
How does vector abundance affect worm burden?



How do coverage levels affect worm burden?

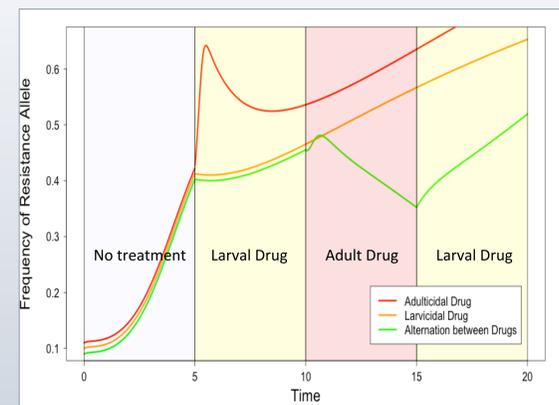


How does the size of initially resistant population affect probability of invasion?



- Size of a *de novo* mutated worm population is hard to predict and success of the allele depends on it
- Large founding populations (~50 worms) are able to survive initial bottleneck
- Small founding populations rarely invade and would most likely die out

How does drug alternation affect level of resistant allele fixation?



- Most heartworm drugs target the infective larval stage
- Adulticidal drugs also exist but are more expensive to purchase and can be harmful for the dog
- Individually, each treatment leads to higher fixation than the alternation of the two
- Manufacturing new drugs for heartworm will be crucial in order to halt drug resistance from fixating at high levels

Conclusions

- We developed some of the first heartworm specific transmission models
- Collectively, these models help to identify factors and regions that are associated with successful and rapid establishment of drug resistant heartworm populations
- High vector abundance and low coverage levels lead to higher average worm burdens
- Large populations of initially resistant microfilariae are more likely to persist
- Drug alternation strategies present a way to keep resistance at low levels in the population
- Anthelmintic resistance has already become a major problem for many animal populations and is a looming threat for both heartworm and human diseases
- These models could apply to understanding mechanisms of human anthelmintic resistance emergence

Future Research

- How do refugia populations and proximity to domestic dogs affect transmission dynamics?
- How does gene flow between subpopulations of heartworm lead to higher rates of resistance emergence?
- How does seasonality, drought, and climate affect worm transmission?
- Present management programs for resistance emergence control (e.g. benefit of improved compliance, mosquito control programs)
- Make predictions about human anthelmintic resistance

Acknowledgements

- National Science Foundation
- University of Georgia
- Dr. Ray Kaplan

References

- Bowman and Atkins, "Heartworm Biology, Treatment, and Control." 2009.
- Courtney, "Heartworm Transmission in the Deep South: Climatologic Considerations." 2002.
- Brown et al., "Key Factors Influencing Canine Heartworm, *Dirofilaria immitis*, in the United States." 2012.
- Bowman, "Heartworms, Macrocyclic Lactones, and the Specter of Resistance to Prevention in the United States." 2012.
- American Veterinary Medical Association, *U.S. Pet Ownership Demographics Sourcebook*. 2012.
- Wolstenholme, et. al. "Drug resistance in veterinary helminths". 2004.