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Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Department of Epidemiology and Public Health
Infectious Disease Modelling Unit

A MECHANISTIC SPATIO-TEMPORAL MODEL TO UNDERSTAND THE OCCURRENCE OF DRUG-RESISTANT INFECTIONS

Tamsin E. Lee and Melissa Penny

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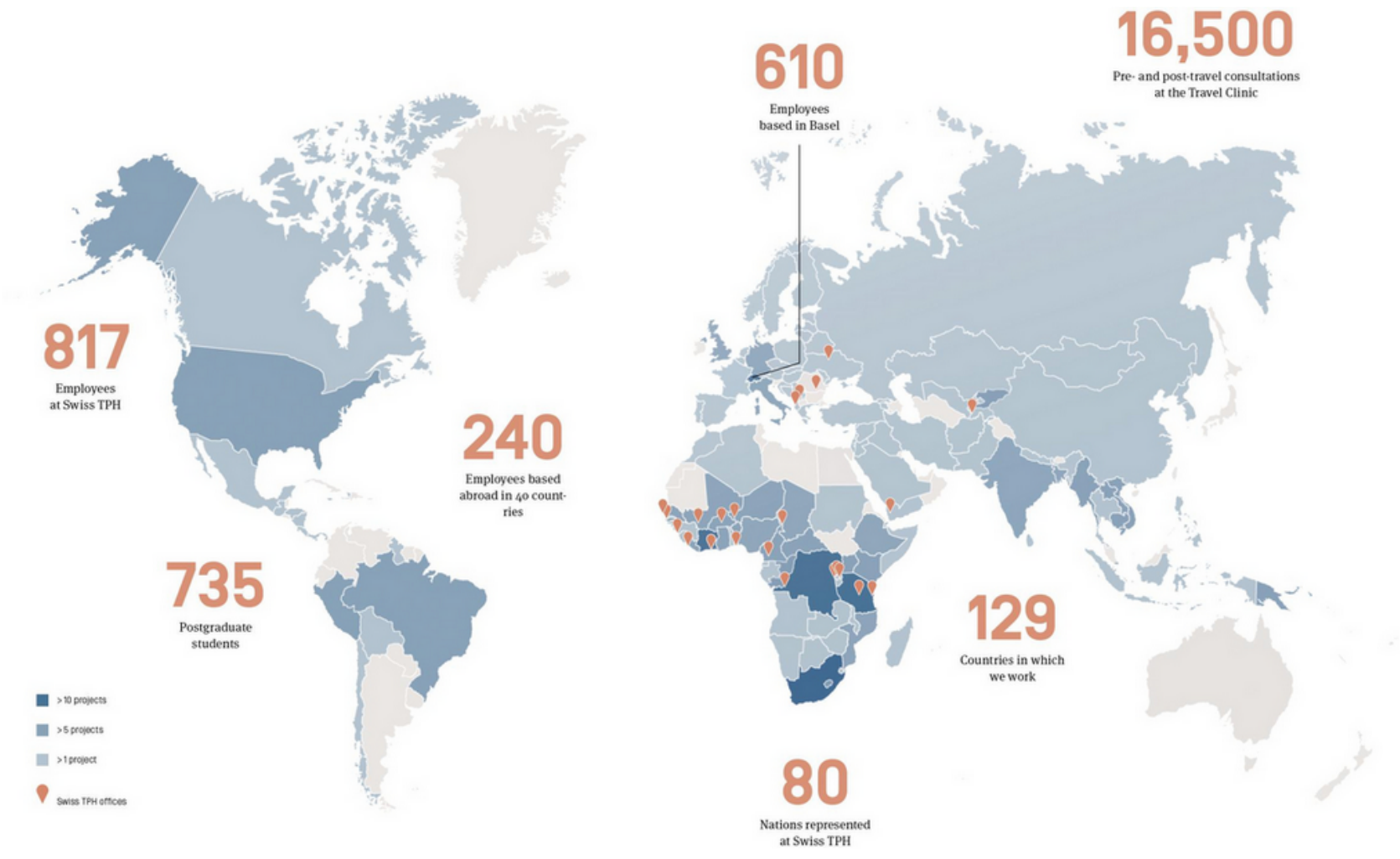
Introduction

Taking Science to Impact

281 Projects in 129 Countries



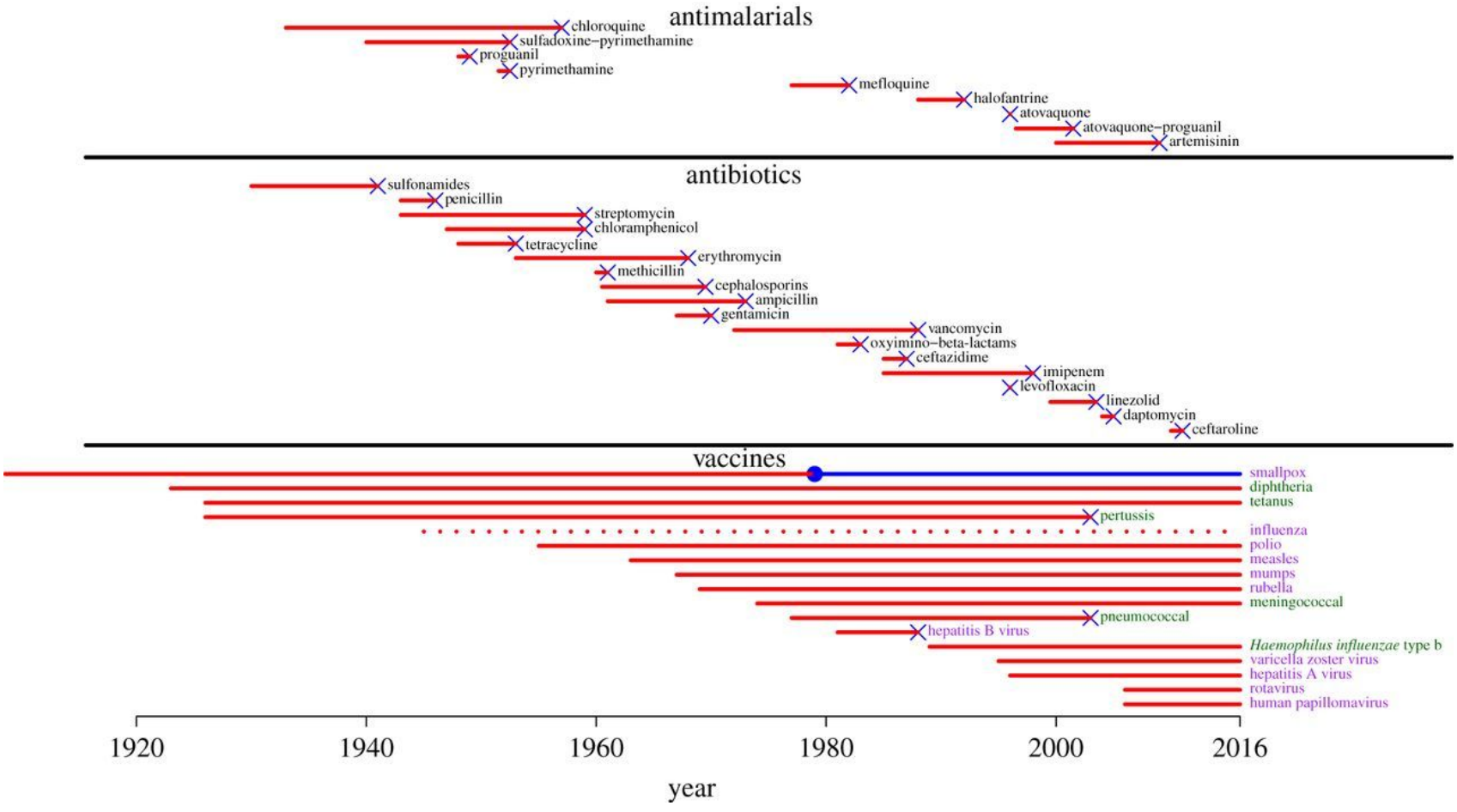
Antimicrobial resistance (AMR)

AMR happens when microorganisms (such as bacteria, fungi, viruses and parasites) **change after exposure to antimicrobial drugs** (such as antibiotics, antifungals, antivirals, antimalarials and anthelmintics).

As a result, these **medicines become ineffective** and infections persist in the body, **increasing the risk of spread to others** and resulting in **prolonged illness, disability and death**.

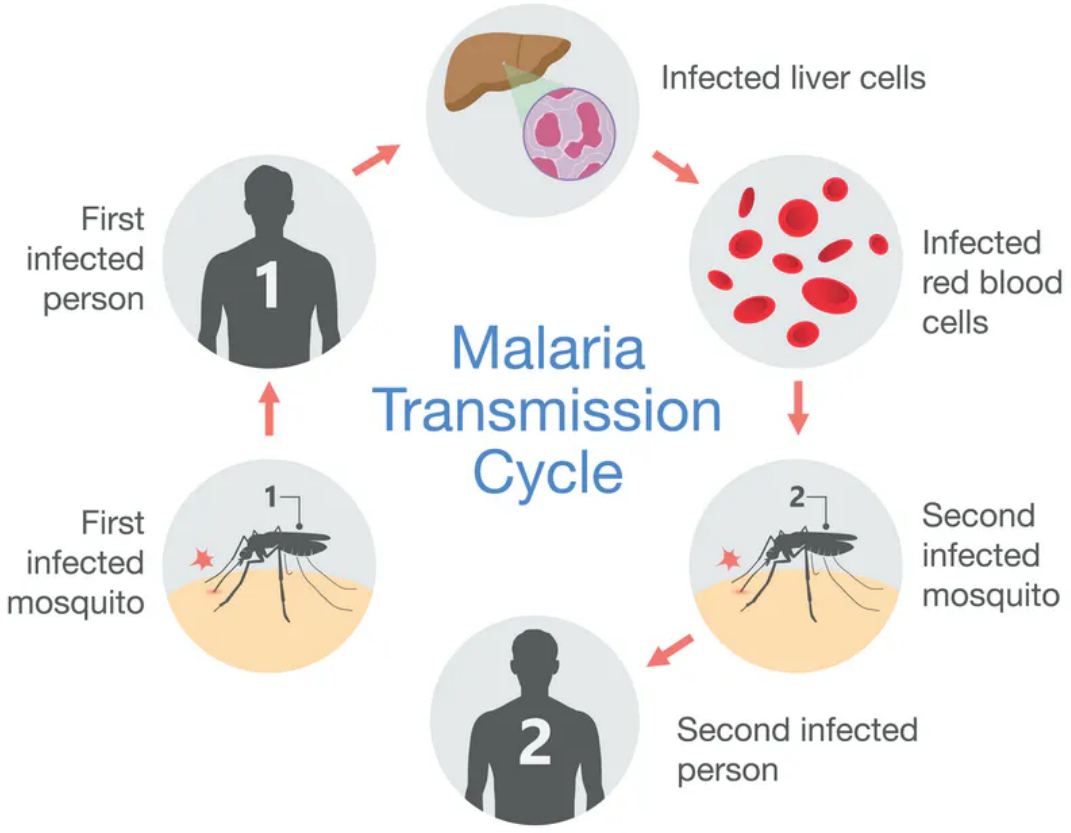
AMR occurs naturally over time, usually through genetic changes. However, the **misuse and overuse of antimicrobials is accelerating** this process.

https://www.who.int/health-topics/antimicrobial-resistance



Time to first detection of human pathogens resistant to vaccines and antimicrobial drugs. (Kennedy & Read 2017)

The malaria transmission cycle



Resistant infections can enter the cycle by:

- a mosquito transmitting a resistant strain,
- treatment killing sensitive parasitaemia within a person, and thus resistant strains are left, and with additional resources.

Drug resistant malaria

DEFINITION: The ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal or higher than those usually recommended, but within the limits of tolerance of the patients.

- Main obstacle to malaria control - including reemergence of malaria.
- Resistance to nearly all antimalarials in current use.
- Curtails the lifespan of antimalarial drugs.
- Increases malaria morbidity, mortality and treatment cost.
- **Accelerated by the way the drugs are used, and by the social and economic conditions in which they are used.**

Chloroquine resistance to *Plasmodium falciparum*

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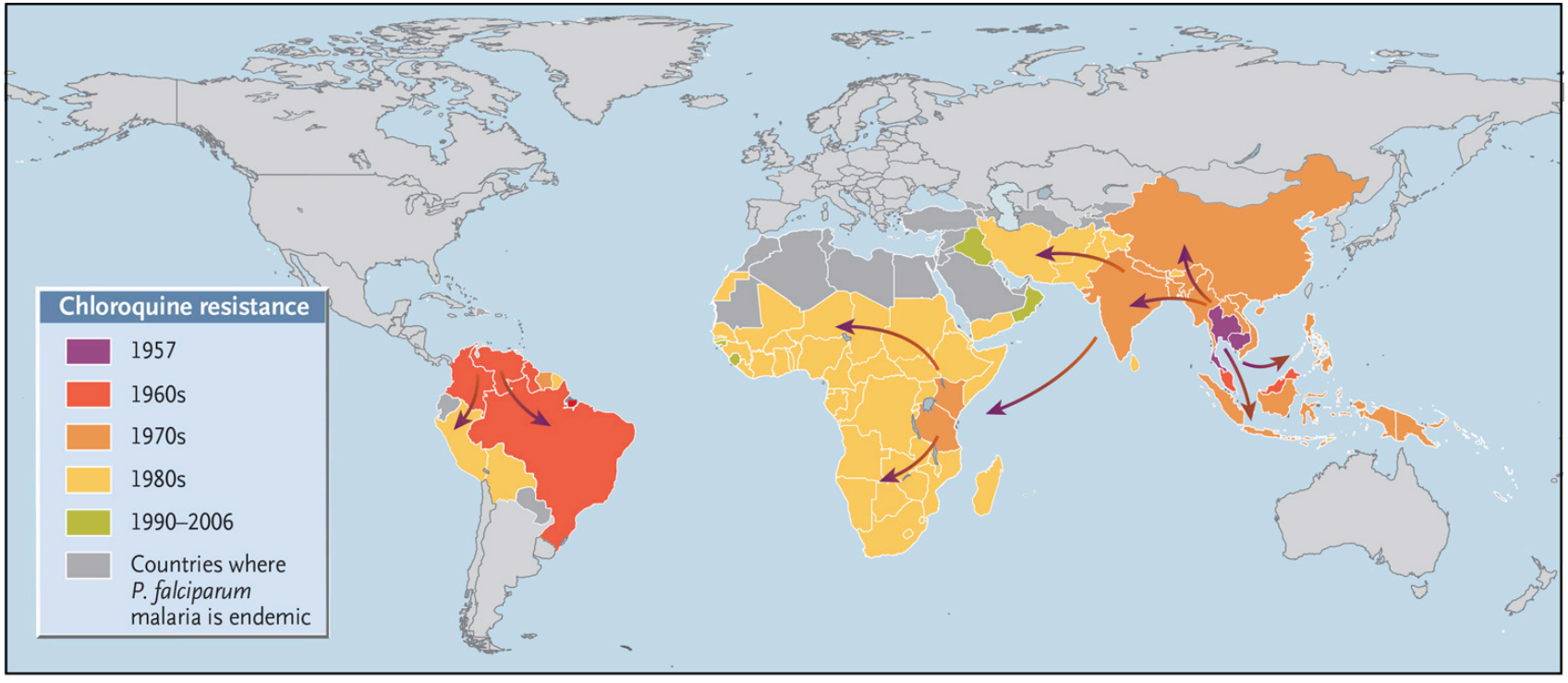
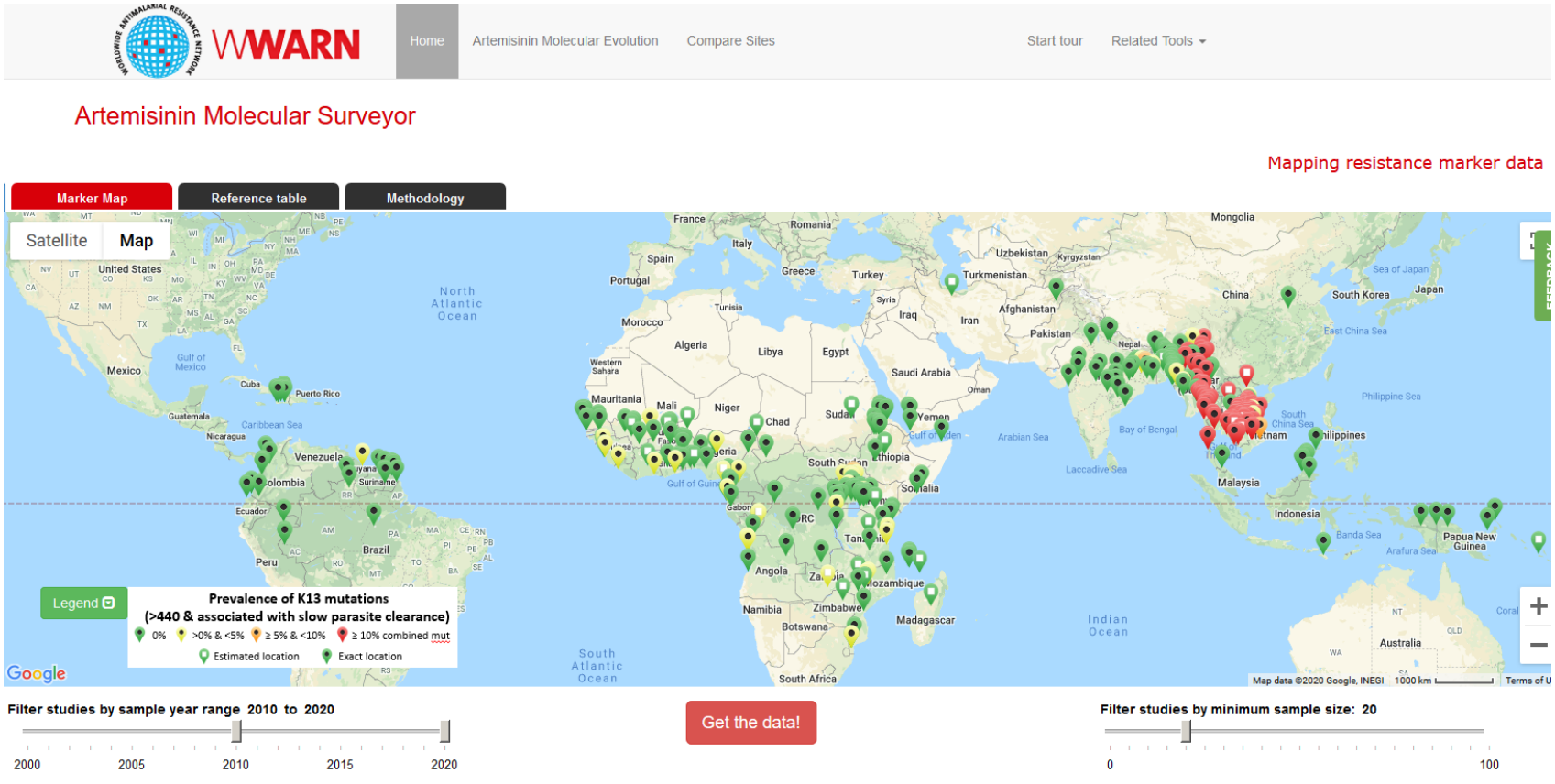


R. M. Packard (2014) *The New England Journal of Medicine*

Detecting resistance with molecular marker data



How does drug resistant malaria arrive in India?

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Detecting resistance with molecular marker data

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continent	val	country	year	tested	prev	lon	lat	mutation	site	estLoc	present
Asia	associated with slow clearance	Thailand	2014	88	19.32% [12.43 - 28.78]	104.84729766845703	15.244845390319824	R539T	Ubon Ratchathani	0	17
Asia	associated with slow clearance	Democratic Republic	2014	111	11.71% [6.97 - 19.01]	105.96998596191406	14.657865524291992	R539T	Champasak Province	0	13
Asia	associated with slow clearance	Cambodia	2011	40	2.5% [0.44 - 12.88]	102.66799926757812	12.909299850463867	R539T	Pailin	0	1
Asia	associated with slow clearance	India	2013	17	5.88% [1.05 - 26.98]	86.36519622802734	23.33209991455078	R539T	Purulia	0	1
Asia	associated with slow clearance	India	2013	27	11.11% [3.85 - 28.06]	87.0624008178711	23.164499282836914	R539T	Bankura	0	3
Asia	associated with slow clearance	India	2013	36	2.78% [0.49 - 14.17]	88.36969757080078	22.569700241088867	R539T	Kolkata	0	1
Asia	associated with slow clearance	Democratic Republic	2015	29	3.45% [0.61 - 17.18]	106.9552993774414	14.748881340026855	R539T	Phouvong DH, Phouvong, Attapeu	0	1
Asia	associated with slow clearance	Democratic Republic	2015	91	6.59% [3.06 - 13.65]	106.5816650390625	14.679998397827148	R539T	Sanamxay DH, Sanamxay, Attapeu	0	6
Asia	associated with slow clearance	Democratic Republic	2015	66	12.12% [6.27 - 22.14]	105.85296630859375	14.117712020874023	R539T	Khong DH, Khong, Champasak	0	8
Asia	associated with slow clearance	Democratic Republic	2015	338	9.17% [6.54 - 12.72]	105.94784545898438	14.841144561767578	R539T	Pathoumphone, Champasak	0	31
Asia	associated with slow clearance	India	2014	22	4.55% [0.81 - 21.8]	87.0624008178711	23.164499282836914	R539T	Bankura	0	1
Asia	associated with slow clearance	India	2015	49	10.2% [4.44 - 21.76]	87.0624008178711	23.164499282836914	R539T	Bankura	0	5
Asia	associated with slow clearance	India	2014	25	4.0% [0.71 - 19.54]	88.36969757080078	22.569700241088867	R539T	Kolkata	0	1
Africa	unknown effect on clearance	Burkina Faso	2010	273	1.1% [0.37 - 3.18]	-1.2999999523162842	12.583333015441895	C542Y	Ziniare	0	3
Africa	unknown effect on clearance	Ghana	2010	76	1.32% [0.23 - 7.08]	-1.0902800559997559	10.884699821472168	G544R	Navrongo	0	1
Africa	unknown effect on clearance	Mali	2009	117	3.42% [1.34 - 8.46]	-9.489500045776367	13.034099578857422	G545E	Kita	0	4

Detecting resistance with molecular marker data

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Up-to-date, quality data are needed on the efficacy of the recommended treatments, to ensure that patients receive efficacious treatment.

Conducting these studies can be challenging, but the investment of time and resources is small when compared with the funding spent on treatments and the millions of patients depending on the continued efficacy of these treatments.

Molecular markers are an asset for confirming resistance, in the analysis of trends and as an early warning signal.

Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance, WHO November 2020.

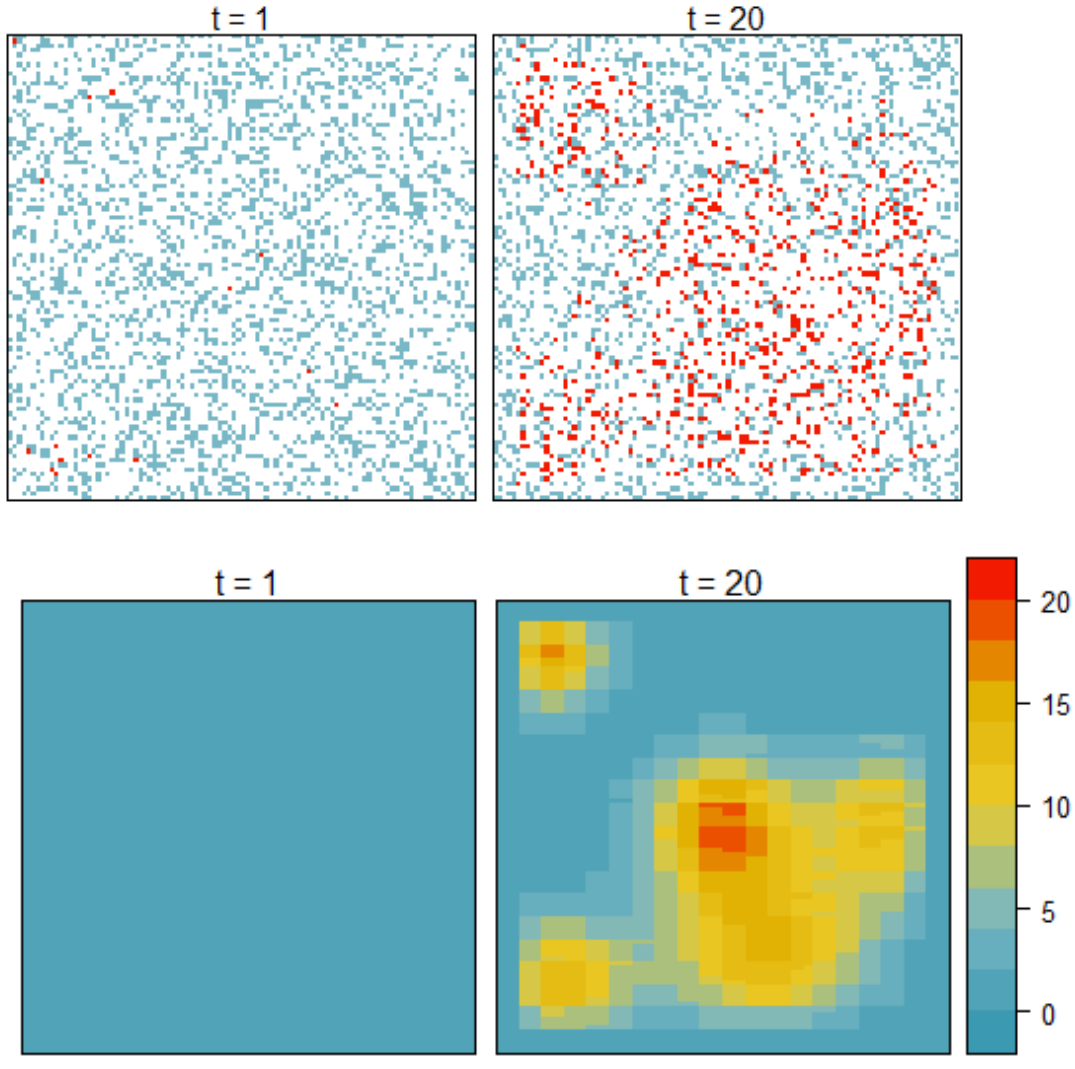
Overview

Using a toy data set:

- The question
- The model
- Results
- Conclusions

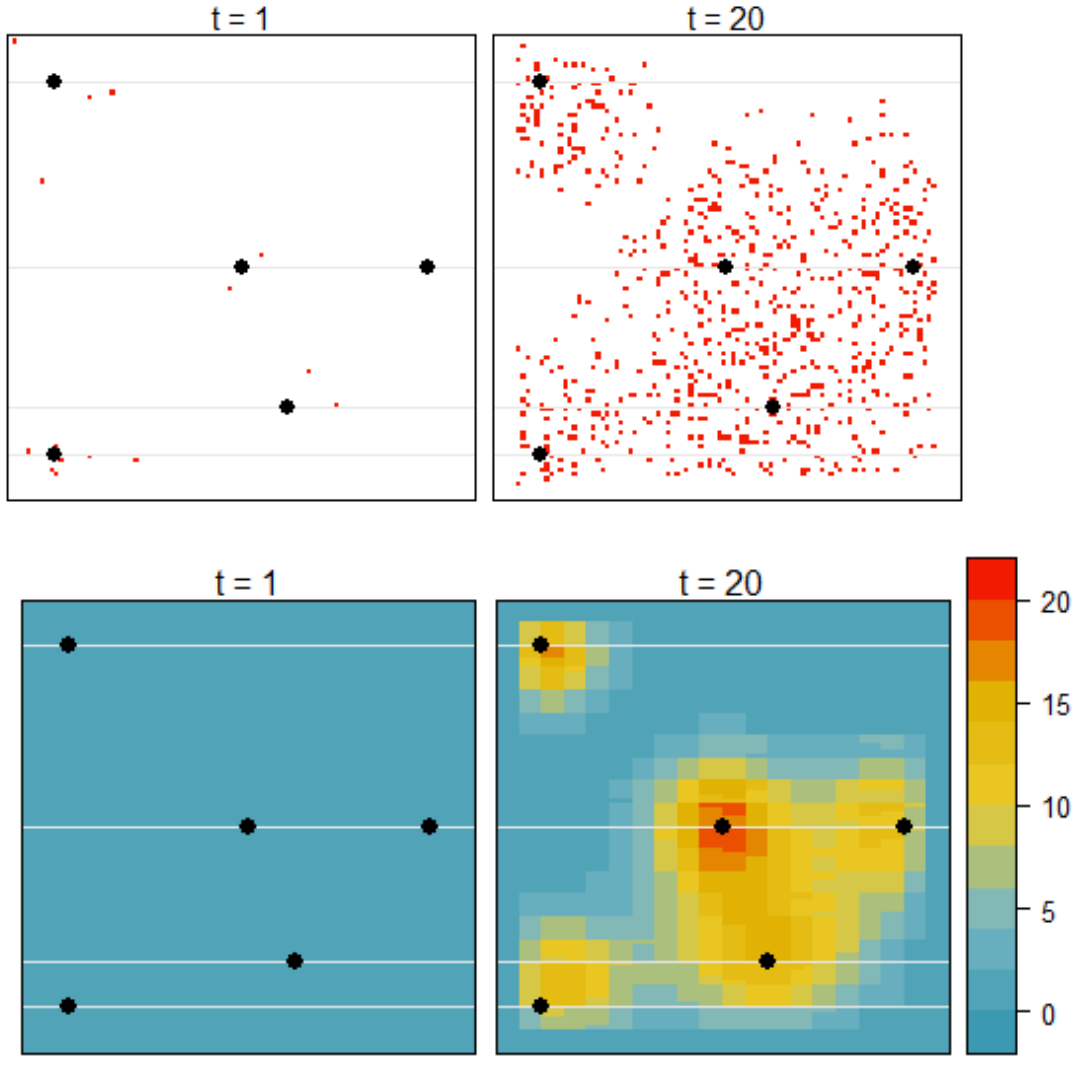
The question

Example collected data and ‘true density’



Red points correspond to a resistant infection detected.
Blue points correspond to no resistant infection detected.

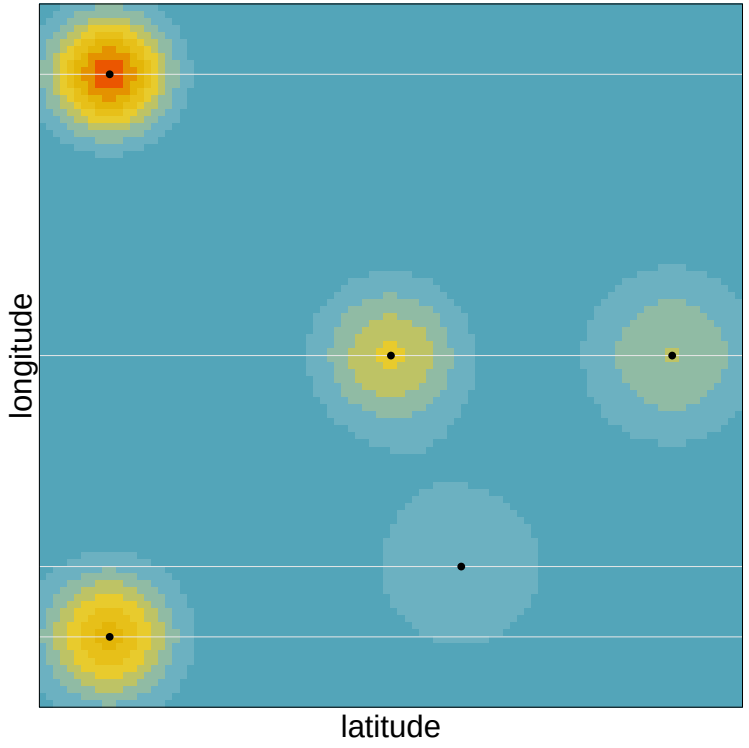
Example collected data and ‘true density’



Red points correspond to a resistant infection detected.
Black dots are resistance introduction hot spots.

Introducing resistance into the population

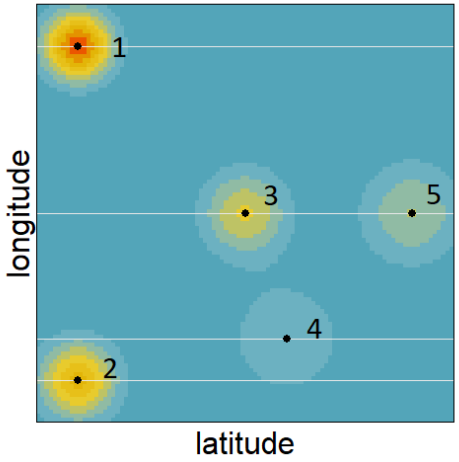
The 'true' density of resistant pathogens in a population at $t = 0$.



Assume that resistant pathogens first enter the population from N resistance introduction hot spots, such as **HEALTH CARE CENTRES** or **MAJOR TRANSPORT HUBS** (black dots).

Each n hot spot has a *magnitude* θ_n of resistant pathogens which it contributes into the population, and *disperses at rate* ϕ_n.

Hot spots which introduce resistance



Each n resistance hot spot has a *magnitude* θ_n of resistant pathogens which it contributes into the population, and *disperses at rate* ϕ_n

$$\text{Resistance introductions} = u(\mathbf{s}, 0) = \sum_{n=1}^{N} \frac{\theta_n e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2}}{\int_{\mathcal{S}} e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2}\, \mathrm{d}\mathbf{s}}$$

We use a scaled bivariate Gaussian kernel with compact (truncated) support centred at a point with coordinate $\mathbf{d_n}$ where $|\mathbf{s} - \mathbf{d_n}|$ is the Euclidean distance.

Using MCMC we estimate ϕ_n and θ_n
(initial estimates assign the same value to all ϕ_n and all θ_n).

The model

The probability of the data

The data $y_i \in \{0, 1\}$ is the presence of a drug resistant infection at a particular location, at a particular time.

The probability of detecting a drug resistant infection depends on the true density $u(\mathbf{s}_i, t_i)$ and individual factors (such as age).

$$\begin{aligned} y_i &= \text{Bernoulli}(p_i) \\ g(p_i) &= u(\mathbf{s}_i, t_i) e^{\mathbf{x}_i' \beta} \end{aligned}$$

$\mathbf{x}_i$ are the covariates regarding the individual (e.g. age).

The density of resistant infections $u(s_i, t_i)$: dispersal

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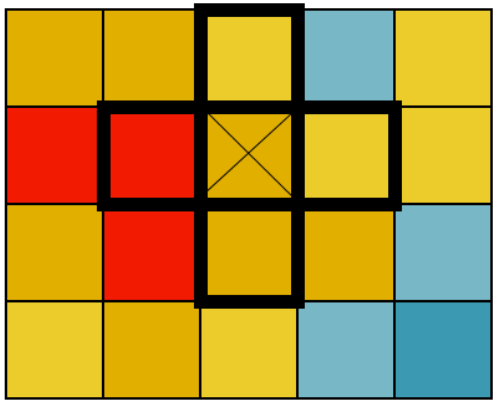
The density of the resistant infection at X depends on the density of resistant infections at neighbouring cells.



642 T. J. Hefley *et al.* Ecology Letters 2017

Table 1 Examples of ecological dynamics addressed by statistical implementation of diffusion models

Ecological dynamic	References
Animal disease	Hooten & Wikle (2010)
Animal resource selection	Moorcroft & Barnett (2008)
Fish migration	Arab (2007, ch. 2)
Insect dispersal	Powell & Bentz (2014)
Invasion/colonisation	Wikle (2003), Hooten & Wikle (2008), Broms *et al.* (2016), and Williams *et al.* (2017)
Plant disease	Zheng & Aukema (2010)

$$\frac{\partial}{\partial t}u(\mathbf{s},t) = \left(\frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2}\right)\left[\mu(\mathbf{s})u(\mathbf{s},t)\right]$$

- $u(\mathbf{s},t)$ is the density of the dispersing resistant infection.
- s_1 and s_2 are the spatial coordinates contained in $\mathbf{s}$.
- $\mu(\mathbf{s},t)$, the diffusion coefficient, could depend on covariates.

The density of resistant infections $u(s_i, t_i)$: growth

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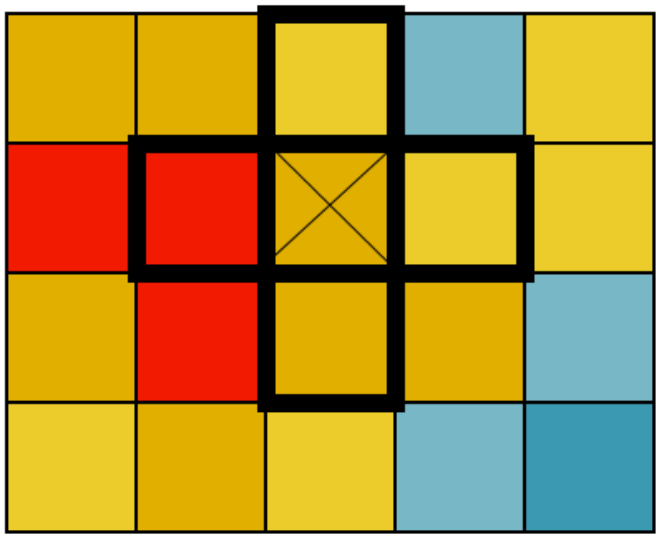
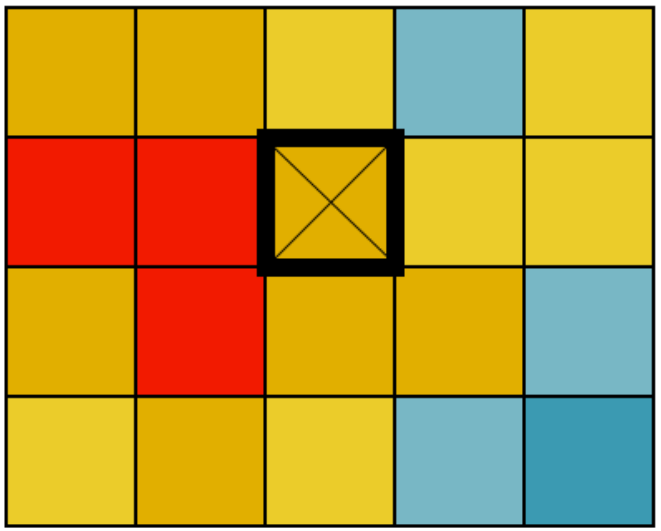
The density of the resistant infection at X depends on the density of resistant infections at neighbouring cells.



The density of the resistant infection at X ALSO depends on a growth component, which depends on the density at X.



$$\frac{\partial}{\partial t}u(\mathbf{s},t) = \left(\frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2}\right)\left[\mu(\mathbf{s})u(\mathbf{s},t)\right] + \lambda(\mathbf{s})u(\mathbf{s},t)$$

- $u(\mathbf{s},t)$ is the density of the dispersing resistant infection.
- s_1 and s_2 are the spatial coordinates contained in $\mathbf{s}$.
- $\mu(\mathbf{s},t)$, the diffusion coefficient, could depend on covariates.
- $\lambda(\mathbf{s})$, the growth coefficient, could depend on covariates.

The density of resistant infections $u(s_i, t)$

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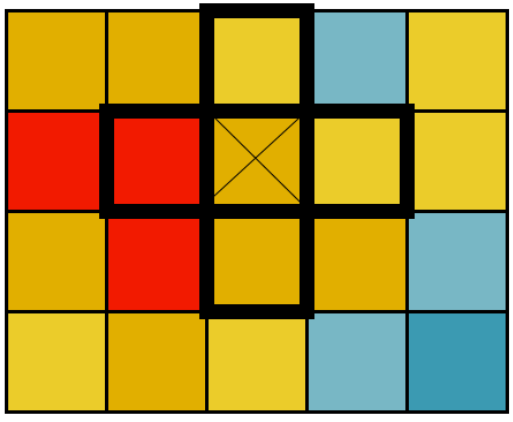
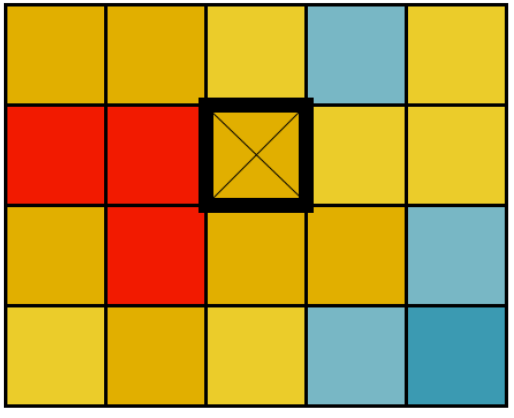
The density of resistant infections at location X at time *t* depends on:

The density of resistant infections at neighbouring cells at time *t – 1*.



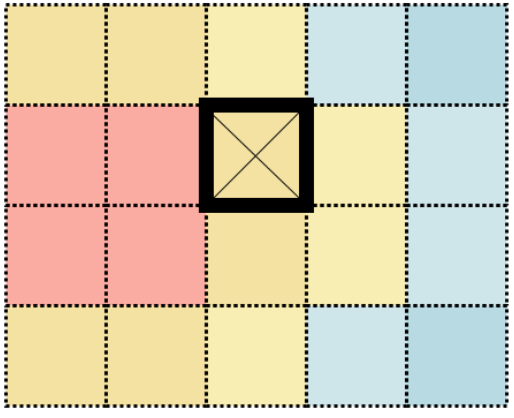
Transmission from neighbouring regions – depends on disease prevalence.

The density of resistant infections at cell X at time *t – 1*.



Local transmission – depends on disease prevalence.

An underlying, time-independent, process.



Resistance introduction – depends on distance from a resistance hot spot

$$\frac{\partial}{\partial t}u(\mathbf{s},t) = \underbrace{\left(\frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2}\right)\left[\mu(\mathbf{s})u(\mathbf{s},t)\right]}_{\text{neighbouring transmission}} + \underbrace{\lambda(\mathbf{s})u(\mathbf{s},t)}_{\text{local transmission}} + \underbrace{u(\mathbf{s},0)}_{\text{introductions}}$$

where $\log(\mu(\mathbf{s})) = \alpha_0 + \mathbf{z}(\mathbf{s})'\alpha_1$ and $\lambda(\mathbf{s}) = \gamma_0 + \mathbf{w}(\mathbf{s})'\gamma_1$, and $\mathbf{z}$ and $\mathbf{w}$ are the spatial covariates that affect onward **transmission** (prevalence).

The data $y_i \in \{0, 1\}$ is the presence of drug resistant malaria at a particular location, at a particular time.

$$
\begin{aligned}
y_i &= \text{Bernoulli}(p_i) \\
g(p_i) &= u(\mathbf{s}_i, t_i) e^{\mathbf{x}_i' \beta} \\
\frac{\partial}{\partial t} u(\mathbf{s}, t) &= \left(\frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2} \right) \left[\mu(\mathbf{s}) u(\mathbf{s}, t) \right] + \lambda(\mathbf{s}) u(\mathbf{s}, t) + u(\mathbf{s}, 0) \\
\log(\mu(\mathbf{s})) &= \alpha_0 + \mathbf{z}(\mathbf{s})' \alpha \\
\lambda(\mathbf{s}) &= \gamma_0 + \mathbf{w}(\mathbf{s})' \gamma \\
u(\mathbf{s}, 0) &= \sum_{n=1}^{N} \frac{\theta_n e^{-(|\mathbf{s} - \mathbf{d_n}|^2)/\phi_n^2}}{\int_{\mathcal{S}} e^{-(|\mathbf{s} - \mathbf{d_n}|^2)/\phi_n^2} \, \mathrm{d}\mathbf{s}}
\end{aligned}
$$

$\mathbf{x}_i$ are the covariates regarding the individual (age).
$\mathbf{z}$ and $\mathbf{w}$ are the spatial covariates that affect onward **transmission** (prevalence).

Sample data on a 10,000 × 10,000 grid

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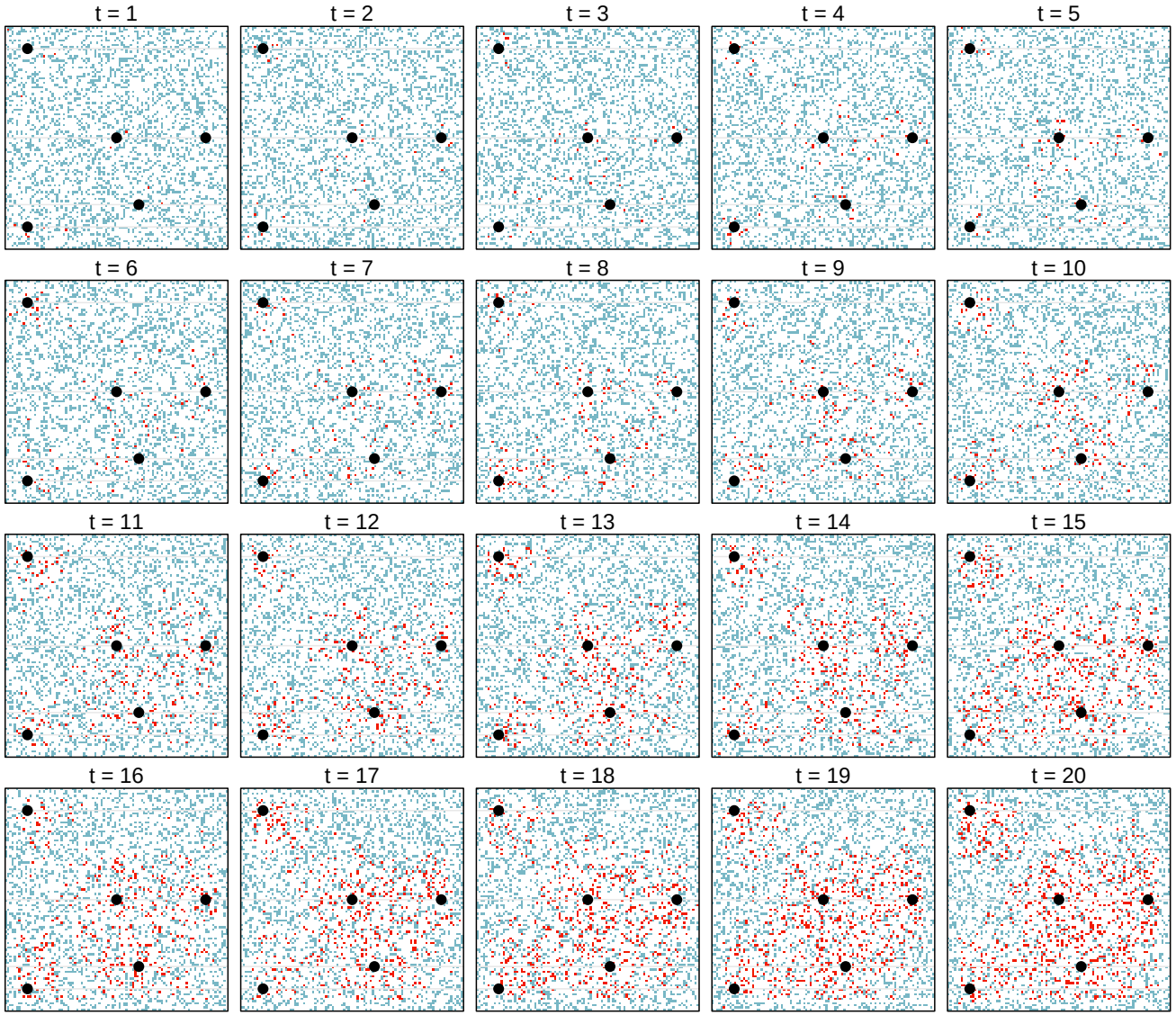
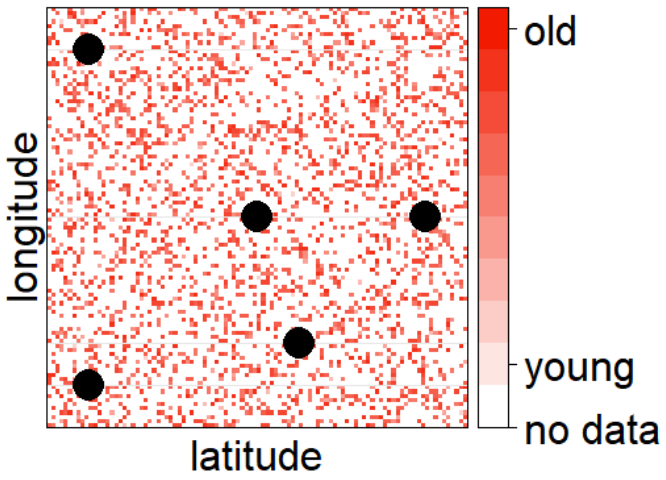


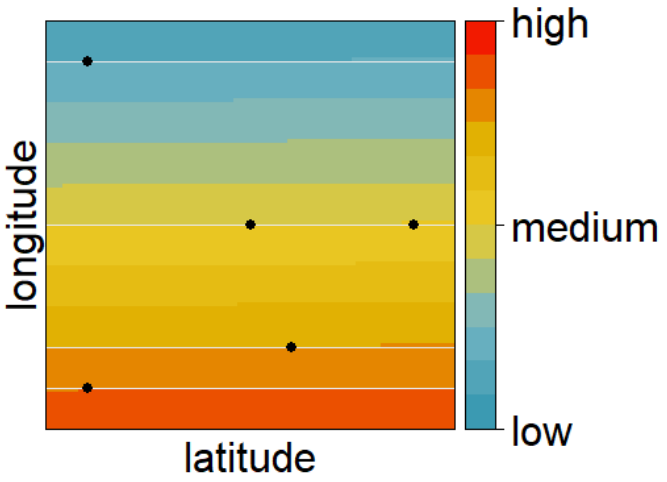
Red / Blue points correspond to a resistant infection detected / not detected.
Black dots are resistance introduction hot spots.

The covariates and priors

x: age of sampled



z(s) and **w(s)**: disease prevalence



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y_i &= \text{Bernoulli}(p_i) \\
g(p_i) &= u(\mathbf{s}_i, t_i) e^{\mathbf{x}_i' \beta} \\
\frac{\partial}{\partial t} u(\mathbf{s}, t) &= \left(\frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2} \right) \left[\mu(\mathbf{s}) u(\mathbf{s}, t) \right] + \lambda(\mathbf{s}) u(\mathbf{s}, t) + u(\mathbf{s}, 0) \\
\log(\mu(\mathbf{s})) &= \alpha_0 + \mathbf{z}(\mathbf{s})' \alpha \\
\lambda(\mathbf{s}) &= \gamma_0 + \mathbf{w}(\mathbf{s})' \gamma \\
u(\mathbf{s}, 0) &= \sum_{n=1}^{N} \frac{\theta_n e^{-(|\mathbf{s} - \mathbf{d_n}|^2)/\phi_n^2}}{\int_{\mathcal{S}} e^{-(|\mathbf{s} - \mathbf{d_n}|^2)/\phi_n^2} \, \mathrm{d}\mathbf{s}}
\end{aligned}
$$

The algorithm

1. Set initial values for $\alpha_0, \alpha_1, \beta, \gamma_0, \gamma_1, \theta_1, \theta_2, \theta_3, \theta_4\ \theta_5, \phi_1, \phi_2, \phi_3, \phi_4, \phi_5$
2. **while** $l < m$ **do**
3. update $u(\mathbf{s}, t)$
4. sample $[\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \phi_1, \phi_2, \phi_3, \phi_4, \phi_5 | \alpha_0, \alpha_1, \beta, \gamma_0, \gamma_1]$
5. update $u(\mathbf{s}, t)$
6. sample $[\alpha_0, \alpha_1 | \beta, \gamma_0, \gamma_1, \theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \phi_1, \phi_2, \phi_3, \phi_4, \phi_5]$
7. update $u(\mathbf{s}, t)$
8. sample $[\beta | \alpha_0, \alpha_1, \gamma_0, \gamma_1, \theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \phi_1, \phi_2, \phi_3, \phi_4, \phi_5]$
9. sample $[\gamma_0, \gamma_1 | \alpha_0, \alpha_1, \beta, \theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \phi_1, \phi_2, \phi_3, \phi_4, \phi_5]$
10. **end while**

Input

- Data: $y_i = [0, 1]$
- Covariates: $\mathbf{x}$, $\mathbf{z}(\mathbf{s})$ and $\mathbf{w}(\mathbf{s})$
- Priors: $\theta_\mathbf{n}, \phi_\mathbf{n} \sim \text{TN}(0, 10^6)$, $\alpha \sim N(0, 10\mathbf{I})$, $\gamma \sim N(0, 10\mathbf{I})$, $\alpha \sim N(0, 10\mathbf{I})$

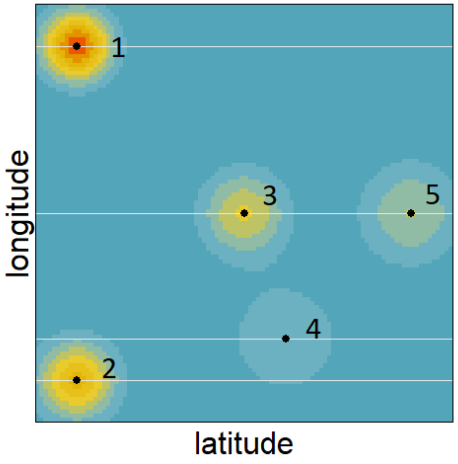
* * *

Output

- **From θ_n and ϕ_n, the important hot spots.**
- From α, the dispersal coefficient (neighbouring transmission), $\mu(\mathbf{s})$.
- From γ, the growth coefficient (local transmission), $\lambda(\mathbf{s})$.
- From all of the above, the true density of resistant infections, $u(\mathbf{s}, t)$.
- From β and $u(\mathbf{s}, t)$, the probability an individual is sampled, $u(\mathbf{s}_i, t_i)e^{\mathbf{x}_i'\beta}$.

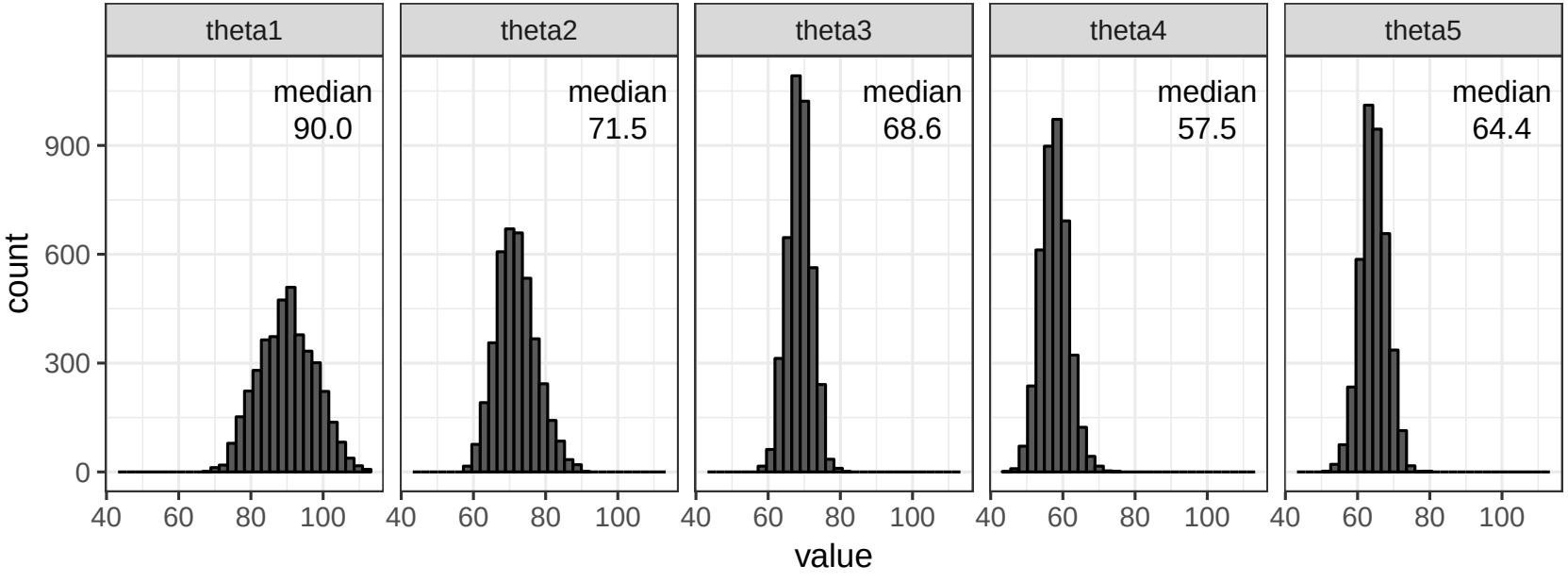
The results

The magnitude of resistance introduction (θ_n)



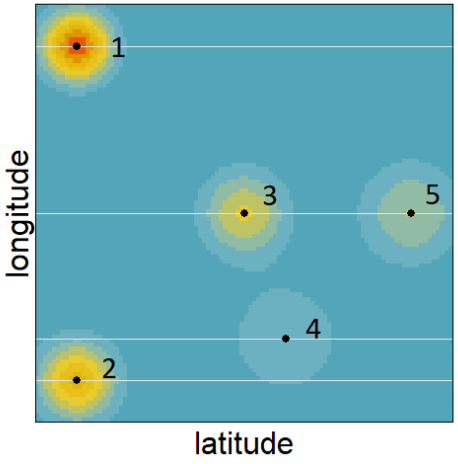
Each n resistance hot spot has a *magnitude* θ_n of resistant pathogens which it contributes into the population, and *disperses at rate* ϕ_n

$$u(\mathbf{s},0) = \sum_{n=1}^{N} \frac{\theta_n e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2}}{\int_{\mathcal{S}} e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2}\, \mathrm{ds}}$$



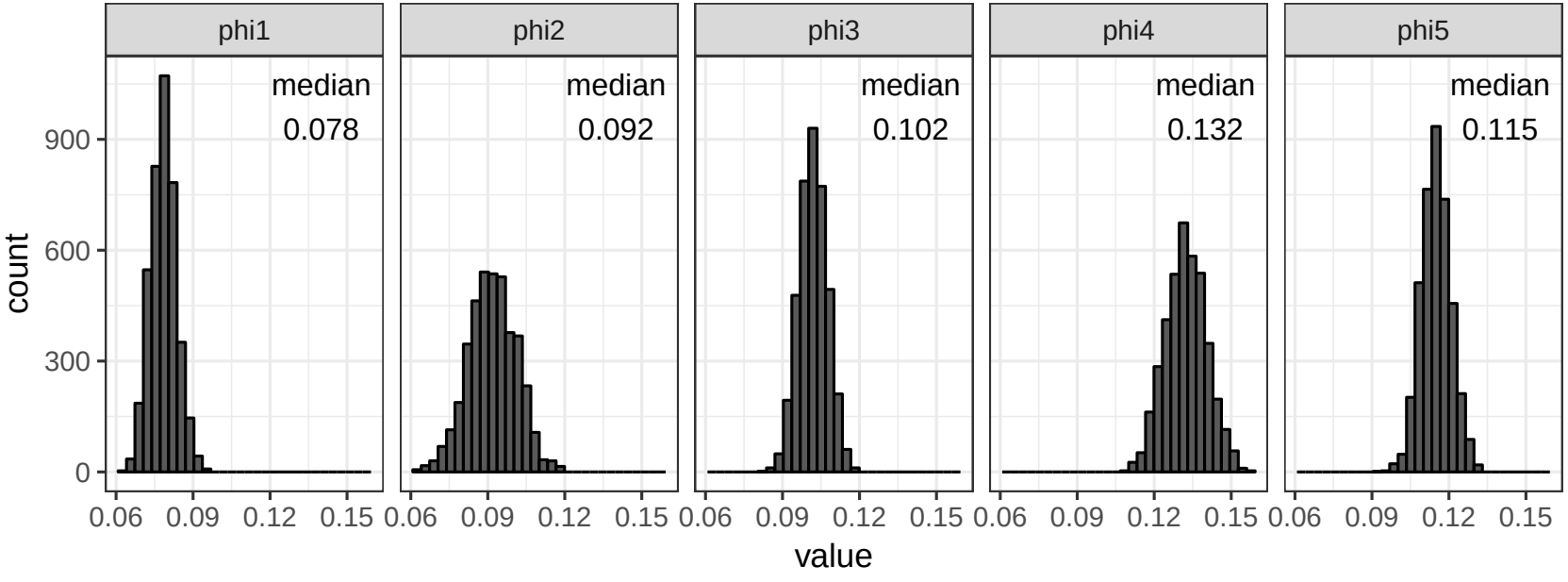
Actual $\theta = (80, 70, 65, 60, 60)$.

The dispersal of resistance introduction (ϕ_n)



Each n resistance hot spot has a *magnitude* θ_n of resistant pathogens which it contributes into the population, and *disperses at rate* ϕ_n

$$u(\mathbf{s}, 0) = \sum_{n=1}^{N} \frac{\theta_n e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2}}{\int_{\mathcal{S}} e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2} \, \mathrm{d}\mathbf{s}}$$



Actual $\phi = (0.08, 0.09, 0.1, 0.15, 0.12)$

Identify resistance introduction hot-spots

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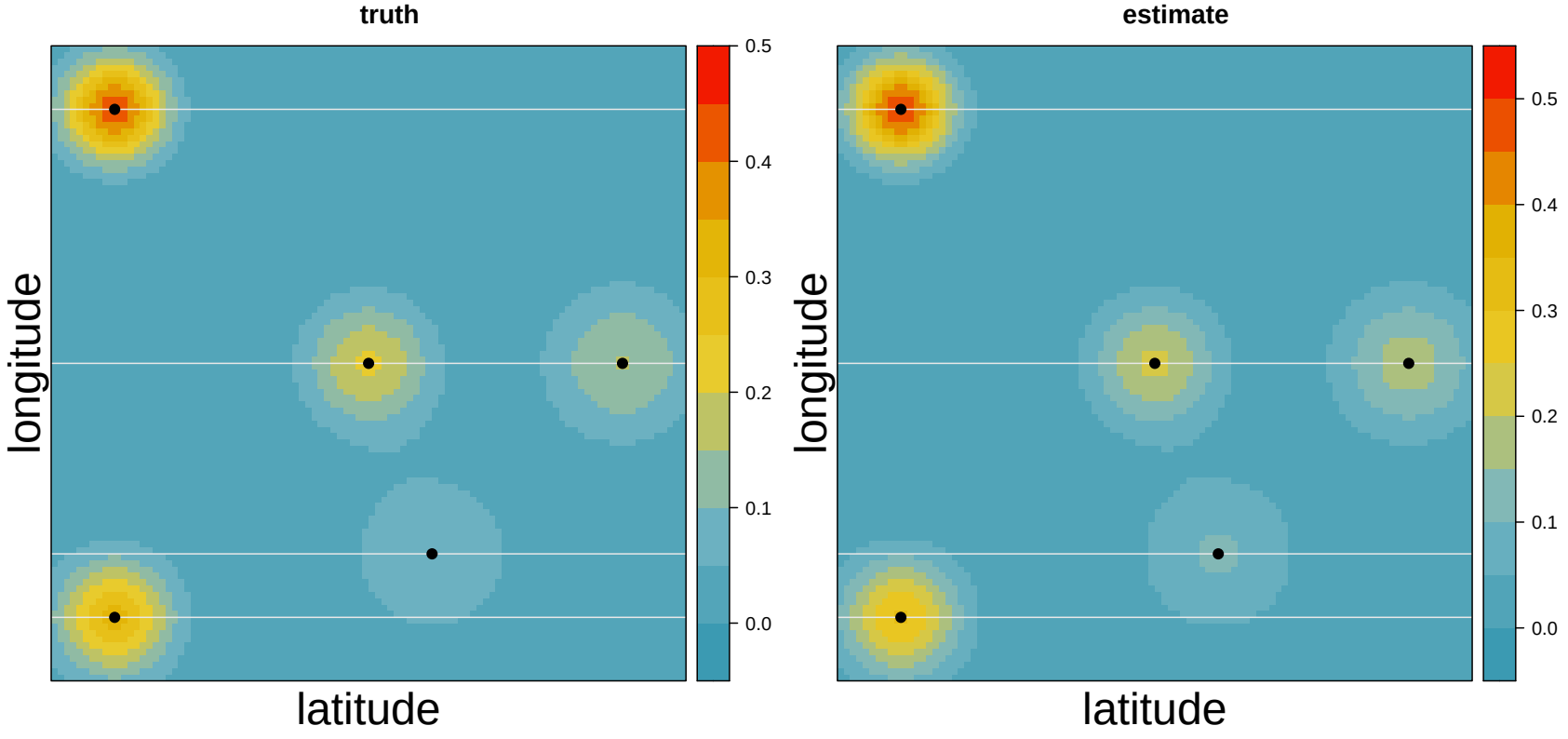
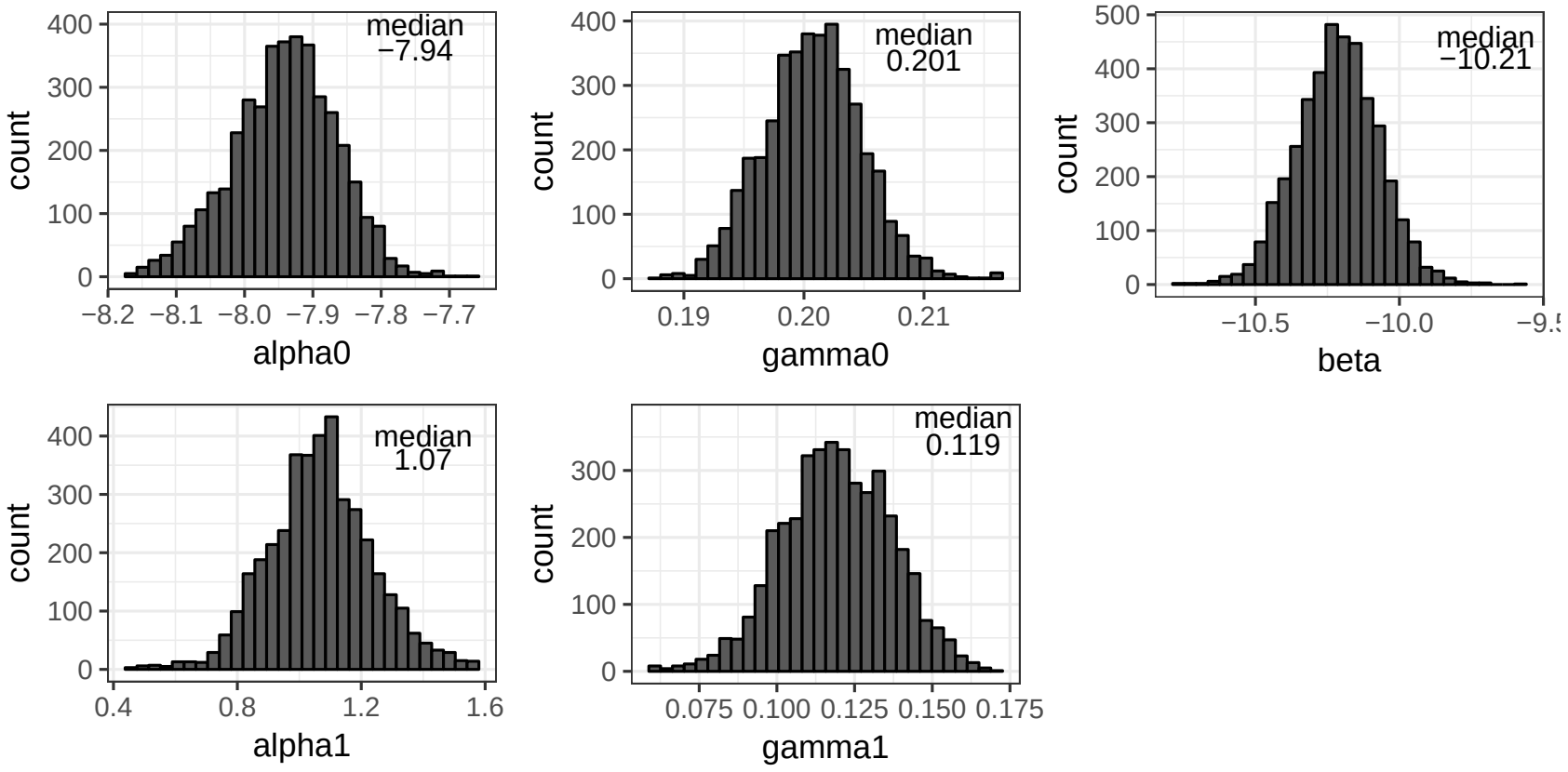
Each n resistance hot spot has a *magnitude* θ_n of resistant pathogens which it contributes into the population, and *disperses at rate* ϕ_n



$$\text{Resistance introductions} = u(\mathbf{s}, 0) = \sum_{n=1}^{N} \frac{\theta_n e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2}}{\int_{\mathcal{S}} e^{-(|\mathbf{s}-\mathbf{d_n}|^2)/\phi_n^2} \, \mathrm{d}\mathbf{s}}$$

Other parameters

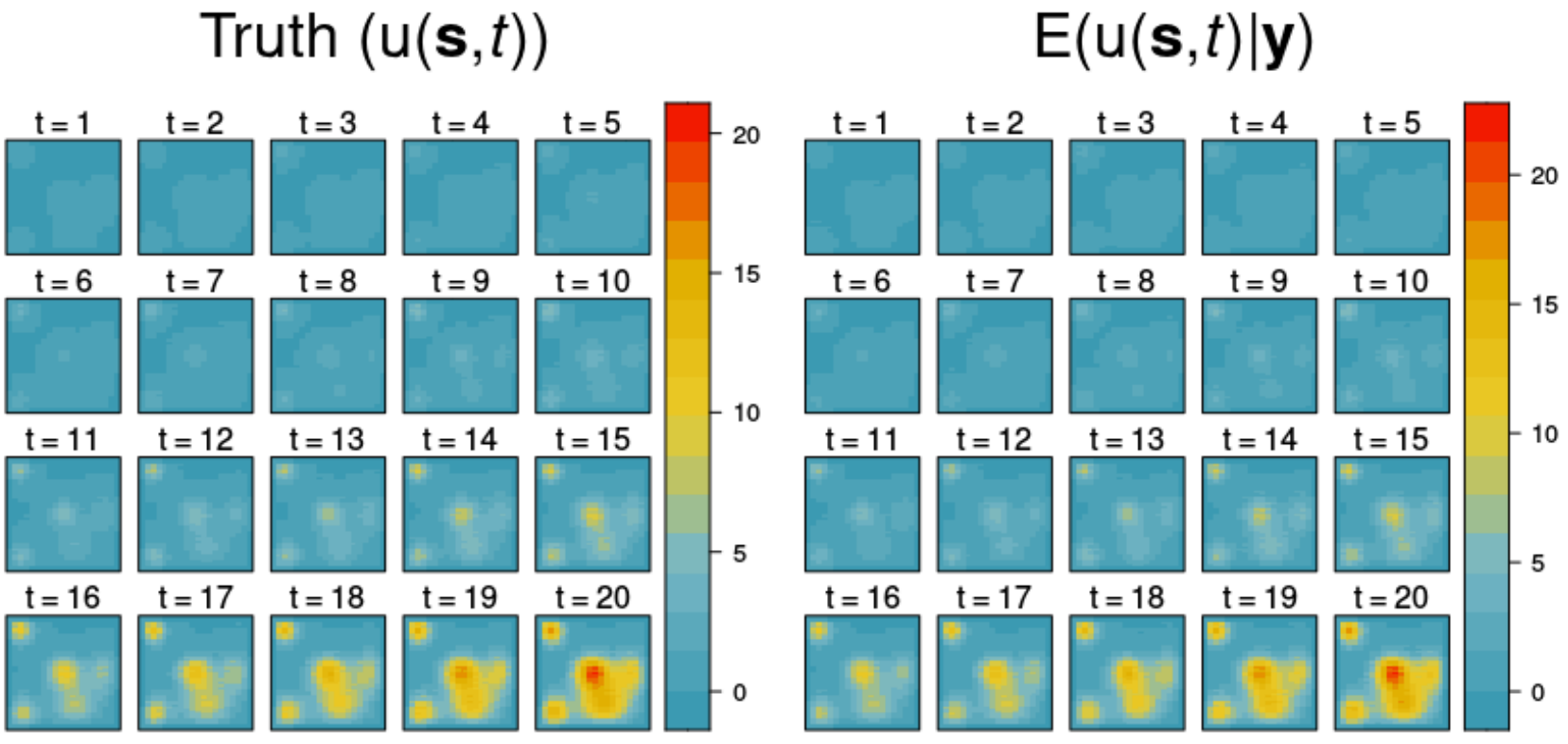


Actual $\alpha = (-8, 1)$, $\gamma = (0.2, 0.1)$, and $\beta = -10$.

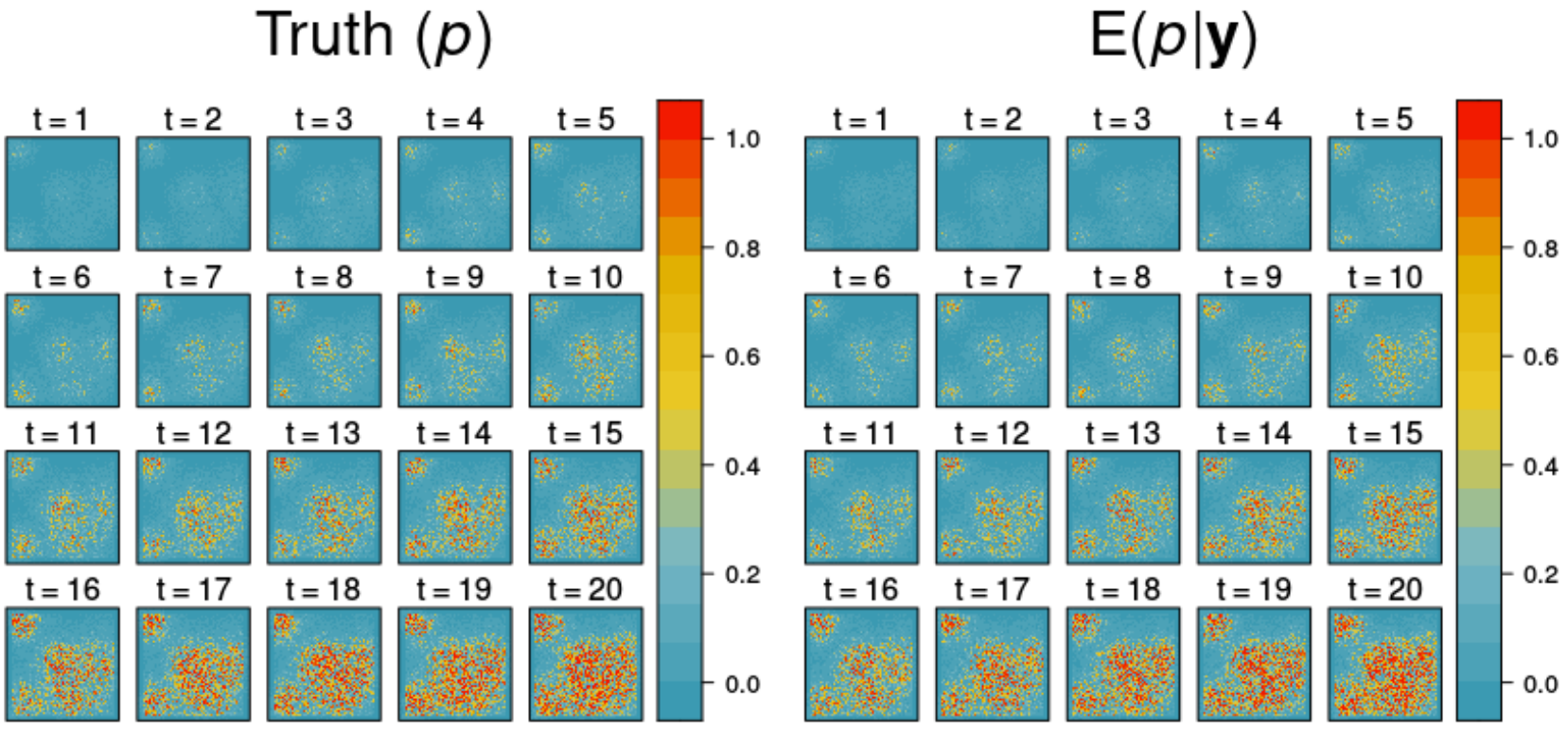
$$\frac{\partial}{\partial t} u(\mathbf{s}, t) = \left(\frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2} \right) \left[\mu(\mathbf{s}) u(\mathbf{s}, t) \right] + \lambda(\mathbf{s}) u(\mathbf{s}, t) + u(\mathbf{s}, 0)$$

where $\log(\mu(\mathbf{s})) = \alpha_0 + \mathbf{z}(\mathbf{s})'\alpha_1$ and $\lambda(\mathbf{s}) = \gamma_0 + \mathbf{w}(\mathbf{s})'\gamma_1$, and $\mathbf{z}$ and $\mathbf{w}$ are the spatial covariates that affect onward **transmission** (prevalence).

Estimated density of resistant infections (25% sampled)



Estimated probability of being sampled (25% sampled)



Error analysis

1. Identifying resistance hot spots.

   Can we still identify resistance hot spots when sampling a reduced proportion of the 10,000 $\times$ 10,000 region?

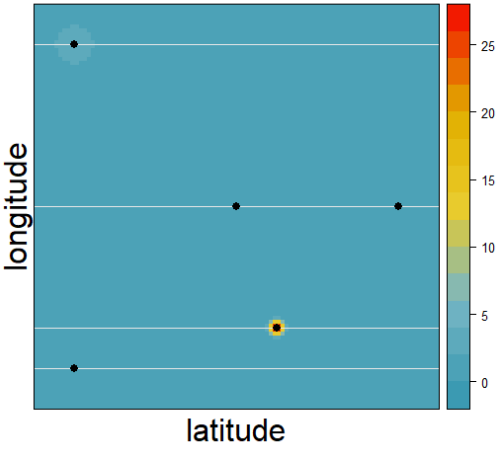
2. Comparing predictive and forecasting accuracy with a Generalised Additive Model (GAM)

   Unlike the partial differential equation in the mechanistic model, the spatial and temporal effects are modelled individually, and do not depend on covariates.

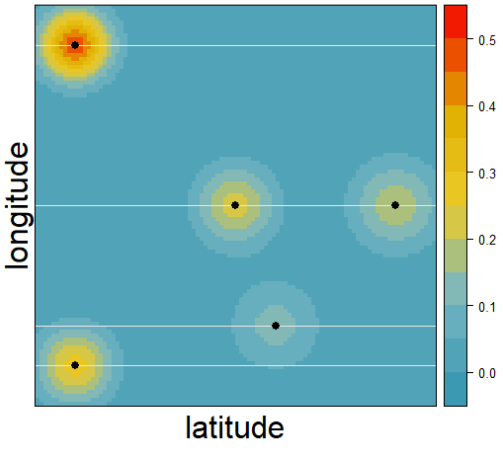
Identifying resistance hot spots

Swiss TPH

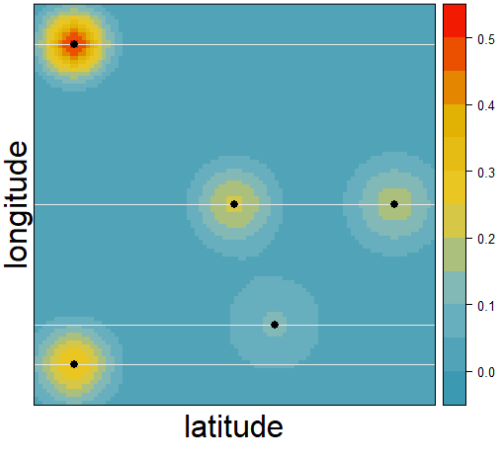
1% sampled



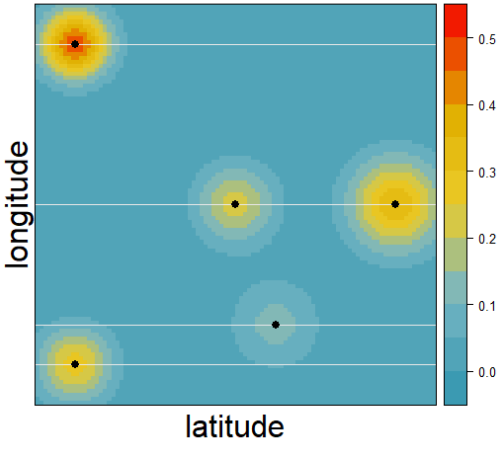
5% sampled



25% sampled



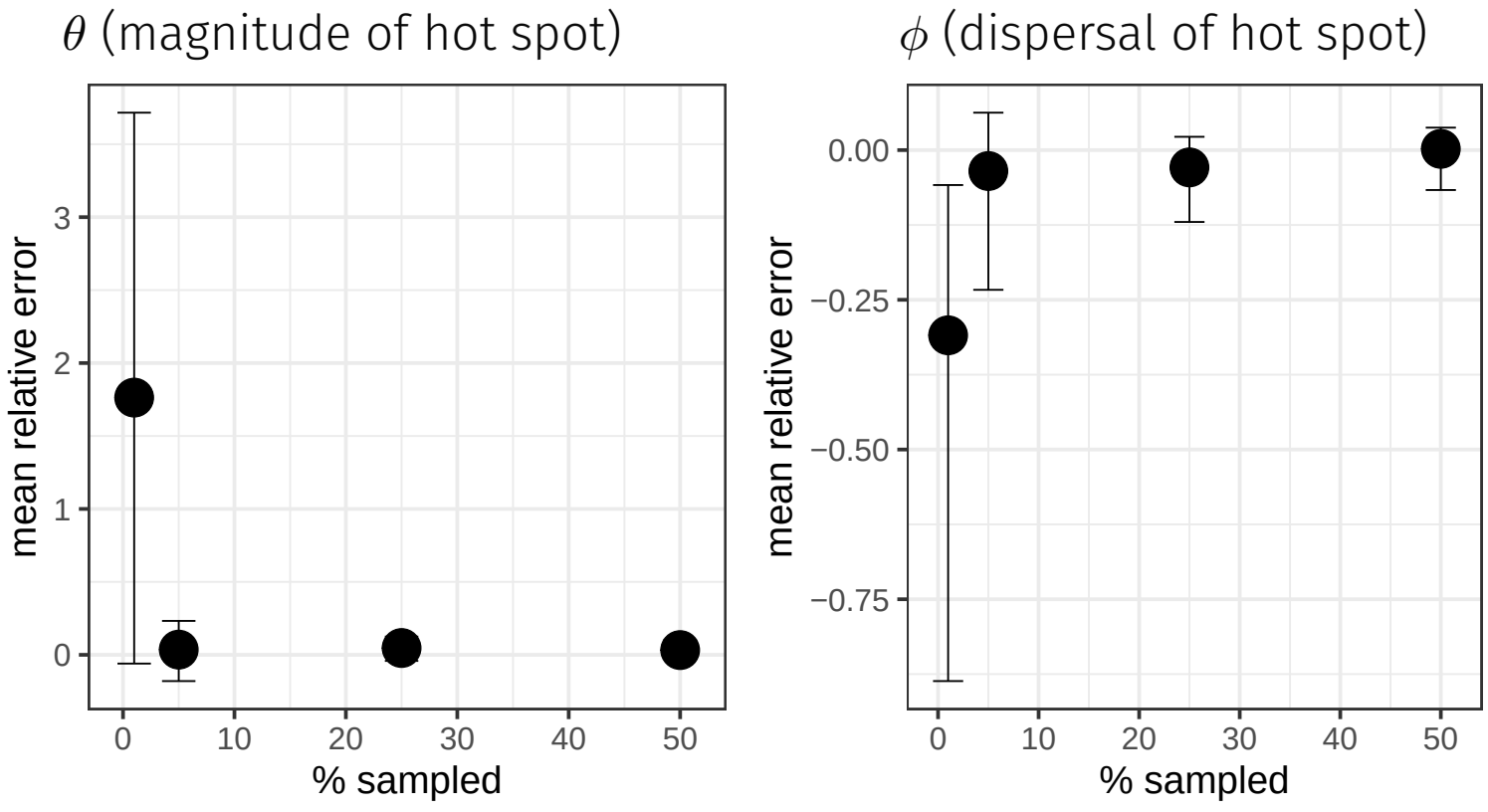
50% sampled



Identify introduction hot-spots

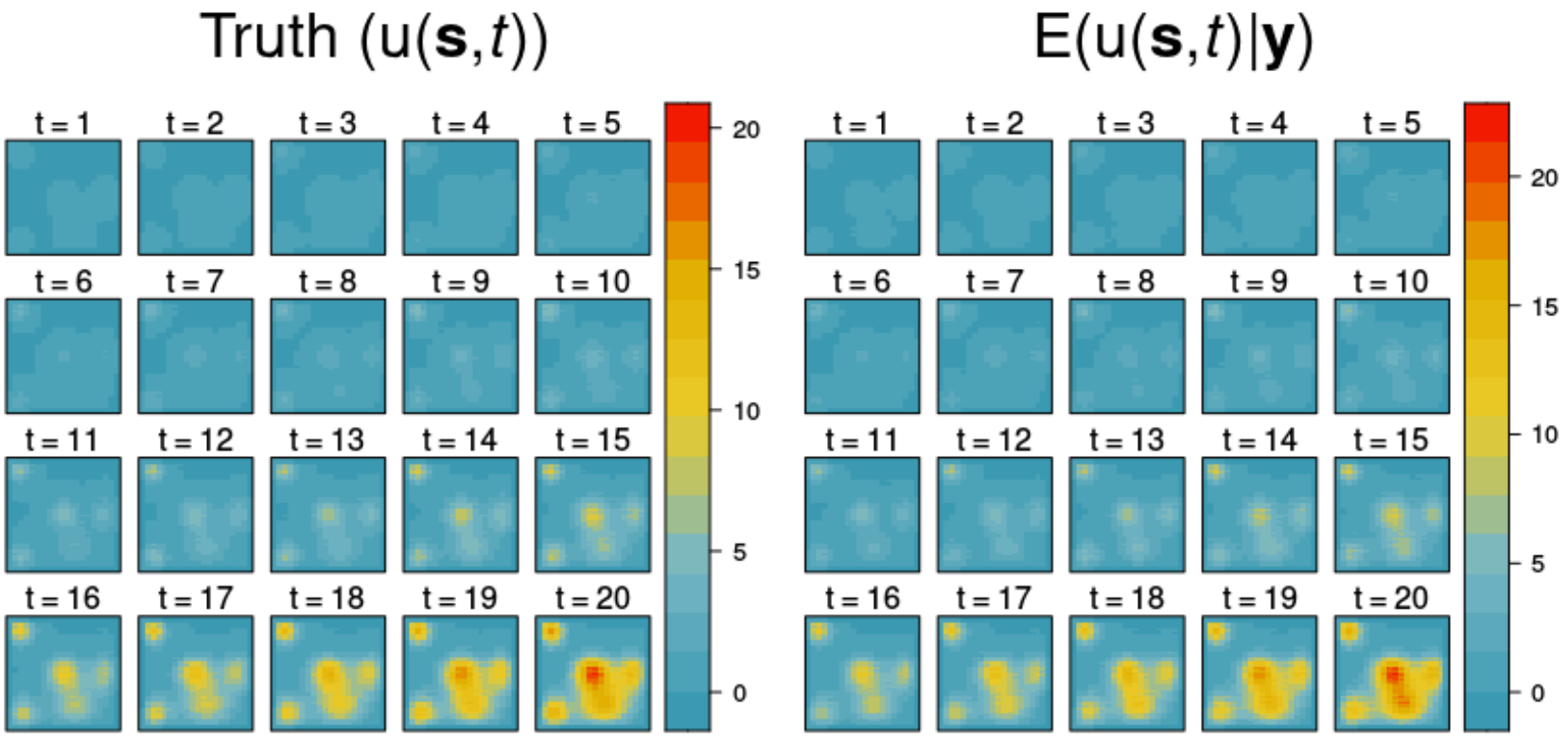
Swiss TPH

The error in θ_n and ϕ_n when sampling 50%, 25%, 5% and 1% at each time.



The black dot is the mean relative error over the $N = 5$ hot spots, $\frac{1}{N}\sum_N \frac{\hat{\phi}_n - \phi_n}{\phi_n}$, and the lines represent the *range* of the error.

Estimated density of resistant infections (5% sampled)



Comparison with Generalised Additive Model (GAM)

$$
\begin{aligned}
y_i &\sim \text{Bernoulli}(p_i) \\
g(p_i) &= \mathbf{x}_i\beta + \eta_t + \eta_s.
\end{aligned}
$$

- All the covariates are included in the vector $\mathbf{x}_i$ (age and disease prevalence).
- The effect of time η_n and space η_s are modelling using reduced dimension thin plate regression splines.
- The spatial and temporal effects are modelled individually, and do not depend on covariates.
- To check for collinearity between covariates and spatial and temporal effects, we also consider

$$
\begin{aligned}
y_i &\sim \text{Bernoulli}(p_i) \\
g(p_i) &= \mathbf{x}_i\beta.
\end{aligned}
$$

Comparison with Generalised Additive Model (GAM)

Swiss TPH

Generalised additive model coefficients

	$g(p_i)$	x	z	w
50%	$\mathbf{x}_i\beta + \eta_t + \eta_s$	-12.9	66.3	15.4
	$\mathbf{x}_i\beta$	-8.8	-63.3	64.7
25%	$\mathbf{x}_i\beta + \eta_t + \eta_s$	-13.1	41.4	15.6
	$\mathbf{x}_i\beta$	-8.8	-64.3	65.7
5%	$\mathbf{x}_i\beta + \eta_t + \eta_s$	-13.2	48.6	15.6
	$\mathbf{x}_i\beta$	-8.8	-62.6	64.1
2%	$\mathbf{x}_i\beta + \eta_t + \eta_s$	-13.0	51.3	59.8
	$\mathbf{x}_i\beta$	-8.6	79.8	-78.4

- **x**: sampling probability
- **z**: neighbouring transmission (diffusion)
- **w**: local transmission (growth)

Comparison with Generalised Additive Model (GAM)

Swiss TPH

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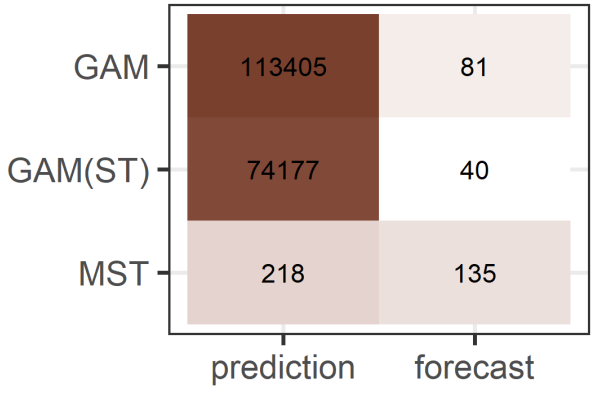
Comparison with Generalised Additive Model (GAM)

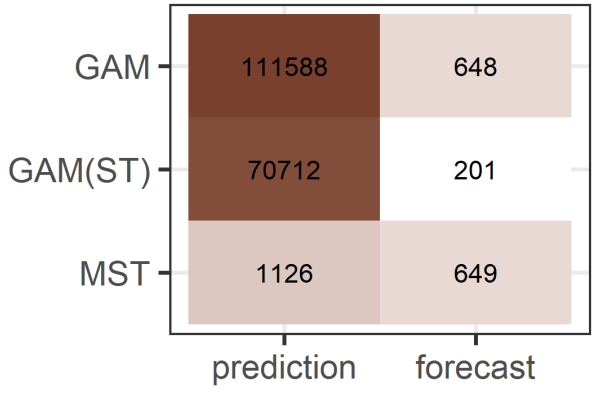
Swiss TPH

Out-of-sample model **prediction** validation for $t = [1, 15]$ and out-of-sample **forecast** validation for $t = [16, 20]$ using binomial deviance (SMALLER IS BETTER).

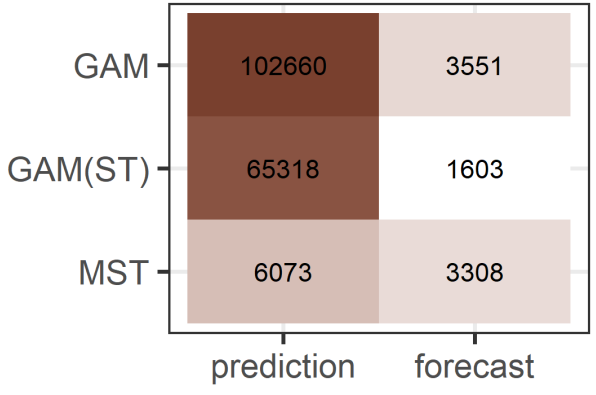
1% sampled



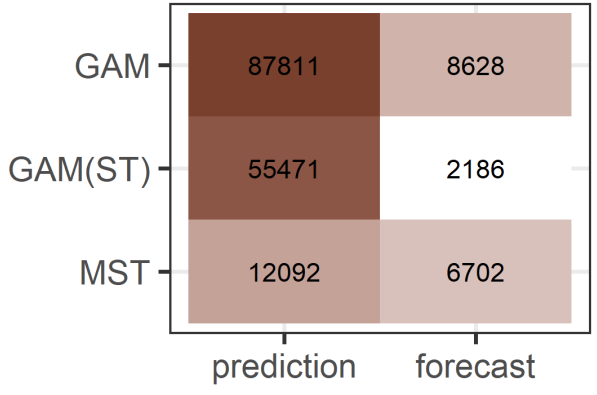
5% sampled



25% sampled



50% sampled



Conclusions

Proof of concept

- The mechanistic spatio-temporal model is more accurate than GAM for prediction.
- GAM encounters difficulty with collinearity when accounting for spatial and temporal autocorrelation.
- The mechanistic spatio-temporal model can identify which resistance hot spots are of most concern, even when only sampling 5% of the region.
- Versatile to different scales - from global, national, to district.
- The location of resistance hot spots can be set as unknown variables instead.
- Depending on the data, can use $y_i \sim \text{Poisson}(\lambda_i)$, not Bernoulli.

Acknowledgements

- Everyone at Swiss TPH, especially the Disease Modelling Unit & Dr. Christian Nsanzabana
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■ TamsinELee.com ■ @t_e_lee ■ Tamsin.Lee@swisstph.ch