Effectiveness of fluralaner treatment regimens for the control of canine Chagas disease: A mathematical modeling study

Edem Fiatsonu and Dr. Martial Ndeffo Mbah

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Overview

- ✓ Named after the Brazilian doctor Carlos Chagas, who discovered the disease in 1909.
- ✓ Caused by the parasite *Trypanosoma cruzi*
- ✓ Parasites transmitted to animals and humans by insect vectors (“Kissing Bugs”)
- ✓ The insects are found only in the Americas
  - ✓ Insects & diseases also occur in the southern US, south Texas appears to be a hotspot
- ✓ *T. cruzi* can cause cardiac damage and long-term heart disease and death in humans, dogs, and other mammals.

Data/Statistics:

Chagas in the Americas

It is estimated that in the Region:

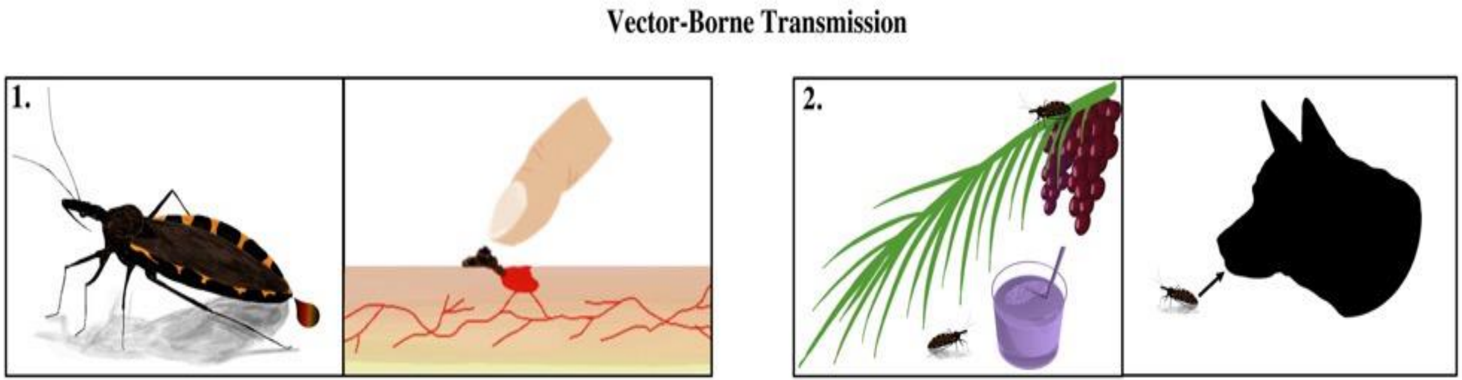
The disease is endemic in **21** countries, and affects **6 million** people

About **70 million** people are at risk of becoming infected

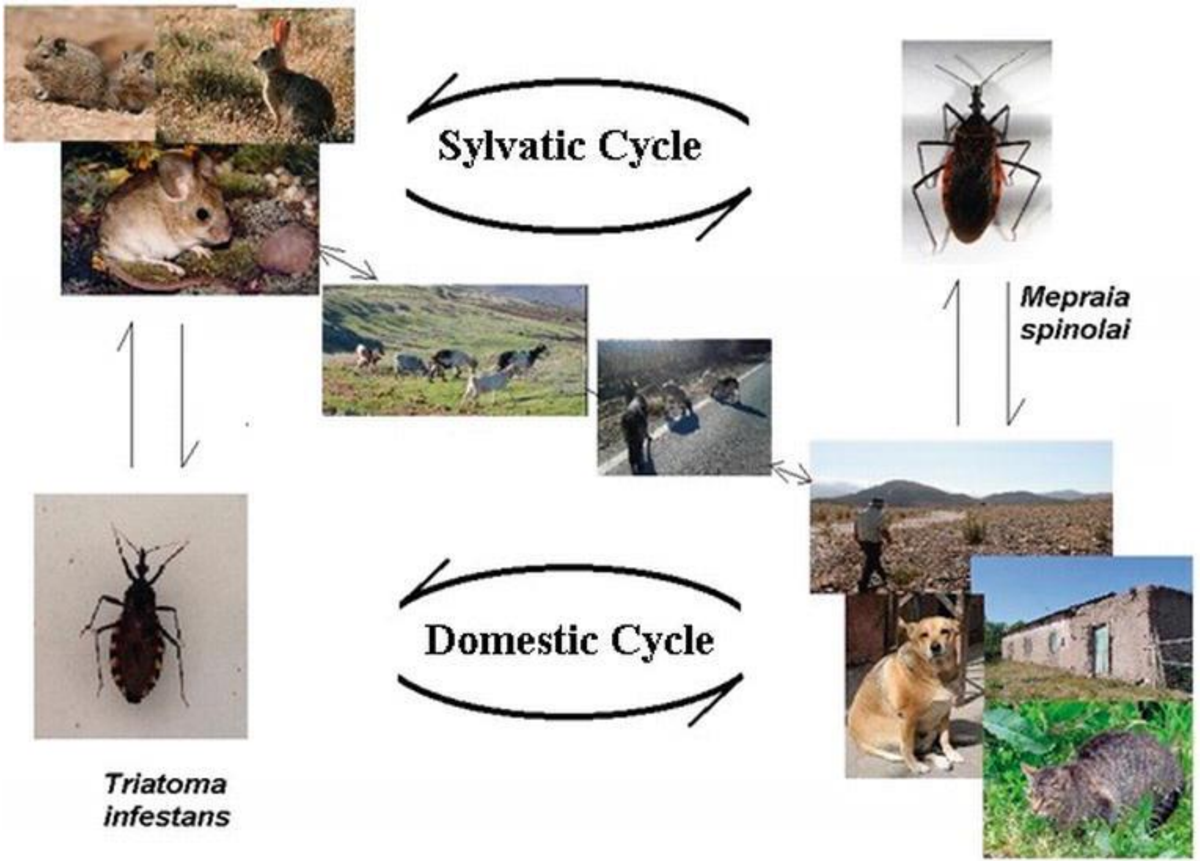
6 million people are already infected, with **30 thousand** new cases annually for all forms of transmission,

causing **12 thousand** annual deaths

Vector-Borne *T. cruzi* infection Transmission



Domestic/Sylvatic Vectors



Zecca and Hamer, Maxcy-Rosenau-Last Public Health 2019

Impact of seasonality on triatomine

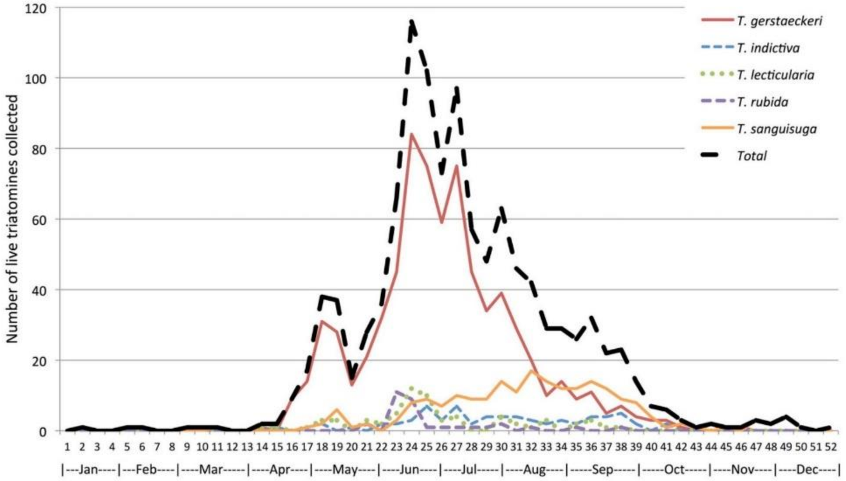
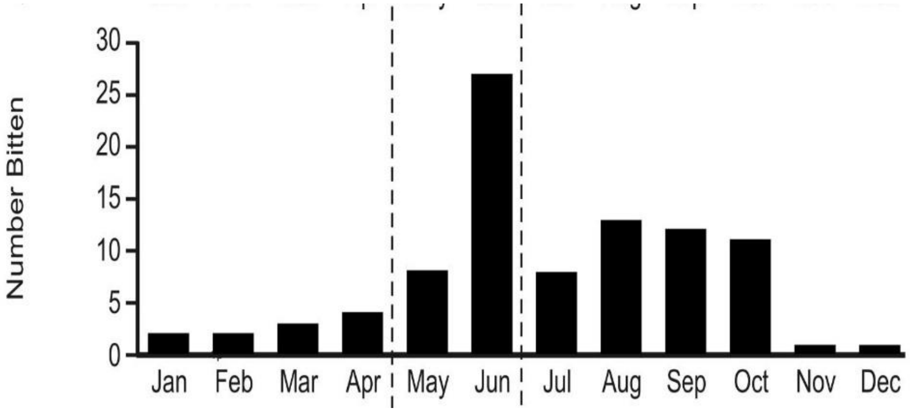


FIGURE 1. Phenology of collection of live triatomines of five species. Seasonal occurrence of five species of triatomines (and the total of those five species) collected alive by citizen scientists in Texas, 2012–2016. Of 39 specimens collected from November through March, 36 had locations specified, of which 27 (75.0%) were found indoors. In addition, four were found outdoors near animal quarters, including three in dog kennels and one in a chicken coop. This figure appears in color at www.ajtmh.org.

Seasonal Occurrence of triatomines



John H Klotz et al (2010)

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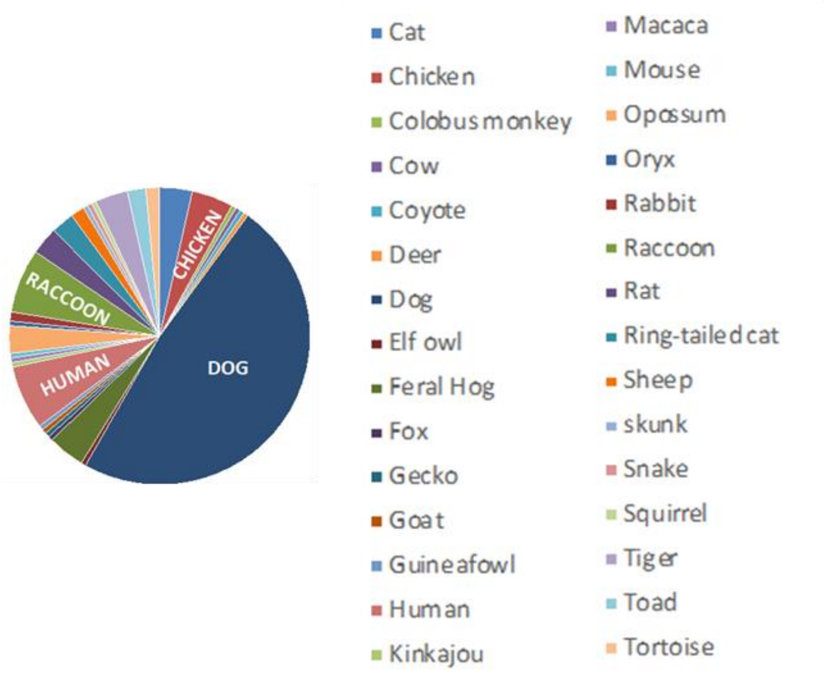
Chagas disease in dogs of Texas

Hamer Lab community science data

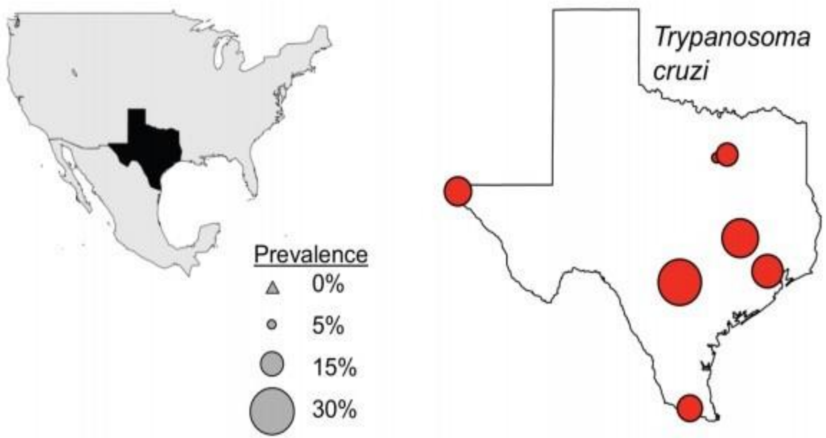


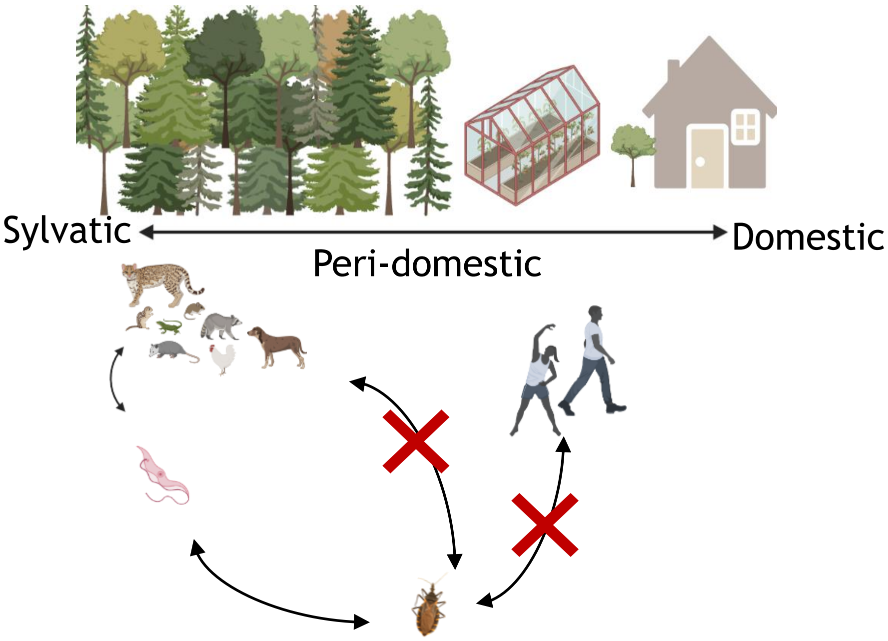
Increasingly recognized in dogs and other mammals

Seroprevalence in dogs in Texas

- ✓ 6-13% in TX shelter dogs; >50% in some kennels (*Meyers et al PLOS Neg Trop Dis 2017*)
- ✓ Detected in all ecoregions in Texas (*Meyers et al J Vet Intern Med 2019*)
- ✓ Odds of infection are greater for dogs with an infected housemate or littermate
- ✓ RGV Colonias infection range 20-55.9%

The best prevention is to interrupt the transmission





Effectiveness of fluralaner treatment regimens for the control of canine Chagas disease: A mathematical modeling study

Aims: To evaluate the effectiveness of fluralaner treatment regimens for the control of canine Chagas disease, create different scenarios and inform the best treatment regimen.

Research Objectives

- ✓ To develop and build mathematical model to describe vector-host interactions.
- ✓ To investigate the efficacy of different fluralaner treatment regimens in 3 endemic transmission settings (high, medium & low) among dog population.
- ✓ To examine the impact of Triatomine migration between domestic and sylvatic settings.

Fiatsonu E, Busselman RE, Hamer GL, Hamer SA, Ndeffo-Mbah ML (2023) Effectiveness of fluralaner treatment regimens for the control of canine Chagas disease: A mathematical modeling study. PLoS Negl Trop Dis 17(1): e0011084. https://doi.org/10.1371/journal.pntd.0011084

Methods

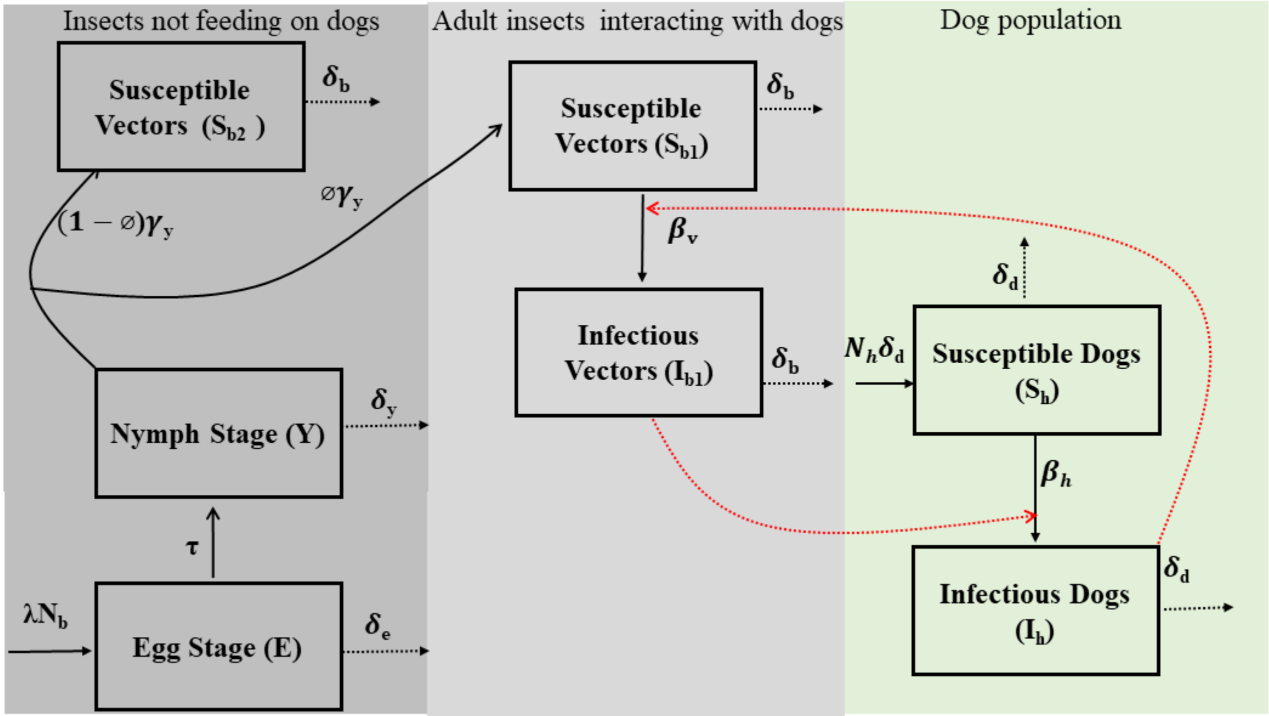
- The three vector-host Susceptible-Infected models developed
  - A baseline model that does not account for the impact of seasonality on triatomine dynamics
  - A model that accounts for the impact of seasonality on triatomine dynamics
  - A model that account for the movement of triatomine between peri domestic and sylvatic

Table 1: Key model input parameters, symbol, value, and reference

Parameter	Symbols	Value
Proportion of adult triatomines feeding at least once on dogs	$\varnothing^*$	0.95
Carrying capacity	K^*	37018.vec/km^2
Triatomine per-female egg production	λ	475/yr
Egg hatching rate	τ	23.7/yr
Nymph maturity rate	γy	1.73/yr
Egg mortality rate	δe	0.36/yr
Nymph mortality rate	δy	1.46/yr
Adult triatomine mortality rate	δ_b	0.56/yr
Triatomine population density	Nb	31600.vec/km^2
Probability of vector infection per bite on infectious dog	ρ	0.3082
Dog mortality rate	δ_d	0.1/yr
Dog population density	N_h	1000.host/km^2

All values are obtained from published literature except for ($\varnothing^*$) and K^*

Model without treatment



S_{b2}--Susceptible vectors not feeding on dogs

S_{b1}--Susceptible vectors feeding on dogs at least once

T.cruzi transmission

System of non-linear ordinary differential equations

$$\frac{dE}{dt} = \lambda Nb - \tau E - \delta_e E \qquad \text{1a}$$

$$\frac{dY}{dt} = \tau E\left(1 - \frac{Y+Nb}{K}\right) - \gamma_y Y - \delta_y Y \qquad \text{1b}$$

$$\frac{dS_{b1}}{dt} = \phi\gamma_y Y - \beta_v S_{b1}\frac{I_h}{N_h} - \delta_b S_{b1} \qquad \text{1c}$$

$$\frac{dI_{b1}}{dt} = \beta_v S_{b1}\frac{I_h}{N_h} - \delta_b I_{b1} \qquad \text{1d}$$

$$\frac{dS_{b2}}{dt} = (1-\phi)\gamma_y Y - \delta_b S_{b2} \qquad \text{1e}$$

$$\frac{dS_h}{dt} = \delta_d N_h - \beta_h S_h \frac{I_{b1}}{N_{b1}} - \delta_d S_h \qquad \text{1f}$$

$$\frac{dI_h}{dt} = \beta_h S_h \frac{I_{b1}}{N_{b1}} - \delta_d I_h \qquad \text{1g}$$

The impact of seasonality is negligible

Trypanosoma cruzi infection prevalence and transmission rates

Table 2: Transmission rates estimate for high, medium, and low prevalence

Description	Variable	High	Medium	Low
Dog prevalence	id	0.30	0.15	0.08
Triatomine prevalence	ib	0.56	0.25	0.13
Annual host transmission rate (1/year)	β_h	0.0745	0.0687	0.0651
Annual vector transmission rate (1/year)	βv	2.5351	1.2941	1.0823

The values for the prevalence are justified based on empirical data

Key Notes

The behavior of triatomine bugs has two seasonality functions defined;

- the nymph’s maturation rate at time t
- the transmission rate at time t

The functional form of seasonality

We define the maturation rate as a stepwise function:

$$\gamma_y(t) = \gamma_y{}^0 g(t, \varepsilon) \text{ With } \int_0^1 g(t, \varepsilon)dt = 1$$

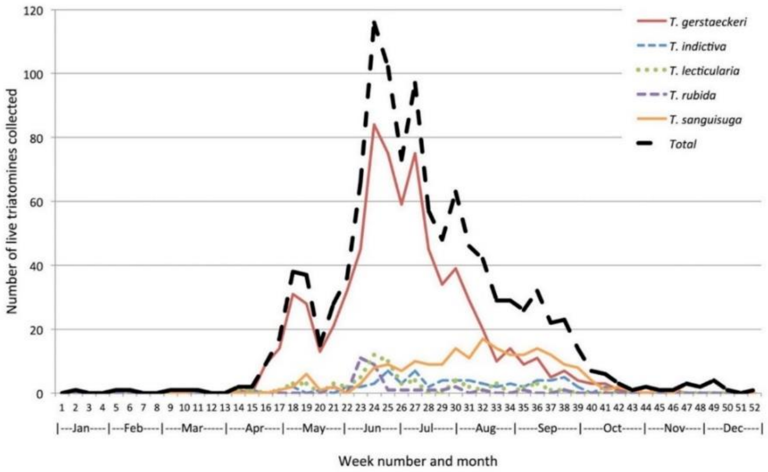
$\boldsymbol{\varepsilon}$ is the relative activity level of triatomines during summer and fall compared to spring.

$$\beta_v(t) = \beta_v{}^0 h(t) \text{ and } \beta_h(t) = \beta_h{}^0 h(t)$$

$$\int_0^1 h(t)dt = 1$$

Annual transmission rates when seasonality is negligible.

Seasonal Occurrence of triatomines



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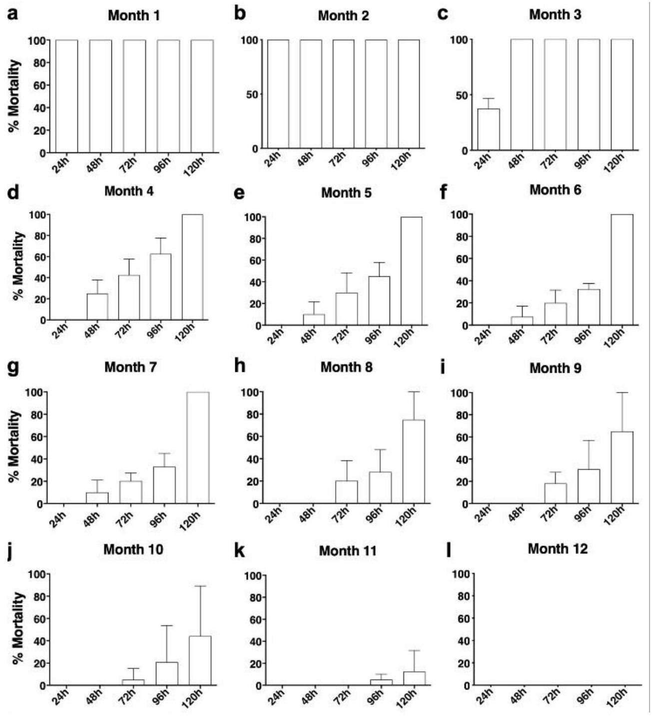
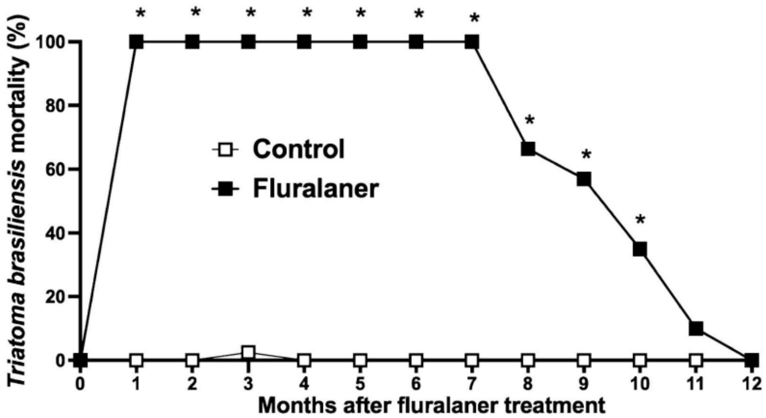
Experiment on dogs with fluralaner bravecto treatment in a laboratory setting

Tamyres Bernadete Dantas Queiroga et al (2021)

Time to achieve full insecticidal efficacy of fluralaner



Tamyres Bernadete Dantas Queiroga et al (2021)



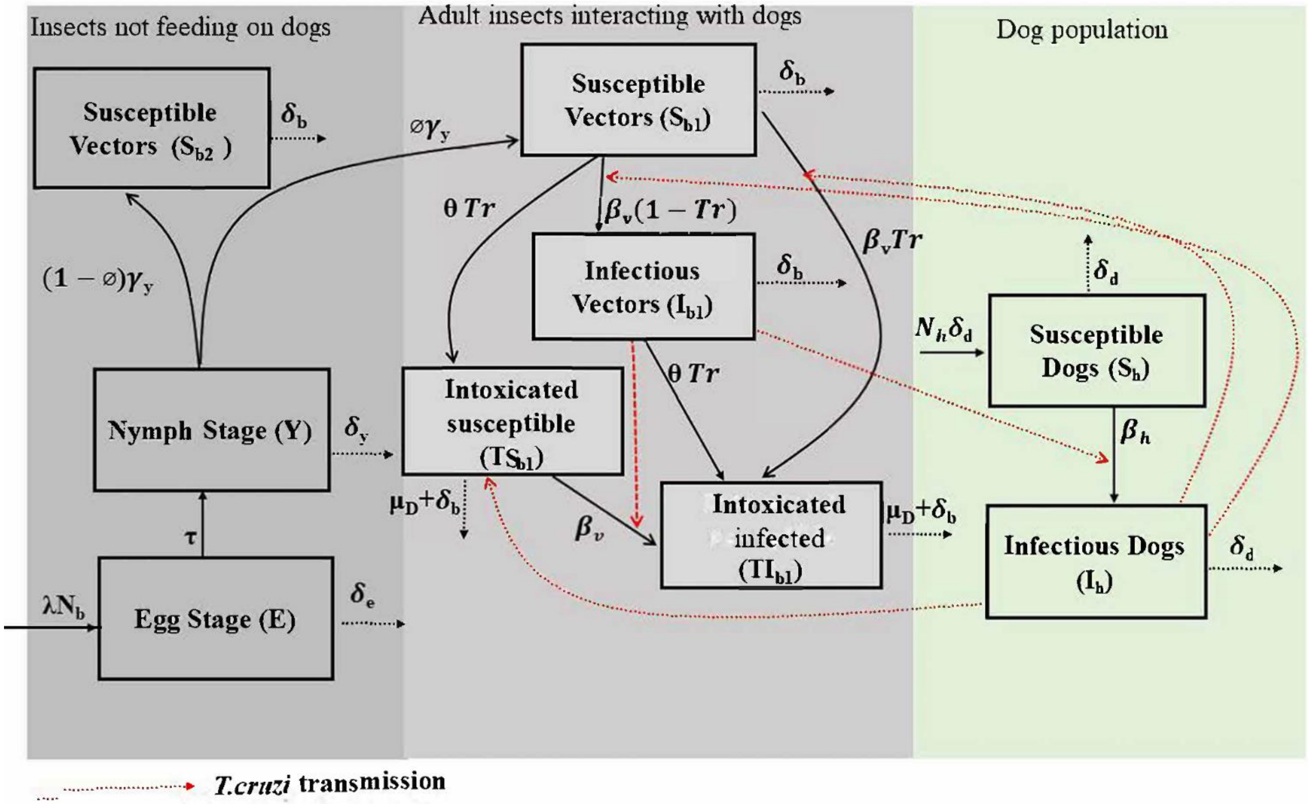
When 100% mortality is achieved post-exposure

- Within 1 day for 1st and 2nd month
- 2 days in the 3rd month
- 5 days in the 4th 5th 6th and 7th month

Triatomines mortality 5 days post-blood meals

- 66% in the 8th month, 57% in the 9th month
- 35% in the 10th month, 10% in the 11th month
- 0% in the 12th month

Model with treatment



Spatial coupled model

$$\frac{dE}{dt} = \lambda Nb - \tau E - \delta_e E$$ 3a

$$\frac{dY}{dt} = \tau E\left(1 - \frac{Y+Nb}{K}\right) - \gamma_y(t)Y - \delta_y Y$$ 3b

$$\frac{dS_{b1}}{dt} = \phi\gamma_y(t)Y - \beta_v(t)S_{b1}\frac{I_h}{N_h} - \delta_b S_{b1} - \eta(t)S_{b1} + \zeta(t)\,\phi S_{bw}$$ 3c

$$\frac{dI_{b1}}{dt} = \beta_v(t)S_{b1}\frac{I_h}{N_h} - \delta_b I_{b1} - \eta(t)S_{b1} + \zeta(t)\,S_{bw}$$ 3d

$$\frac{dS_{b2}}{dt} = (1-\phi)\gamma_y(t)Y - \delta_b S_{b2} - \eta(t)S_{b1} + \zeta(t)(1-\phi)S_{bw}$$ 3e

$$\frac{dS_h}{dt} = \delta_d N_h - \beta_h(t)S_h\frac{I_{b1}}{N_{b1}} - \delta_d S_h$$ 3f

$$\frac{dI_h}{dt} = \beta_h(t)S_h\frac{I_{b1}}{N_{b1}} - \delta_d I_h$$ 3g

$$\frac{dE_w}{dt} = \lambda Nb - \tau Ew - \delta_e E_w$$ 3h

$$\frac{dY}{dt} = \tau Ew\left(1 - \frac{Y_w+Nb}{K}\right) - \gamma_y(t)Y_w - \delta_y Y_w$$ 3i

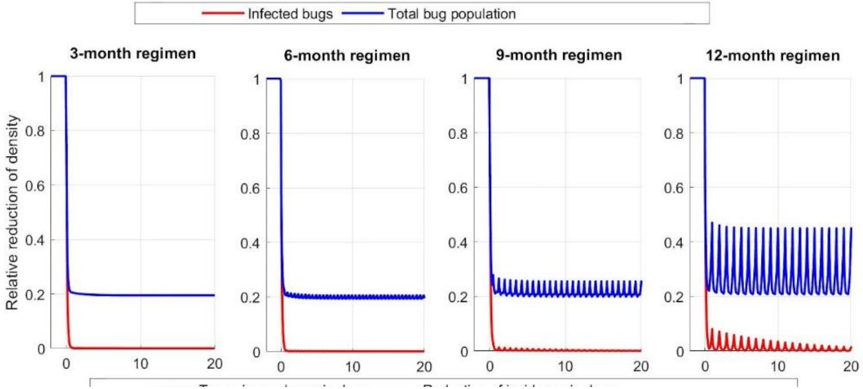
$$\frac{dS_{bw}}{dt} = \phi\gamma_y(t)Y_w - \beta_{vw}(t)S_{bw}\frac{I_w}{N_w} - \delta_b S_{bw} + \eta(t)(S_{b1}+S_{b2}) - \zeta(t)\,S_{bw}$$ 3j

$$\frac{dI_{bw}}{dt} = \beta_{vw}(t)S_{bw}\frac{Iw}{N_w} - \delta_b I_{bw} + \eta(t)S_{b1} - \zeta(t)\,I_{bw}$$ 3k

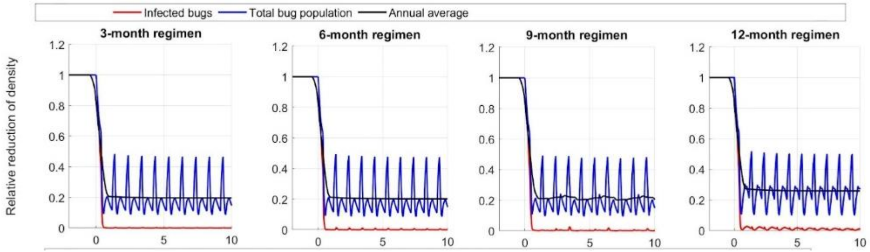
$$\frac{dS_w}{dt} = \delta_w(Sw + Iw) - \beta_{hw}(t)S_w\frac{S_w I_{bw}}{S_w + Iw} - \delta_w S_w$$ 3l

$$\frac{dI_w}{dt} = \beta_{hw}(t)S_w\frac{S_w I_{bw}}{S_w + Iw} - \delta_w I_w$$ 3m

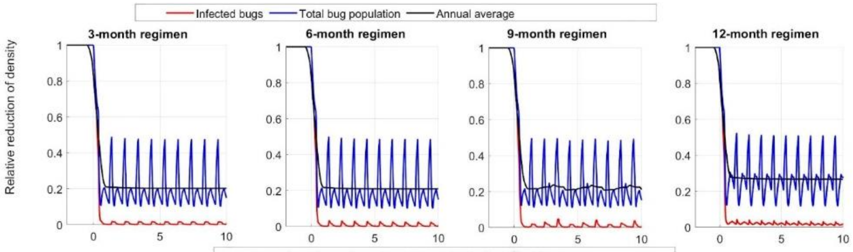
Single vector-host model without seasonality



Single vector-host model with seasonality



Spatial coupled model



- ✓ **Without seasonality impact**, the bug's population density reduced average by 80.4%, 75.8%, 74.4%, and 66.4% respectively for the regimens
- ✓ **With seasonality impact**, triatomine density, the triatomine population density was reduced on average by 80.4%, 79.8%, 78.3%, and 74.1%
- ✓ In The **spatially coupled scenario**; the bug's population density was reduced on average by 79.7%, 79.7, 77.2%, and 72.4%

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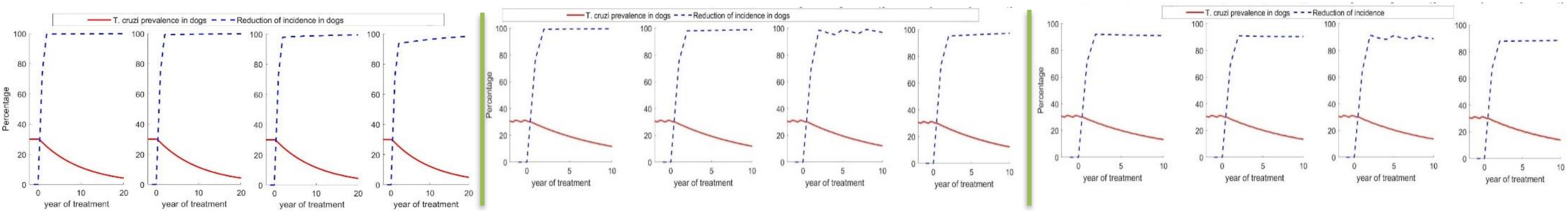
Effectiveness of systemic insecticide treatment of dogs with fluralaner for the control of canine Chagas in a high transmission setting



Reduction of *T. cruzi* prevalence among a dog population given different treatment regimens of a systematic insecticide in the high transmission setting

Regimen	Year	% reduction
3-month	5	37.70 %
	10	63.13 %
6-month	5	37.57 %
	10	61.97 %
9-month	5	37.10 %
	10	61.37 %
12-month	5	35.70 %
	10	59.37 %

Without seasonality

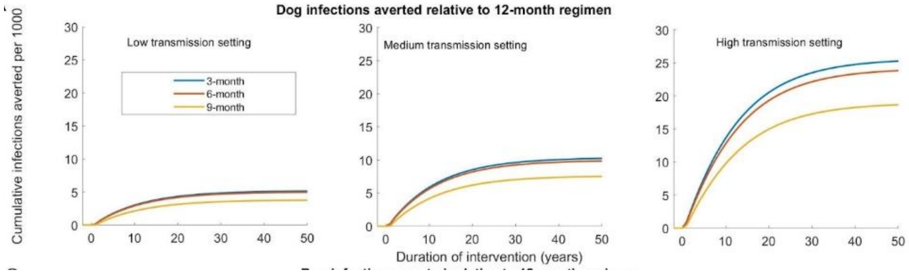
Regimen	Year	% reduction
3-month	5	36.20 %
	10	61.13 %
6-month	5	35.73 %
	10	60.50 %
9-month	5	35.03 %
	10	59.60 %
12-month	5	34.70 %
	10	59.13 %

Seasonality

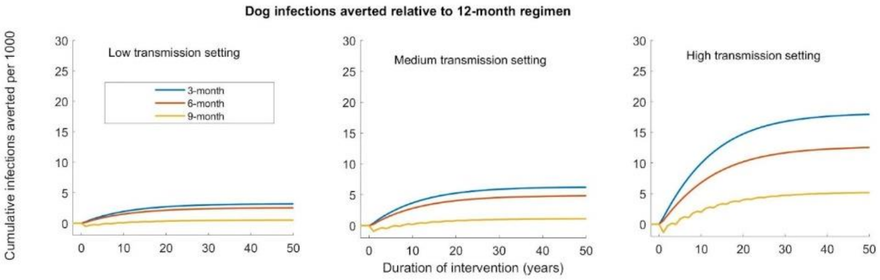
Regimen	Year	% reduction
3-month	5	33.20 %
	10	55.97 %
6-month	5	32.73 %
	10	55.33 %
9-month	5	32.13 %
	10	54.57 %
12-month	5	31.67 %
	10	53.87 %

Spatial coupled

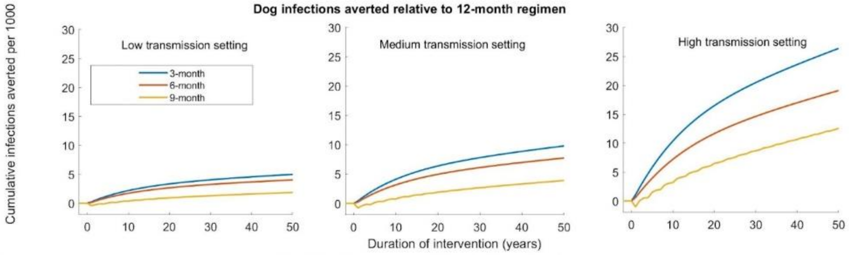
Infections Averted Relative to 12-Month Regimen



Single vector-host model without seasonality



Single vector-host model (Svh) with seasonality



Spatially coupled model

Average *T. cruzi* infections averted after 10 years of treatment:

- ✓ Svh without seasonality, there are 14, 13, and 10 per 1000 dogs.
- ✓ Svh with seasonality, there are 10, 7, and 2 per 1000 dogs adverted
- ✓ With spatial coupled, there are 11, 8, and 4 per 1000 dogs averted

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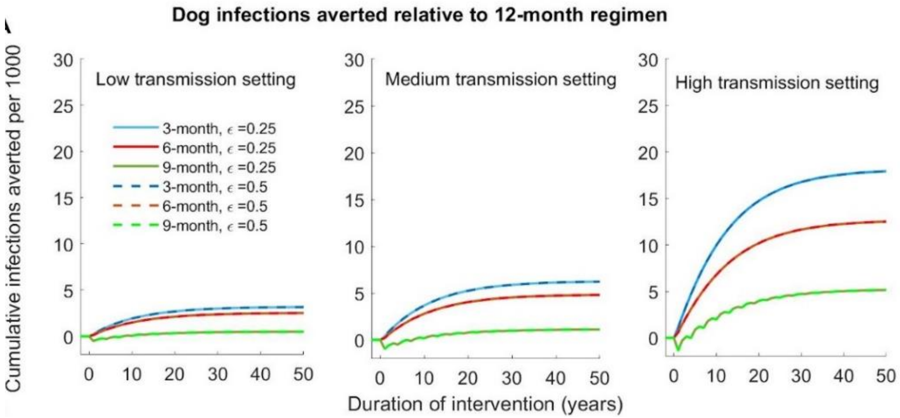
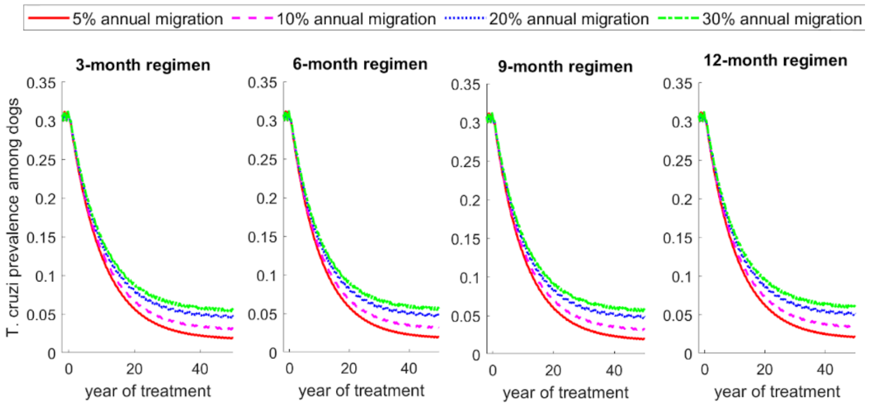
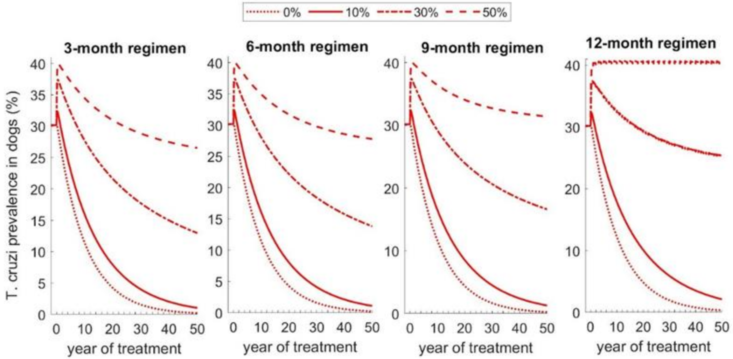
Relative activity level of triatomines during summer and fall compared to spring



T. Cruzi prevalence among dogs with varying migration rates



Impact of varying consumption rate of dead triatomines by dogs on *T. cruzi* prevalence



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Conclusion

- ✓ Our analysis shows that treating dogs every three to six months could be an effective measure to reduce *T. cruzi* infections in dogs and triatomines in peri-domestic transmission settings.
- ✓ We show that canine and triatomine *T. cruzi* infections may be substantially averted with the routine use of systemic insecticides.

- ✓ In low and medium transmission settings, less frequent treatment may be sufficient to reduce T. cruzi in dogs and triatomines compared to high transmission settings.

- ✓ The use of systemic insecticides may potentially increase canine *T. cruzi* infections if increased triatomine mortality results in a substantial increase in dog's oral consumption of dead triatomines.

What need to be done in the future?

- ✓ Further studies at the local scale are needed to better understand the potential impact of routine use of fluralaner treatment on increasing dogs' consumption of dead triatomines.

- ✓ A study is needed to model Latin American settings where there are a lot of stray dogs. The previous study modeled a scenario where dogs are domestic and treated frequently.

    - ✓ What is the impact of stray dogs on the effectiveness of insecticide treatment of dogs?
    - ✓ Cost-effectiveness analysis of administering treatment in this scenario.

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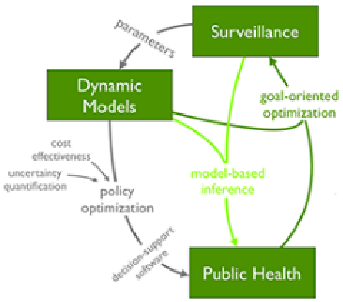
Ndeffo Laboratory



Epidemiological Modeling of Infectious Disease Dynamics

Collaborators

Sarah Hamer, MS, PhD,
Gabriel Hamer, PhD
Rachel Busselman

Texas A&M Veterinary Medicine & Biomedical Sciences

Thank you!

Question????

Contact Information
Edem Fiatsonu
mailto:e.fiatsonu@tamu.edu