

# Geostatistical modelling of the relationship between microfilariae and antigenaemia prevalence of lymphatic filariasis infection

Emanuele Giorgi<sup>1</sup>, Jorge Cano<sup>2</sup>, Rachel Pullan<sup>2</sup>

<sup>1</sup> Lancaster Medical School, Lancaster University, Lancaster, UK

<sup>2</sup> London School of Hygiene and Tropical Medicine, London, UK



RSS 2016 International Conference, 5-8 September, University of Manchester

# Overview

- Lymphatic filariasis: what is it? What diagnostics?
- Bivariate geostatistical modelling of prevalence from two different diagnostics.
  - ① A semi-mechanistic model for lymphatic filariasis microfilariae and antigenaemia prevalence.
  - ② An empirical model for prevalence from any two diagnostics.
- Application to lymphatic filariasis prevalence data from West Africa.
- Discussion.

# Lymphatic filariasis: the disease



Figure 1: Microfilaria of *Wuchereria*.



Figure 2: Microfilaria of *Brugia malayi*.



Figure 3: Patient with lymphedema.

## Lymphatic filariasis: the disease



Figure 4: Endemic areas for LF in red.

# Lymphatic filariasis: the vector



Figure 5: *Anopheles*.

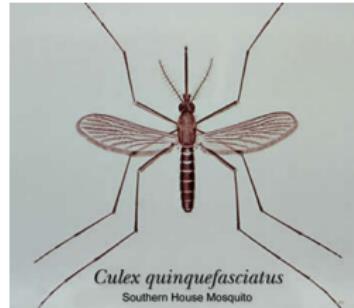


Figure 6: *Culex*.



Figure 7: *Aedes*.

# Lymphatic filariasis: the life cycle

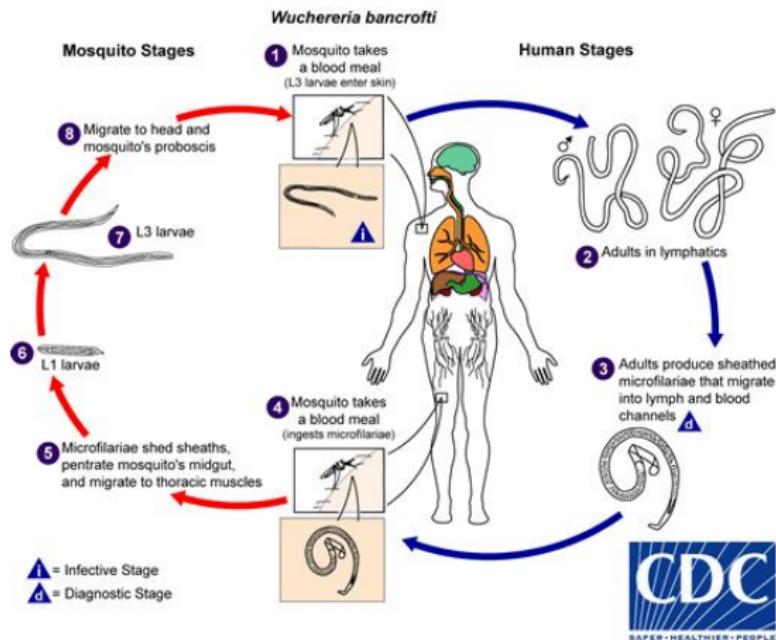


Figure 8: Life Cycle of *Wuchereria bancrofti*.

# Lymphatic filariasis: diagnosis



**Figure 9:** Counting microfilariae at night.



**Figure 10:** ICT card for LF antigens detection.

# Research question

- The data

$$\begin{aligned}\mathcal{D}_{MF} &= \{(x_{i,1}, n_{i,1}, y_{i,1}) : x_{i,1} \in A\}, \\ \mathcal{D}_{ICT} &= \{(x_{i,2}, n_{i,2}, y_{i,2}) : x_{i,2} \in A\}.\end{aligned}$$

# Research question

- The data

$$\begin{aligned}\mathcal{D}_{MF} &= \{(x_{i,1}, n_{i,1}, y_{i,1}) : x_{i,1} \in A\}, \\ \mathcal{D}_{ICT} &= \{(x_{i,2}, n_{i,2}, y_{i,2}) : x_{i,2} \in A\}.\end{aligned}$$

- A model for the data

$$Y_{i,j} | S_j(x_{i,j}), U_{i,j} \sim \text{Binomial}(n_{i,j}, p_j(x_{i,j})), i = 1, \dots, n_j, j = 1, 2.$$

# Research question

- The data

$$\begin{aligned}\mathcal{D}_{MF} &= \{(x_{i,1}, n_{i,1}, y_{i,1}) : x_{i,1} \in A\}, \\ \mathcal{D}_{ICT} &= \{(x_{i,2}, n_{i,2}, y_{i,2}) : x_{i,2} \in A\}.\end{aligned}$$

- A model for the data

$$Y_{i,j} | S_j(x_{i,j}), U_{i,j} \sim \text{Binomial}(n_{i,j}, p_j(x_{i,j})), i = 1, \dots, n_j, j = 1, 2.$$

## Objective

How should we build a bivariate geostatistical model for  $p_1(x)$  and  $p_2(x)$ ?

# A semi-mechanistic approach (1)

# A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.
- **Assumptions.**  $W \sim \text{Poisson}(\lambda)$ ,  $M|W = w \sim \text{Poisson}(rw)$ .

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.
- **Assumptions.**  $W \sim \text{Poisson}(\lambda)$ ,  $M|W = w \sim \text{Poisson}(rw)$ .
- ICT:  $p_1 = P(W > 0) = \phi(1 - \exp\{-\lambda\})$ . ( $\phi = 0.97$ )

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.
- **Assumptions.**  $W \sim \text{Poisson}(\lambda)$ ,  $M|W = w \sim \text{Poisson}(rw)$ .
- ICT:  $p_1 = P(W > 0) = \phi(1 - \exp\{-\lambda\})$ . ( $\phi = 0.97$ )
- MF:

$$p_2 = P(M > 0) = 1 - P(M = 0)$$

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.
- **Assumptions.**  $W \sim \text{Poisson}(\lambda)$ ,  $M|W = w \sim \text{Poisson}(rw)$ .
- ICT:  $p_1 = P(W > 0) = \phi(1 - \exp\{-\lambda\})$ . ( $\phi = 0.97$ )
- MF:

$$\begin{aligned} p_2 = P(M > 0) &= 1 - P(M = 0) \\ &= 1 - \sum_{w=0}^{+\infty} P(M = m|W = w)P(W = w) \end{aligned}$$

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.
- **Assumptions.**  $W \sim \text{Poisson}(\lambda)$ ,  $M|W = w \sim \text{Poisson}(rw)$ .
- ICT:  $p_1 = P(W > 0) = \phi(1 - \exp\{-\lambda\})$ . ( $\phi = 0.97$ )
- MF:

$$\begin{aligned} p_2 = P(M > 0) &= 1 - P(M = 0) \\ &= 1 - \sum_{w=0}^{+\infty} P(M = m|W = w)P(W = w) \\ &= 1 - \exp[-r(1 - \exp\{-\lambda\})] \end{aligned}$$

## A semi-mechanistic approach (1)

- $W$  = “number of worms in a sampled individual”.
- $M$  = “MF counts”.
- **Assumptions.**  $W \sim \text{Poisson}(\lambda)$ ,  $M|W = w \sim \text{Poisson}(rw)$ .
- ICT:  $p_1 = P(W > 0) = \phi(1 - \exp\{-\lambda\})$ . ( $\phi = 0.97$ )
- MF:

$$\begin{aligned} p_2 = P(M > 0) &= 1 - P(M = 0) \\ &= 1 - \sum_{w=0}^{+\infty} P(M = m|W = w)P(W = w) \\ &= 1 - \exp[-r(1 - \exp\{-\lambda\})] \\ &= 1 - \exp[-r\phi^{-1}p_1] \end{aligned}$$

## A semi-mechanistic approach (2)

- What varies spatially?

## A semi-mechanistic approach (2)

- What varies spatially?
- Density-independence:  $\lambda(x)$  and  $r(x) = \alpha > 0$  for all  $x$ .

## A semi-mechanistic approach (2)

- What varies spatially?
- Density-independence:  $\lambda(x)$  and  $r(x) = \alpha > 0$  for all  $x$ .
- Density-dependence:  $\lambda(x)$  and  $r(x) = \alpha\lambda(x)^\gamma$ ,  $\gamma \in \mathbb{R}$ .

## A semi-mechanistic approach (2)

- What varies spatially?
- Density-independence:  $\lambda(x)$  and  $r(x) = \alpha > 0$  for all  $x$ .
- Density-dependence:  $\lambda(x)$  and  $r(x) = \alpha\lambda(x)^\gamma$ ,  $\gamma \in \mathbb{R}$ .
- $\log\{\lambda(x)\} = d(x)^\top \beta + S(x) + Z(x)$ .

## A semi-mechanistic approach (2)

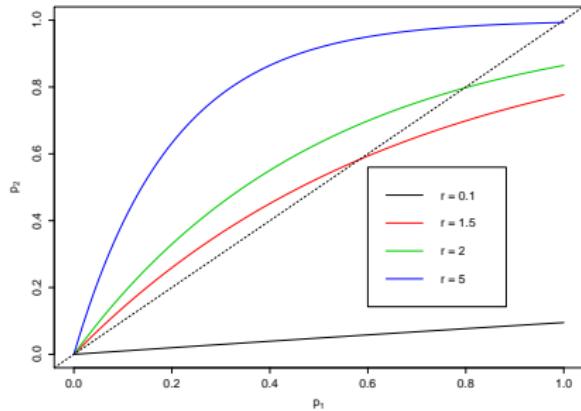
- What varies spatially?
- Density-independence:  $\lambda(x)$  and  $r(x) = \alpha > 0$  for all  $x$ .
- Density-dependence:  $\lambda(x)$  and  $r(x) = \alpha\lambda(x)^\gamma$ ,  $\gamma \in \mathbb{R}$ .
- $\log\{\lambda(x)\} = d(x)^\top \beta + S(x) + Z(x)$ .
- $S(x) \sim \text{GP}(0, \sigma^2, \rho(\cdot; \phi))$ .

## A semi-mechanistic approach (2)

- What varies spatially?
- Density-independence:  $\lambda(x)$  and  $r(x) = \alpha > 0$  for all  $x$ .
- Density-dependence:  $\lambda(x)$  and  $r(x) = \alpha\lambda(x)^\gamma$ ,  $\gamma \in \mathbb{R}$ .
- $\log\{\lambda(x)\} = d(x)^\top \beta + S(x) + Z(x)$ .
- $S(x) \sim \text{GP}(0, \sigma^2, \rho(\cdot; \phi))$ .
- $Z(x) \sim N(0, \tau^2)$  i.i.d.

## A semi-mechanistic approach (2)

- What varies spatially?
- Density-independence:  $\lambda(x)$  and  $r(x) = \alpha > 0$  for all  $x$ .
- Density-dependence:  $\lambda(x)$  and  $r(x) = \alpha\lambda(x)^\gamma$ ,  $\gamma \in \mathbb{R}$ .
- $\log\{\lambda(x)\} = d(x)^\top \beta + S(x) + Z(x)$ .
- $S(x) \sim \text{GP}(0, \sigma^2, \rho(\cdot; \phi))$ .
- $Z(x) \sim N(0, \tau^2)$  i.i.d.



# An empirical approach (1)

# An empirical approach (1)

- ICT:  $\log \{p_1(x)/[1 - p_1(x)]\} = d_1(x)^\top \beta_1 + S_1(x) + Z_1(x).$

# An empirical approach (1)

- ICT:  $\log \{p_1(x)/[1 - p_1(x)]\} = d_1(x)^\top \beta_1 + S_1(x) + Z_1(x).$
- MF:

$$\begin{aligned}\log \{p_2(x)/[1 - p_2(x)]\} &= d_2(x)^\top \beta_2 + S_2(x) + Z_2(x) + \\ &\quad \gamma f(p_1(x))\end{aligned}$$

where  $f : [0, 1] \rightarrow I \subseteq \mathbb{R}$  continuous non-decreasing.

# An empirical approach (1)

- ICT:  $\log \{p_1(x)/[1 - p_1(x)]\} = d_1(x)^\top \beta_1 + S_1(x) + Z_1(x).$
- MF:

$$\log \{p_2(x)/[1 - p_2(x)]\} = d_2(x)^\top \beta_2 + S_2(x) + Z_2(x) + \gamma f(p_1(x))$$

where  $f : [0, 1] \rightarrow I \subseteq \mathbb{R}$  continuous non-decreasing.

- Separate models if  $\gamma = 0$ .

# An empirical approach (1)

- ICT:  $\log \{p_1(x)/[1 - p_1(x)]\} = d_1(x)^\top \beta_1 + S_1(x) + Z_1(x).$
- MF:

$$\log \{p_2(x)/[1 - p_2(x)]\} = d_2(x)^\top \beta_2 + S_2(x) + Z_2(x) + \gamma f(p_1(x))$$

where  $f : [0, 1] \rightarrow I \subseteq \mathbb{R}$  continuous non-decreasing.

- Separate models if  $\gamma = 0$ .
- If  $S_2(x) = 0$ , for all  $x$ , and  $f(p_1(x)) = \log\{p_1(x)/[1 - p_1(x)]\}$ , we recover Crainiceanu, Diggle and Rowlingson (2008).

# An empirical approach (1)

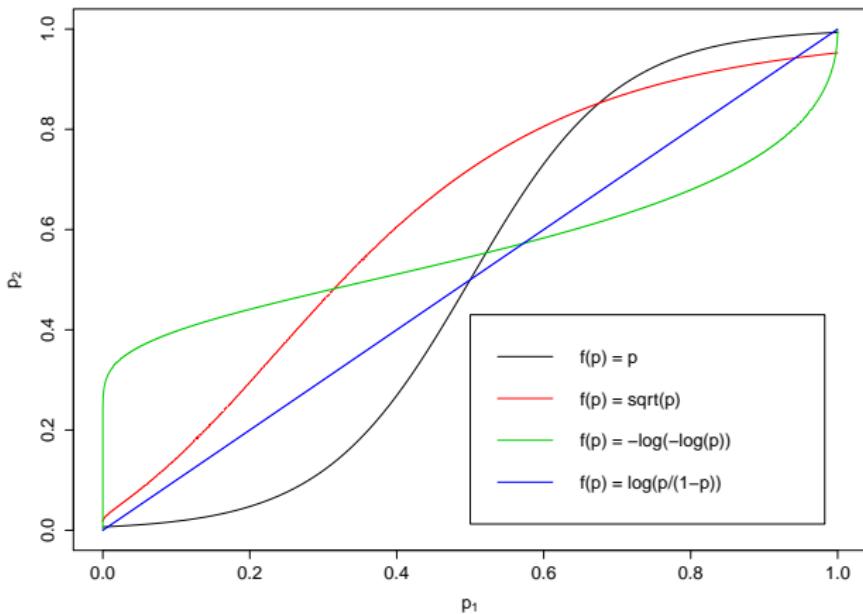
- ICT:  $\log \{p_1(x)/[1 - p_1(x)]\} = d_1(x)^\top \beta_1 + S_1(x) + Z_1(x).$
- MF:

$$\log \{p_2(x)/[1 - p_2(x)]\} = d_2(x)^\top \beta_2 + S_2(x) + Z_2(x) + \gamma f(p_1(x))$$

where  $f : [0, 1] \rightarrow I \subseteq \mathbb{R}$  continuous non-decreasing.

- Separate models if  $\gamma = 0$ .
- If  $S_2(x) = 0$ , for all  $x$ , and  $f(p_1(x)) = \log\{p_1(x)/[1 - p_1(x)]\}$ , we recover Crainiceanu, Diggle and Rowlingson (2008).
- If  $\gamma = 1$  and  $f(p_1(x)) = \log\{p_1(x)/[1 - p_1(x)]\} - d_1(x)^\top \beta_1 - Z_1(x)$ , we recover Giorgi, Sesay, Terlouw and Diggle (2015).

## An empirical approach (2)



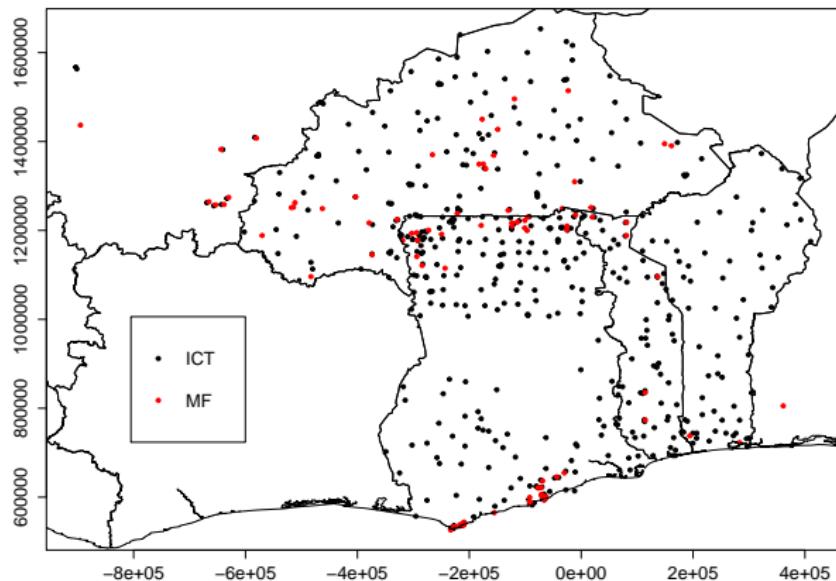
# Application: LF mapping in West Africa

## Application: LF mapping in West Africa

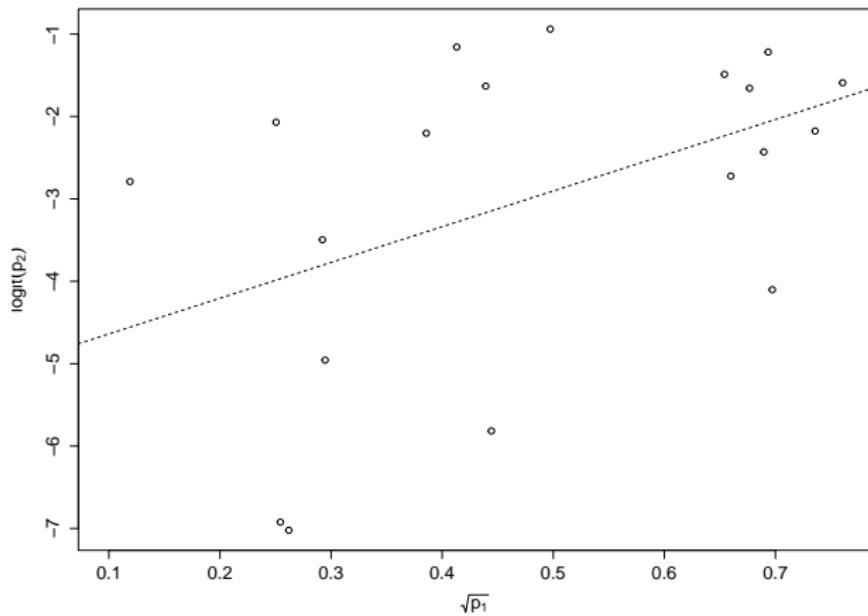
- MF and ICT surveys conducted from 1997 to 2003.

# Application: LF mapping in West Africa

- MF and ICT surveys conducted from 1997 to 2003.
- 479 ICT surveys; on average 61 individuals sampled per village.
- 90 MF surveys; on average 245 individuals sampled per village.



# Empirical relationship



# Estimation (1)

## **Semi-mechanistic model with density-dependence**

- $\log\{\lambda(x)\} = \mu + S(x) + Z(x)$ ,  $r(x) = \alpha\lambda(x)^\gamma$  for all  $x$ .

## Semi-mechanistic model with density-dependence

- $\log\{\lambda(x)\} = \mu + S(x) + Z(x)$ ,  $r(x) = \alpha\lambda(x)^\gamma$  for all  $x$ .
- $\text{cov}\{S(x), S(x + h)\} = \sigma^2 \exp(-\|h\|/\phi)$ .  
 $\text{var}\{Z(x)\} = \nu^2 \sigma^2$ .

# Estimation (1)

## Semi-mechanistic model with density-dependence

- $\log\{\lambda(x)\} = \mu + S(x) + Z(x)$ ,  $r(x) = \alpha\lambda(x)^\gamma$  for all  $x$ .
- $\text{cov}\{S(x), S(x+h)\} = \sigma^2 \exp(-\|h\|/\phi)$ .  
 $\text{var}\{Z(x)\} = \nu^2 \sigma^2$ .

Term	Estimate	95% CI
$\mu$	-2.562	(-3.991, -1.132)
$\alpha$	0.722	(0.636, 0.820)
$\gamma$	0.106	(0.010, 0.203)
$\sigma^2$	2.974	(1.392, 6.355)
$\phi$	275.995	(117.374, 648.980)
$\nu^2$	0.201	(0.091, 0.445)

## Estimation (2)

### Empirical model

- $\log\{p_1(x)/[1 - p_1(x)]\} = \mu_1 + S_1(x) + Z_1(x).$   
 $\log\{p_2(x)/[1 - p_2(x)]\} = \mu_2 + S_2(x) + Z_2(x) + \gamma\sqrt{p_1(x)}$

## Estimation (2)

### Empirical model

- $\log\{p_1(x)/[1 - p_1(x)]\} = \mu_1 + S_1(x) + Z_1(x).$   
 $\log\{p_2(x)/[1 - p_2(x)]\} = \mu_2 + S_2(x) + Z_2(x) + \gamma\sqrt{p_1(x)}$
- $\text{cov}\{S_i(x), S_i(x + h)\} = \sigma_i^2 \exp(-\|h\|/\phi_i).$   
 $\text{var}\{Z_i(x)\} = \nu_i^2 \sigma_i^2, i=1,2.$

## Estimation (2)

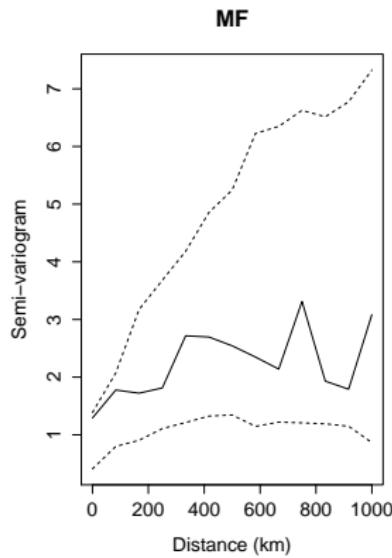
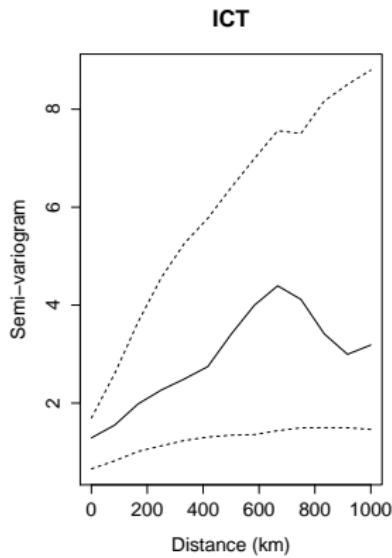
### Empirical model

- $\log\{p_1(x)/[1 - p_1(x)]\} = \mu_1 + S_1(x) + Z_1(x).$   
 $\log\{p_2(x)/[1 - p_2(x)]\} = \mu_2 + S_2(x) + Z_2(x) + \gamma \sqrt{p_1(x)}$
- $\text{cov}\{S_i(x), S_i(x + h)\} = \sigma_i^2 \exp(-\|h\|/\phi_i).$   
 $\text{var}\{Z_i(x)\} = \nu_i^2 \sigma_i^2, i=1,2.$

Term	Estimate	95% CI
$\mu_1$	-2.244	(-4.201, -0.287)
$\mu_2$	-3.055	(-3.763, -2.348)
$\gamma$	0.476	(0.200, 0.752)
$\sigma_1^2$	4.205	(1.667, 10.608)
$\phi_1$	354.055	(126.608, 990.106)
$\nu_1^2$	0.172	(0.066, 0.449)
$\sigma_2^2$	1.796	(0.909, 3.550)
$\phi_2$	82.555	(34.412, 198.052)
$\nu_2^2$	0.228	(0.069, 0.760)

# Model diagnostic (1)

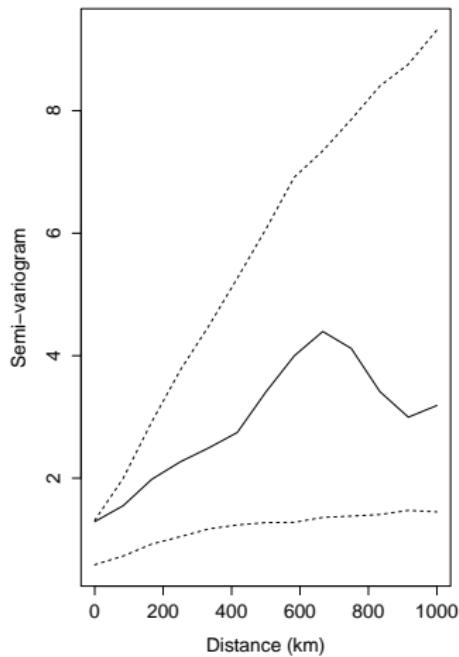
## Semi-mechanistic model with density-dependence



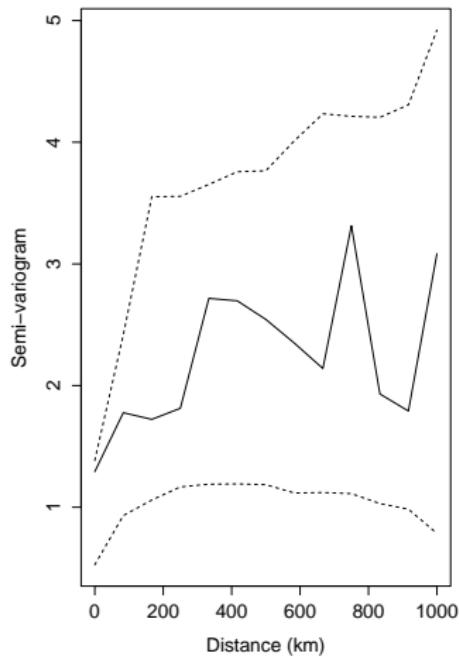
# Model diagnostic (2)

## Empirical model

ICT



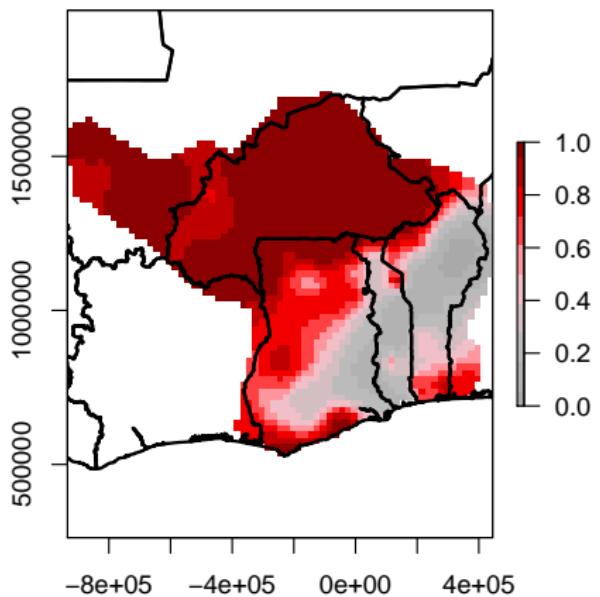
MF



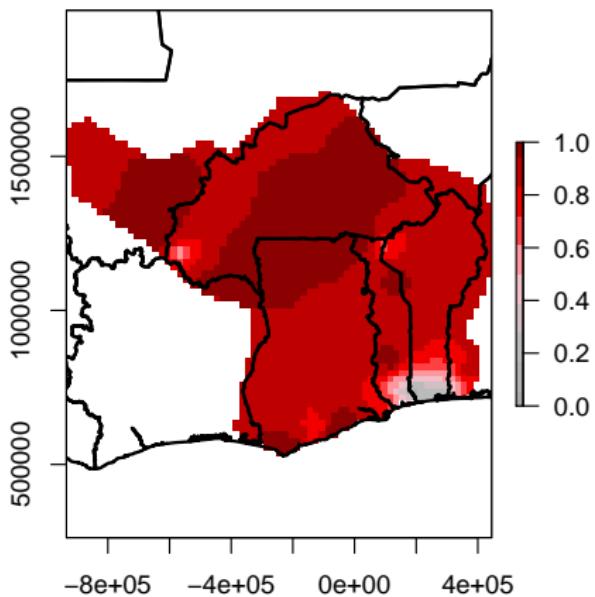
# Exceeding 1% MF prevalence

# Exceeding 1% MF prevalence

Semi-mechanistic model



Empirical model



# Discussion

- Which model is the best with respect to the scientific knowledge?

# Discussion

- Which model is the best with respect to the scientific knowledge?
- **Simulation study:** empirical model provides robust inferences against the misspecification of  $f$ .
- **Simulation study:** misspecification of the model may still yield accurate point predictions but actual coverage of CI may be very different from the nominal.

# Discussion

- Which model is the best with respect to the scientific knowledge?
- **Simulation study:** empirical model provides robust inferences against the misspecification of  $f$ .
- **Simulation study:** misspecification of the model may still yield accurate point predictions but actual coverage of CI may be very different from the nominal.

Thank you for your attention!

# Bibliography

- ① M. A. Irvine, S. M. Njenga, S. Gunawardena, C. N. Wamae, J. Cano, S. J. Brooker, and T. D. Hollingsworth. **Understanding the relationship between prevalence of microfilariae and antigenaemia using a model of lymphatic filariasis infection.** Trans R Soc Trop Med Hyg (2016) 110(5): 317 doi:10.1093/trstmh/trw024
- ② C. Crainiceanu, P.J. Diggle, and B.S. Rowlingson. **Bivariate modelling and prediction of spatial variation in Loa loa prevalence in tropical Africa (with Discussion).** (2008) Journal of the American Statistical Association, 103, 21-43.
- ③ E. Giorgi, S.S. Sesay, D.J. Terlouw and P.J., Diggle. **Combining data from multiple spatially referenced prevalence surveys using generalized linear geostatistical models.** (2015) Journal of the Royal Statistical Society A 178, 445-464.