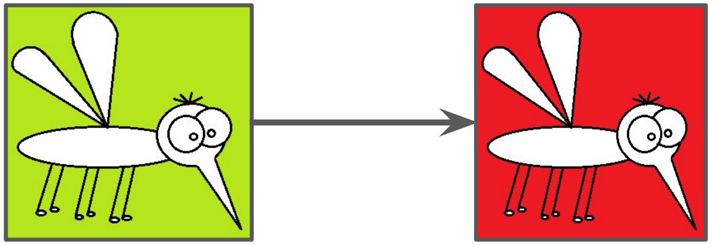
Spatio-temporal modelling of visceral leishmaniasis (VL) among domestic dogs in rural Brazil

Elizabeth Buckingham-Jeffery[1] (@Ebucksjeff)
& Edward Hill[2] (@EdMHill)

[1] School of Mathematics, The University of Manchester.
[2] Zeeman Institute: SBIDER, University of Warwick.

Zoonotic VL

- A vector-borne disease spread by **sandflies**.



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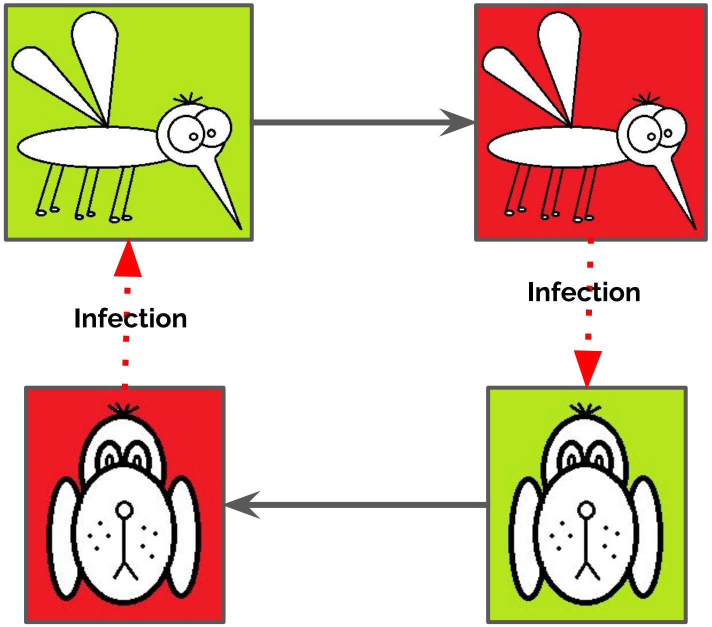
- In Brazil, **domestic dogs** are the main reservoir.



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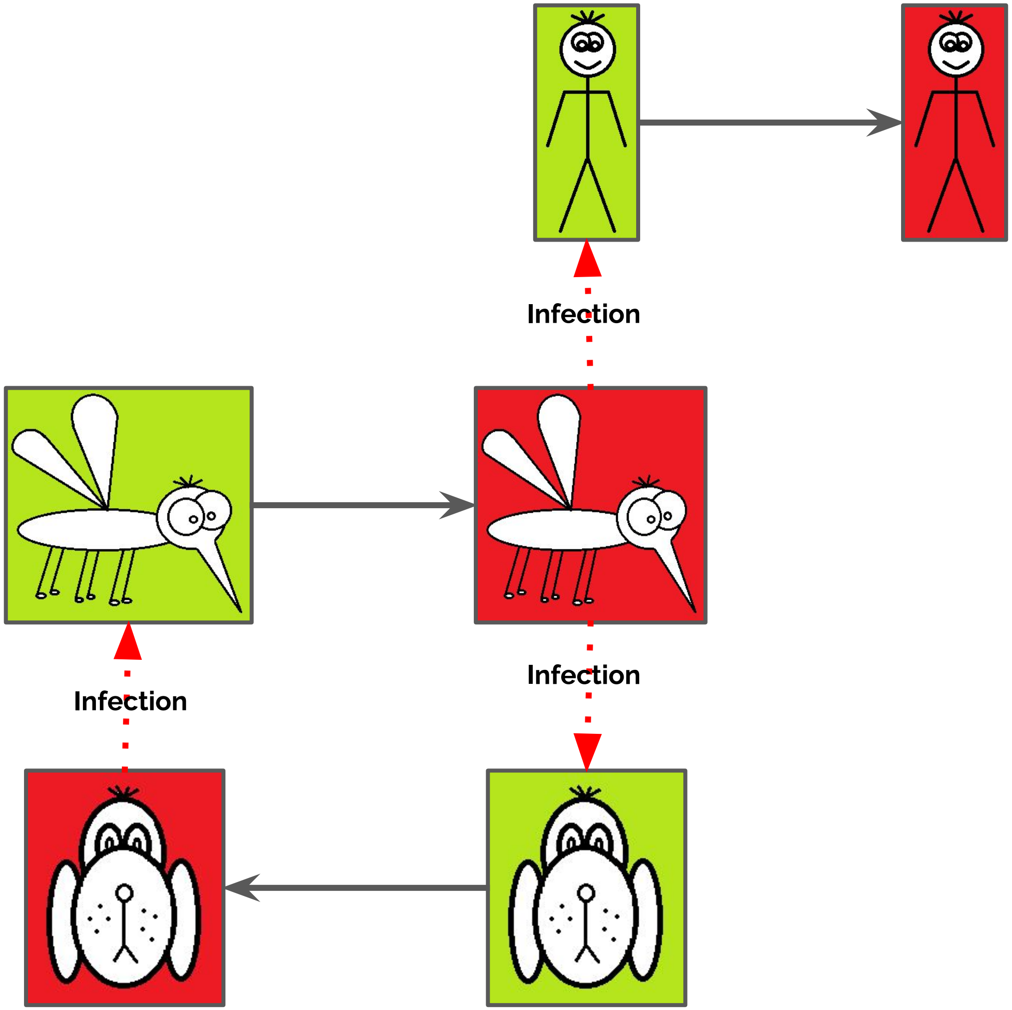
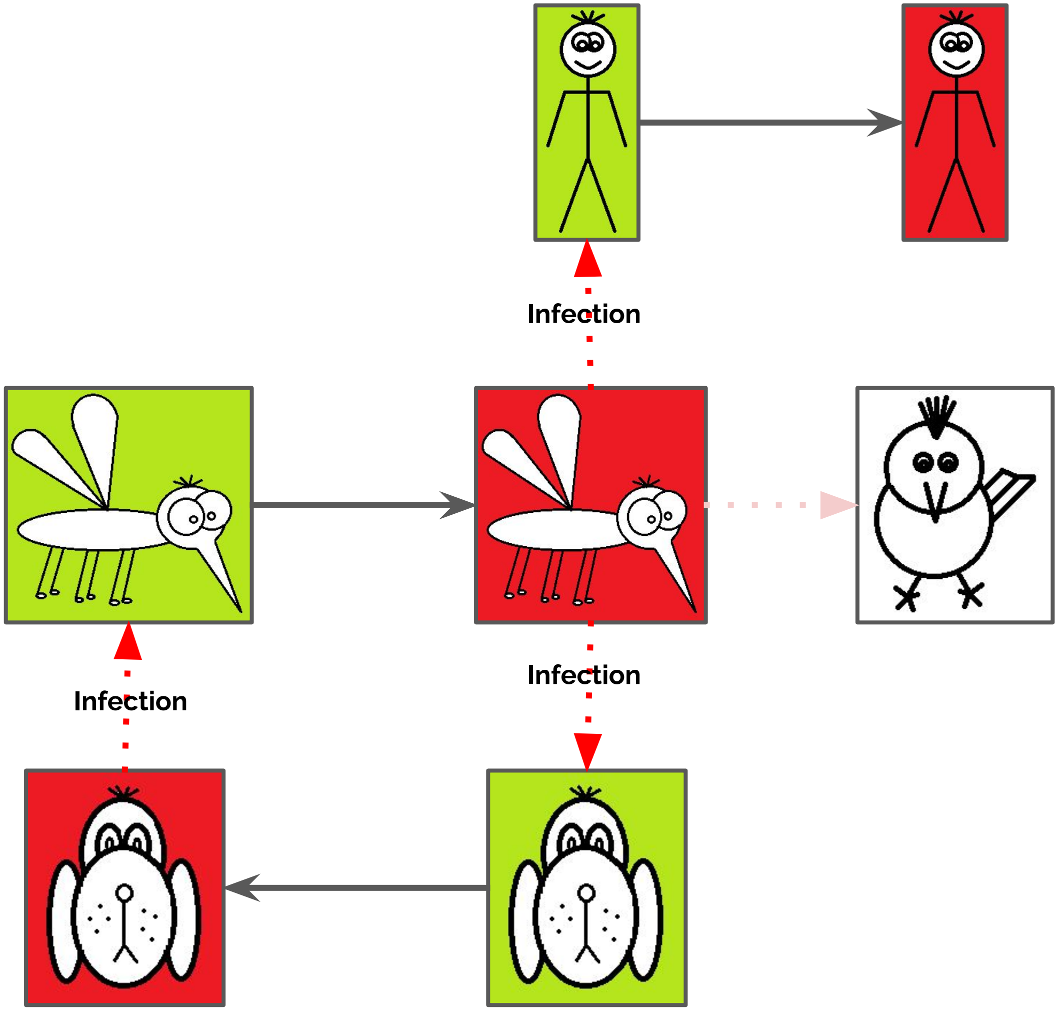


Zoonotic VL

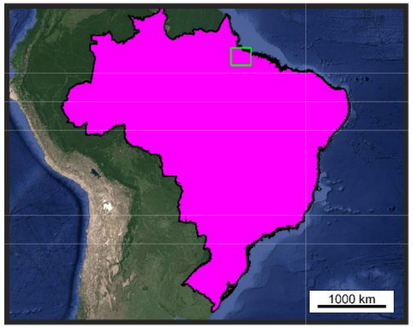
- A vector-borne disease spread by **sandflies**.
- In Brazil, **domestic dogs** are the main reservoir.
- **Human infection** alone cannot maintain transmission.
- Sandflies feed on other dead-end hosts: for example, **chickens.**



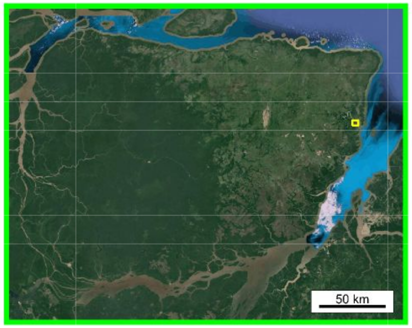
VL in Brazil

- VL is endemic in parts of Brazil.
- Serological studies have estimated **prevalence in dogs** to range between 25% and 50% in endemic northern regions.
- The number of **human cases has increased rapidly** in the last 30 years: 3,500 reported cases per year, 4,200 - 6,300 with underreporting.

Marajó island, north Brazil.



Calderao village, Marajo



Households within Calderao

Previous VL models

Table 1. Summary of VL modelling papers

	Refs																							
	Anthroponotic studies								Zoonotic studies															
	[16]	[61]	[13]	[62]	[10][a]	[17]	[12][a]	[11][a]	[63]	[57]	[40]	[64]	[65]	[41]	[58]	[66]	[67]	[42]	[28][b]	[29][b]	[14]	[15][b]	[68]	[59]
Model structure																								
Deterministic	✓[c]		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Host-only	✓	✓		✓		✓			✓			✓	✓	✓	✓		✓							✓
Assumption																								
Asymptomatic humans					✓	✓	✓	✓																
PKDL					✓	✓	✓	✓											✓	✓		✓		
Humans	✓	✓	✓	✓	✓	✓	✓	✓				†					†	†	✓	✓		✓	✓	
Asymptomatic dogs										✓					✓									✓
Spatial aspects																					✓	✓		
Seasonality											✓		✓	✓				✓						
Intervention																								
Human treatment		✓	✓	✓	✓	✓	✓	✓											✓	✓		✓		
Human vaccination						✓						✓										✓		
Vector control					✓			✓				✓								✓			✓	
Dog culling															✓	✓	✓						✓	✓
Dog collar																✓							✓	
Dog treatment												✓									*		✓	
Dog vaccination												✓											✓	
Region	India	Sudan	India	ISC	ISC	India	India	ISC	France	–	–	Brazil/ Malta	-	Brazil	Brazil	Brazil	Brazil	Morocco	Sudan	–	France	–	Brazil	Brazil

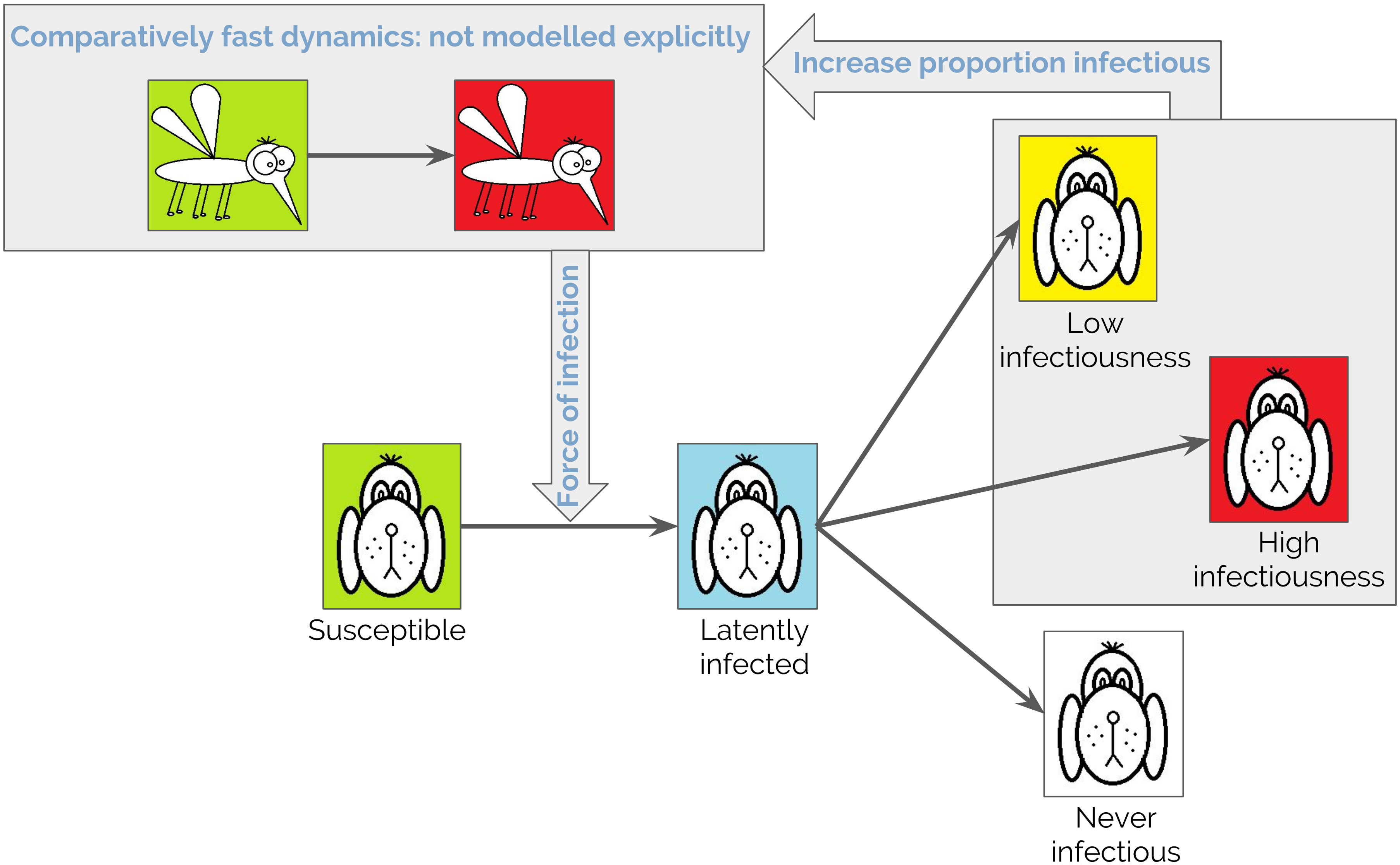
[a]Denotes studies by Stauch *et al.* that use the same basic model.

[b]Denotes studies by ELmojtaba *et al.* that use the same basic model.

[c]✓, included in model; †, dead-end hosts; *, implicitly included in other terms; –, unclear or unknown region.

<u>Reference</u>:
K.S.Rock et al (2015) Uniting mathematics and biology for control of visceral leishmaniasis. *Trends in Parasitology*, **31**(6):251-259..

Our spatial modelling framework



Force of infection breakdown

- **Probability of** susceptible dog at household *h* **becoming infected** on day *t*:

$$p_h(t) = 1 - e^{-\lambda_h(t)}$$

- **Force of infection** comprised five components:

$$\lambda_h(t) = \alpha \times \delta \times L_h(t) \times \eta_{h,\text{dog}}(t) \times \phi_h(t)$$

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Daily biting rate of sandflies.

Probability of parasite transmission to dog from an infected bite.

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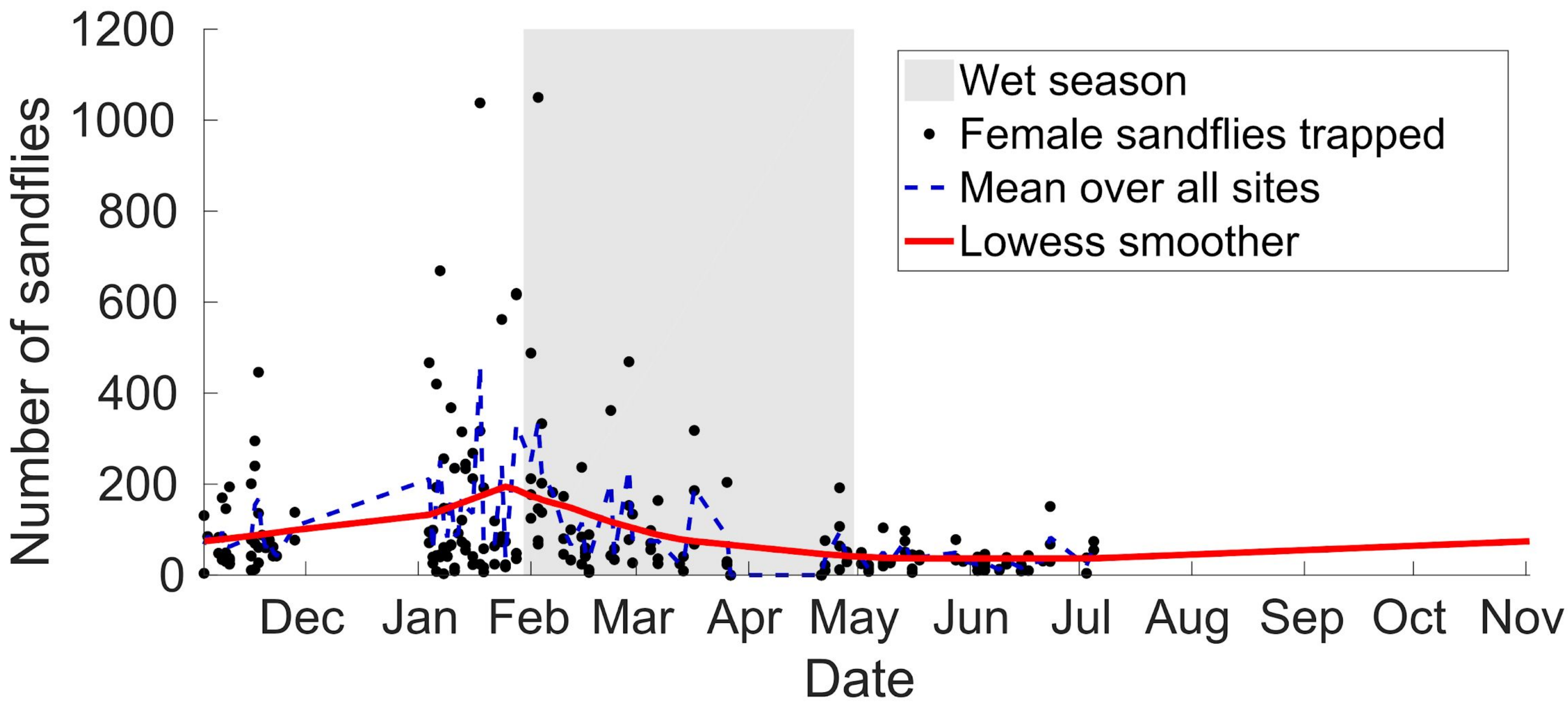
Daily biting rate of sandflies.

Sandfly abundance

Probability of parasite transmission to dog from an infected bite.

Figure 1: Seasonality of sandfly abundance



- **Peak in January,** at the transition from the dry to wet season.
- Minimum attained in May-June.

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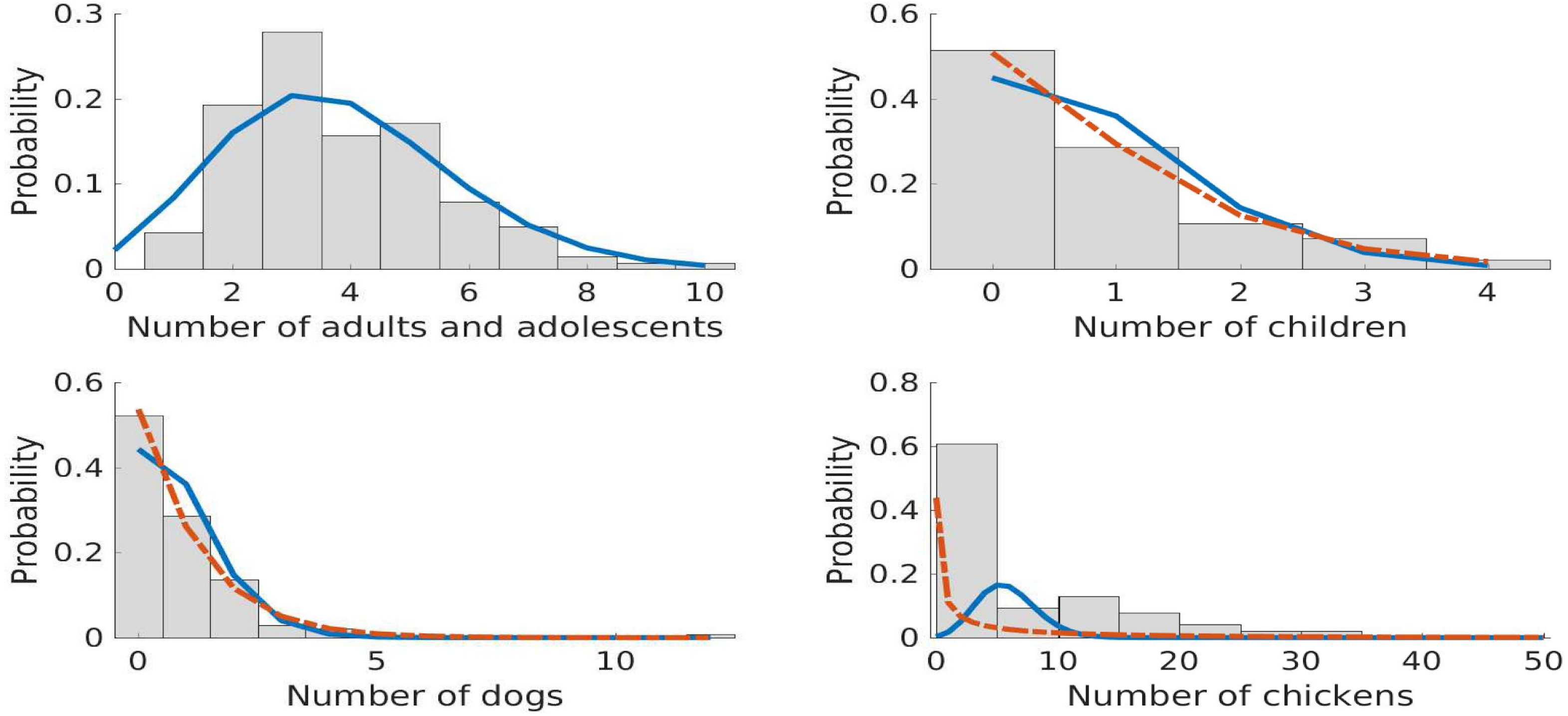
Host preference towards dogs

Figure 2: Distributions of the number of hosts per household. Empirical data (bars), best fit Poisson distributions (blue, solid line) and negative binomial distributions (red, dashed line)



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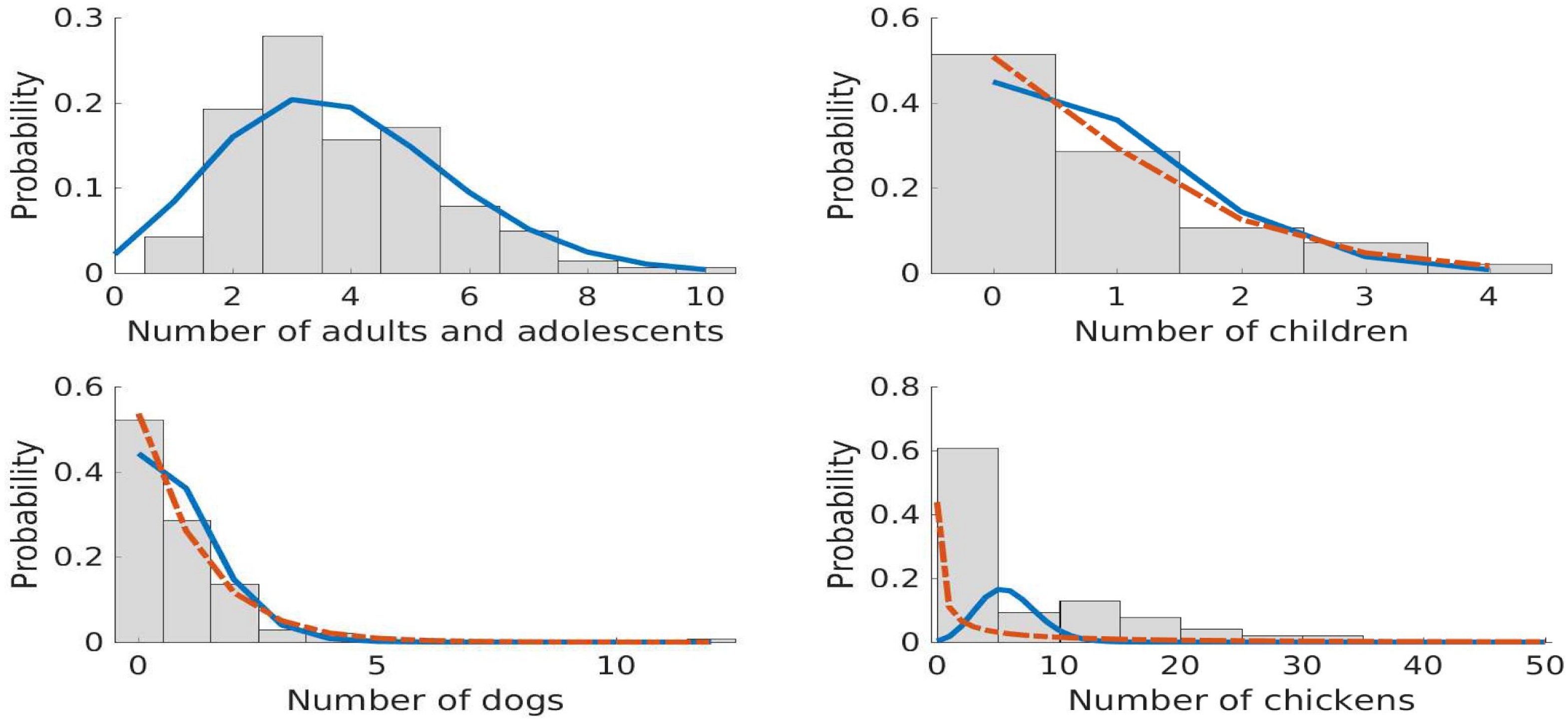

- Sandfly biting preference towards host of interest drew on field and laboratory experiments.

Reference: R.J. Quinnel et al (1992) Host preferences of the phlebotomine sandfly Lutzomyia longipalpis in Amazonian Brazil. *Med. Vet. Entomol*, **6**(3):195-200.

Force of infection breakdown

- **Probability of** susceptible dog at household *h* **becoming infected** on day *t*:

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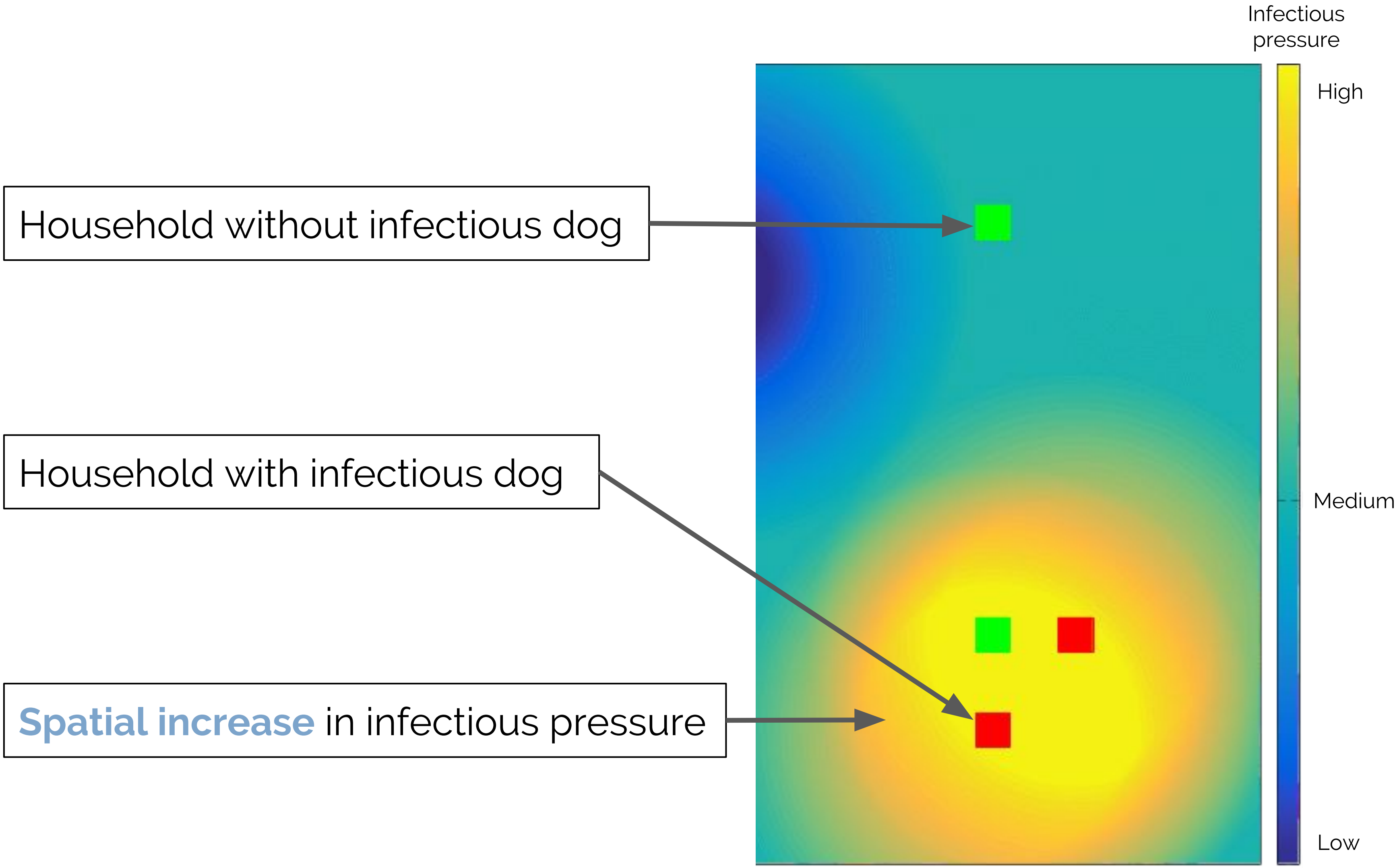
$$\lambda_h(t) = \alpha \times \delta \times L_h(t) \times \eta_{h,\text{dog}}(t) \times \phi_h(t)$$

- α: Daily biting rate of sandflies.
- δ: Probability of parasite transmission to dog from an infected bite.
- $L_h(t)$: Sandfly abundance
- $\eta_{h,\text{dog}}(t)$: Host preference towards dogs
- $\phi_h(t)$: Proportion of sandflies infectious

Figure 3: Spatial impact of infectious dogs on force of infection



Model simulations

- Used spatial configuration of households in Calderao village.

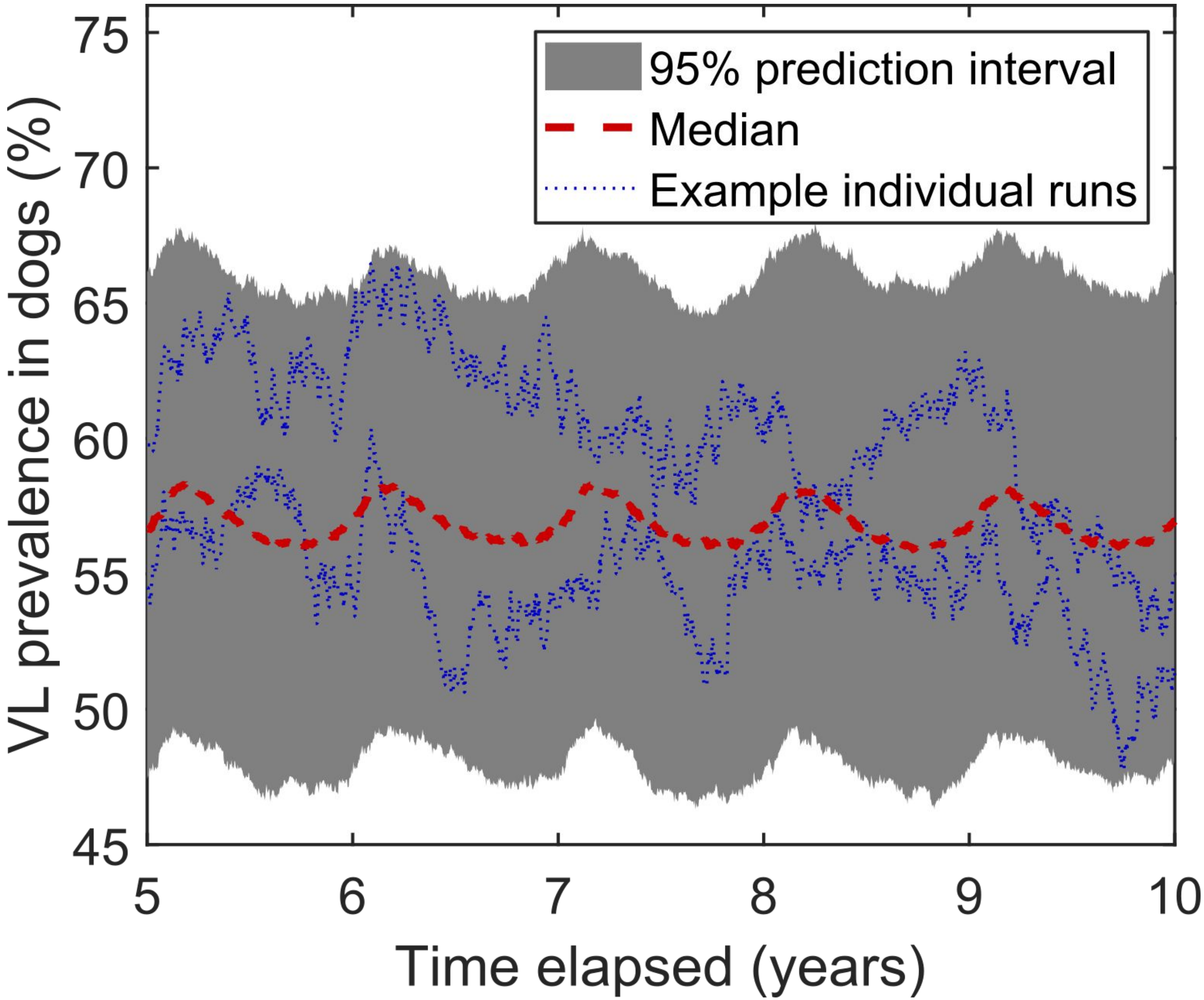
- Force of infection used to compute probability of each susceptible dog becoming infected on current day.

- We keep track of the number of infected dogs each day: model output was **prevalence**.

- Outcomes were averaged over 1000 separate model runs.

Households within Calderao

Figure 4: Simulated VL prevalence in domestic dogs



Sensitivity Analysis

Parameter ID	Symbol	Description	Baseline value	Other values tested
1	r	Interaction range of sandflies (km).	0.30	0.02, 0.7, 2
2	π_{never}	Proportion of infected dogs that are never infectious.	0.55	0.14, 0.28, 0.42
3	$\tilde{\pi}_{\text{high}}$	Proportion of infectious dogs that are highly infectious.	0.37	0.25, 0.60, 0.80
4	ξ	Probability of a newly introduced dog being infected.	0.130	0.0064, 0.29, 0.43
5	ν	Per capita rate of progression of dogs from latently infected to a further state (Days^{-1}). $1/\nu$ is the average duration of the latent period (Days).	0.0055	0.0042, 0.0047, 0.0065
⋮	⋮		⋮	⋮

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- **Measure:** Average prevalence

$$\text{Average VL prevalence} = \frac{\sum_{t=T-364}^{T} \text{VL prevalence}(t)}{365}$$

- Performed a **one-at-a-time** sensitivity analysis.

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Analysed by:

- violin plots
- computing stochastic sensitivity coefficients

Reference:
Damiani et al (2013) Parameter sensitivity analysis of stochastic models: Application to catalytic reaction networks. *Computational biology and chemistry* **42**: 5-17.

Figure 5A: Violin plots for average VL prevalence

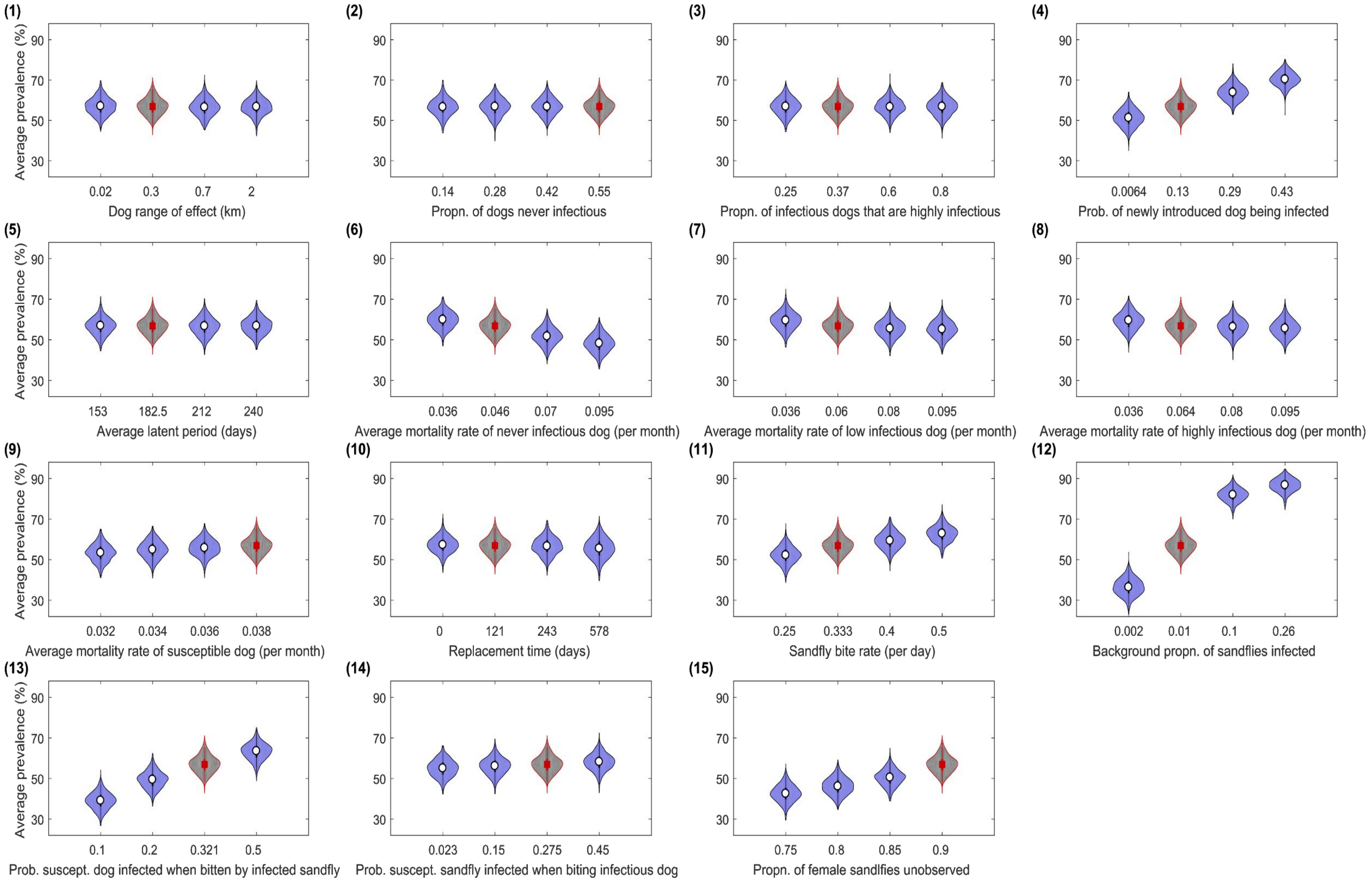


Figure 5A: Violin plots for average VL prevalence

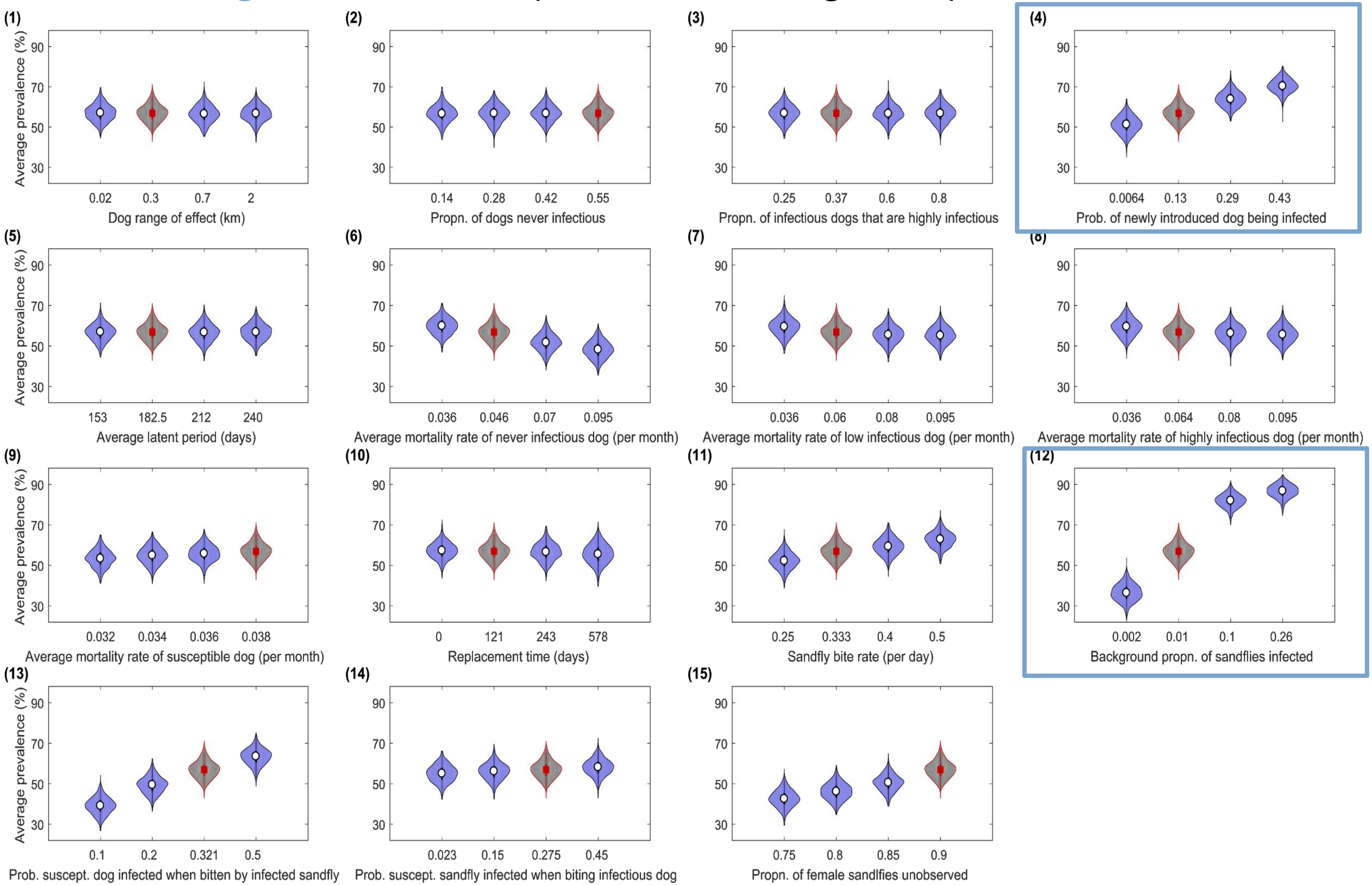
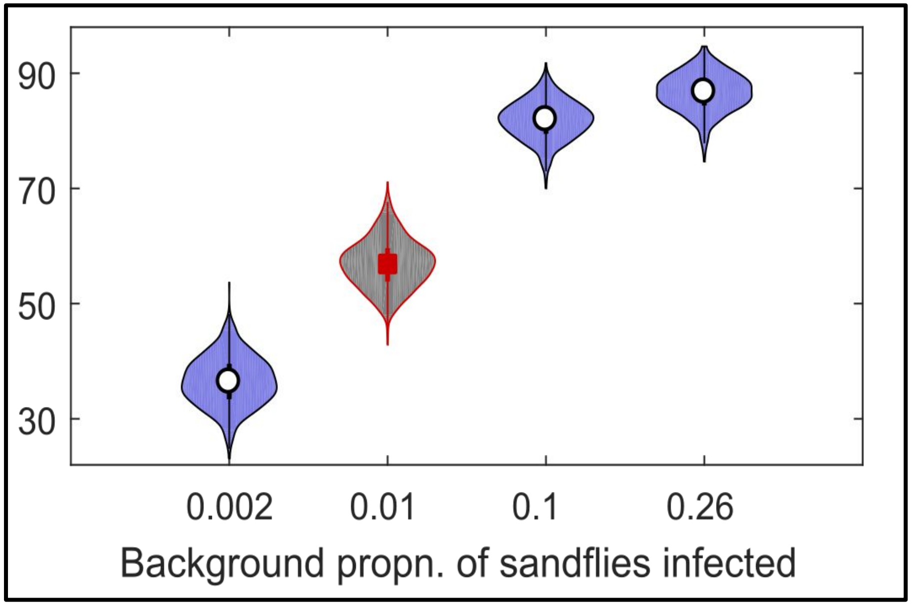


Figure 5B: Violin plots for average VL prevalence.

(Left) Background proportion of infected sandflies



(Right) Probability of a newly introduced dog being infected

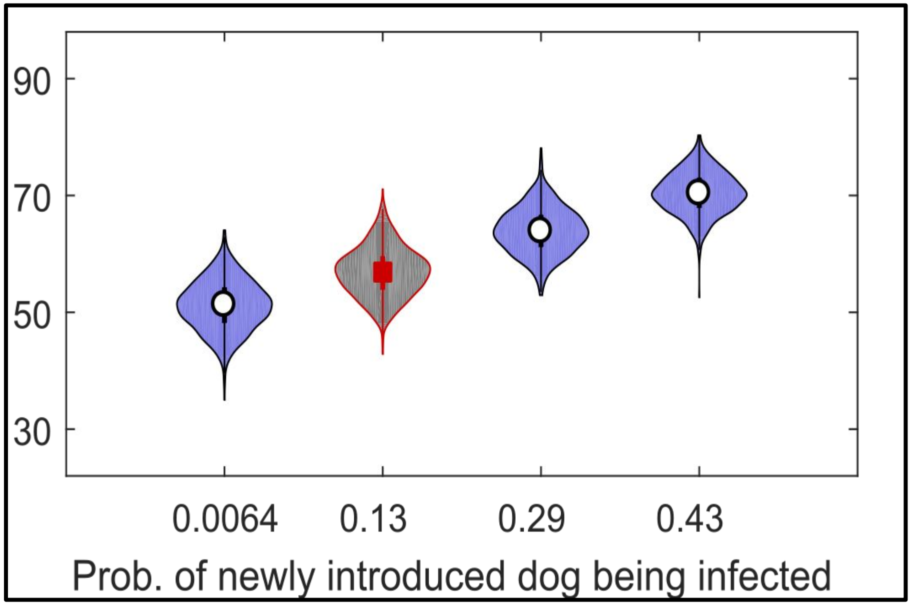
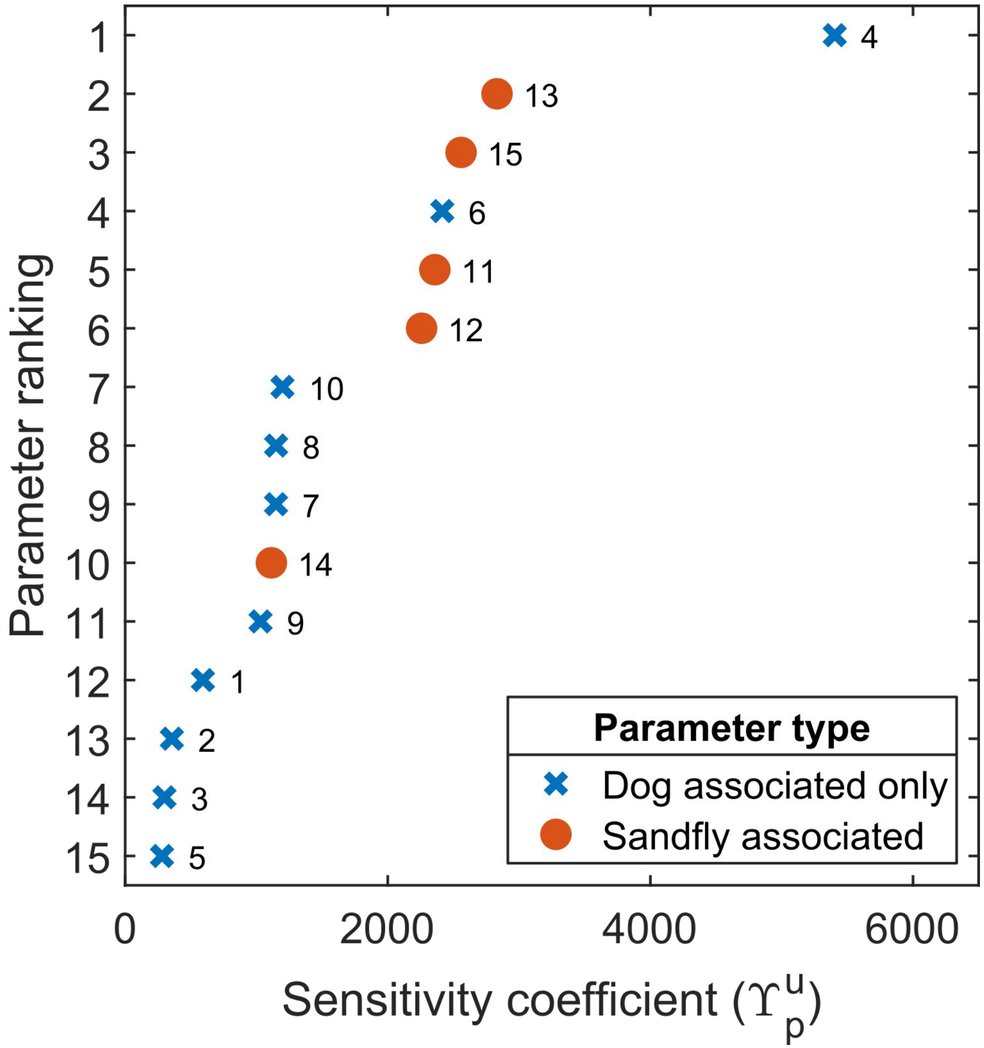


Figure 6: Stochastic sensitivity coefficient parameter ranking



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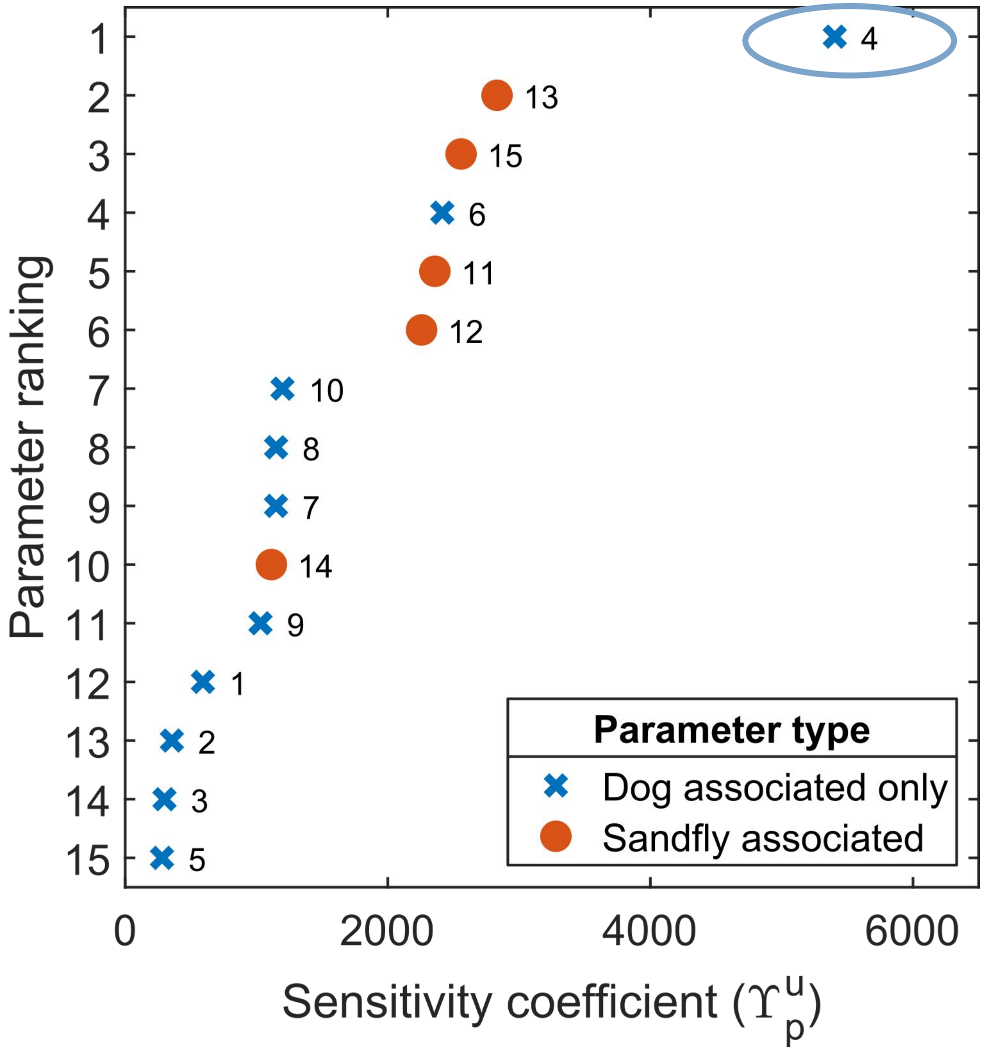

- Average VL disease prevalence was most sensitive to the probability of a newly introduced dog being infected.

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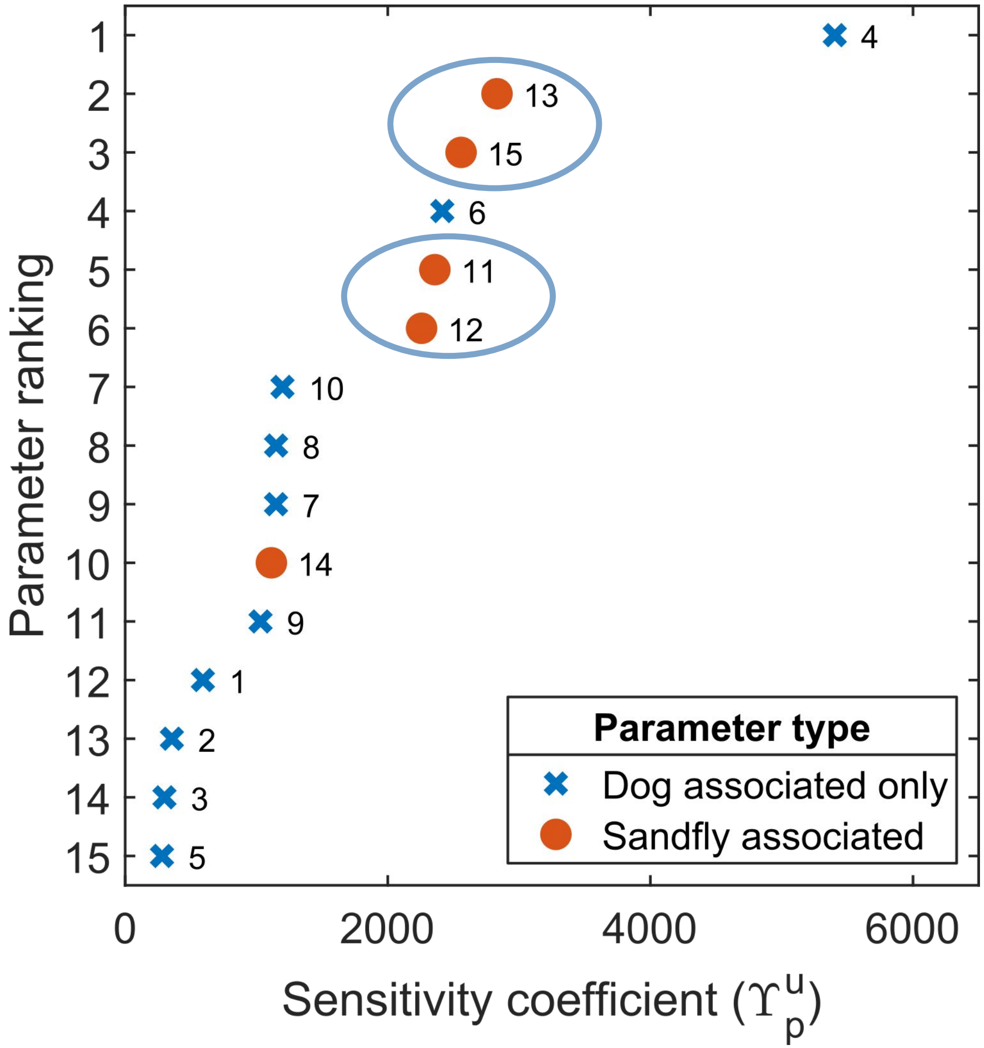

- Four parameters associated with sandflies were among the top six ranked parameters.

Conclusions and next steps

- Developed a novel individual-based, spatio-temporal mechanistic modelling framework for VL in dogs.

- Sensitivity analysis motivates future data collection efforts.

- Provides a platform to stimulate the formulation of innovative mathematical models into:
  - spatial spread of zoonotic VL infection in humans
  - intervention planning

Thank you, questions?

Acknowledgements

This work is in collaboration with Samik Datta, Erin Dilger, and Orin Courtenay, University of Warwick.

wellcome

MANCHESTER 1824
The University of Manchester

WARWICK
THE UNIVERSITY OF WARWICK

Email: e.buckingham-jeffery@manchester.ac.uk
Webpage: ebucksjeff.github.io
Twitter: @Ebucksjeff

Email: Edward.Hill@warwick.ac.uk
Webpage: www.edmhill.com
Twitter: @EdMHill