

# How host heterogeneity governs tuberculosis reinfection

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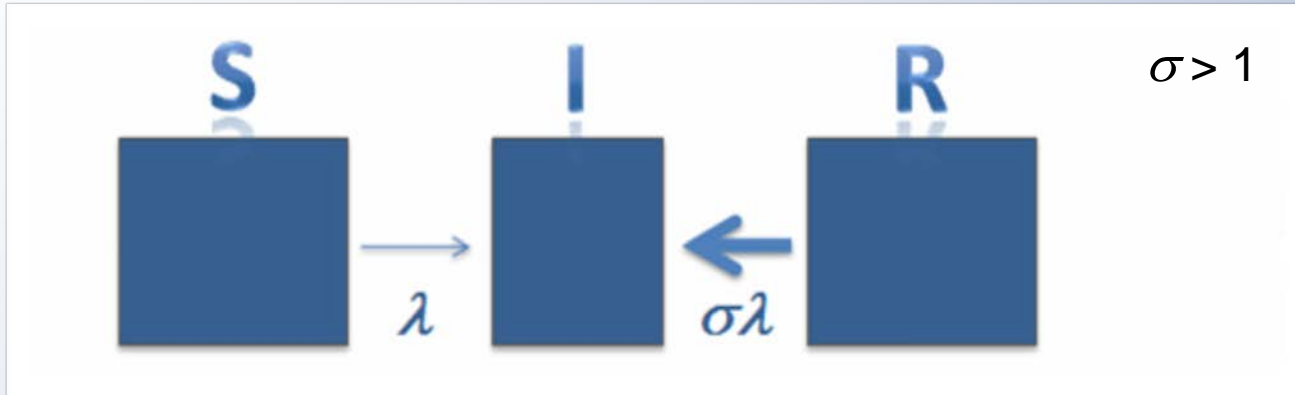
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# Rate of Reinfection Tuberculosis after Successful Treatment Is Higher than Rate of New Tuberculosis

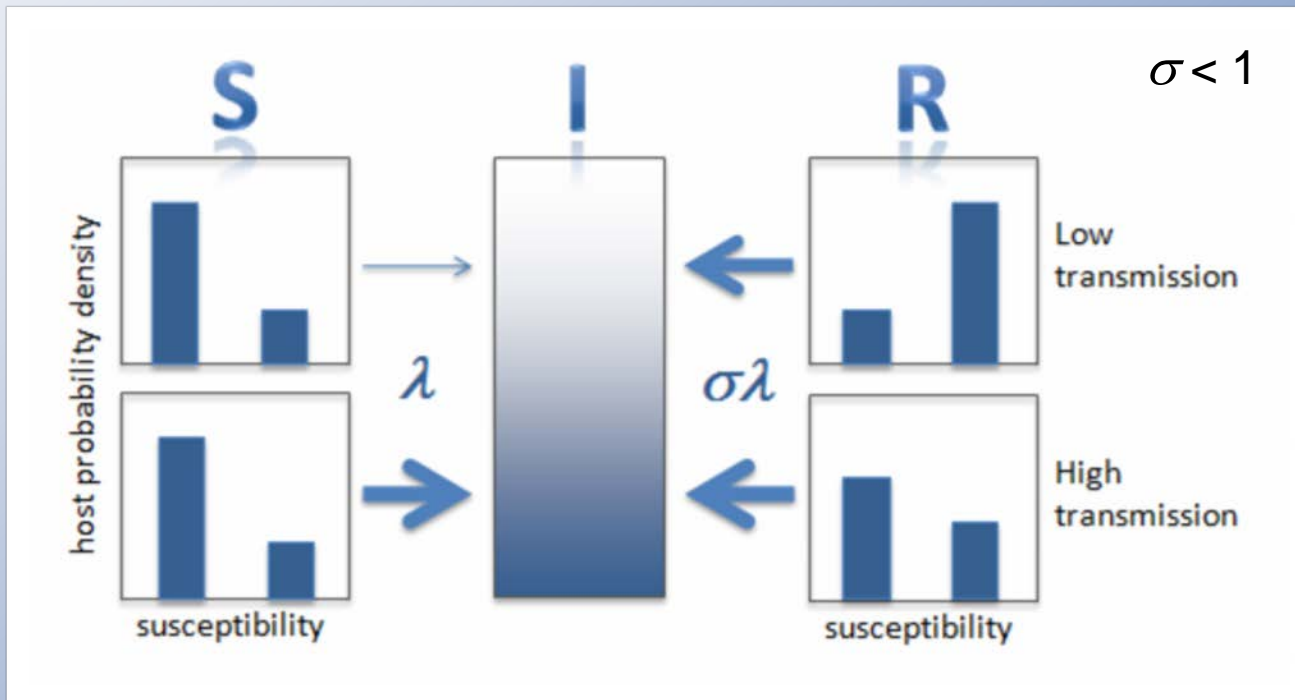
Suzanne Verver, Robin M. Warren, Nulda Beyers, Madalene Richardson,<sup>†</sup> Gian D. van der Spuy, Martien W. Borgdorff, Donald A. Enarson, Marcel A. Behr, and Paul D. van Helden



# Two interpretations



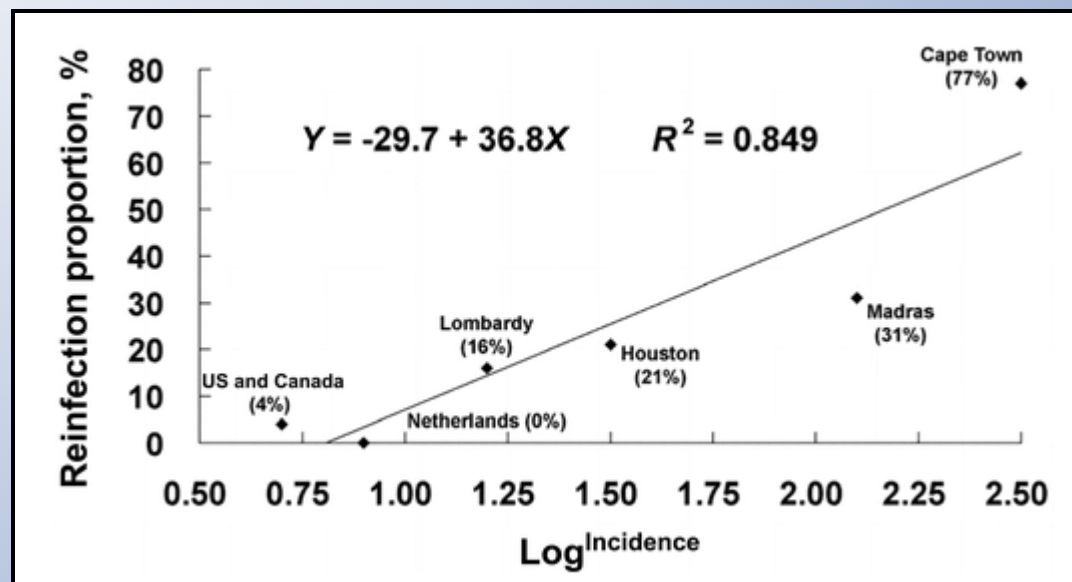
*or*



## Prediction of the Tuberculosis Reinfection Proportion from the Local Incidence

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# Transmission model

$$\frac{dS_i}{dt} = \mu\gamma_i - (\lambda_i + \mu)S_i$$

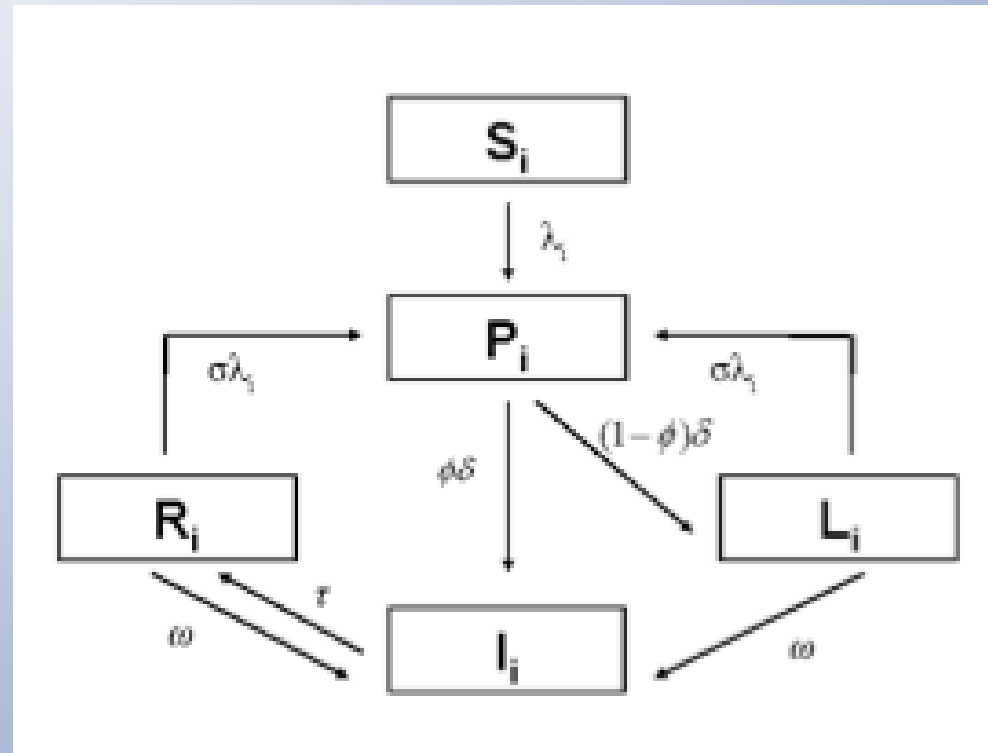
$$\frac{dP_i}{dt} = \lambda_i S_i + \sigma\lambda_i(L_i + R_i) - (\delta + \mu)P_i$$

$$\frac{dI_i}{dt} = \phi\delta P_i + \omega(L_i + R_i) - (\tau + \mu)I_i$$

$$\frac{dL_i}{dt} = (1 - \phi)\delta P_i - (\sigma\lambda_i + \omega + \mu)L_i$$

$$\frac{dR_i}{dt} = \tau I_i - (\sigma\lambda_i + \omega + \mu)R_i$$

$$\lambda_i = \alpha_i \lambda$$

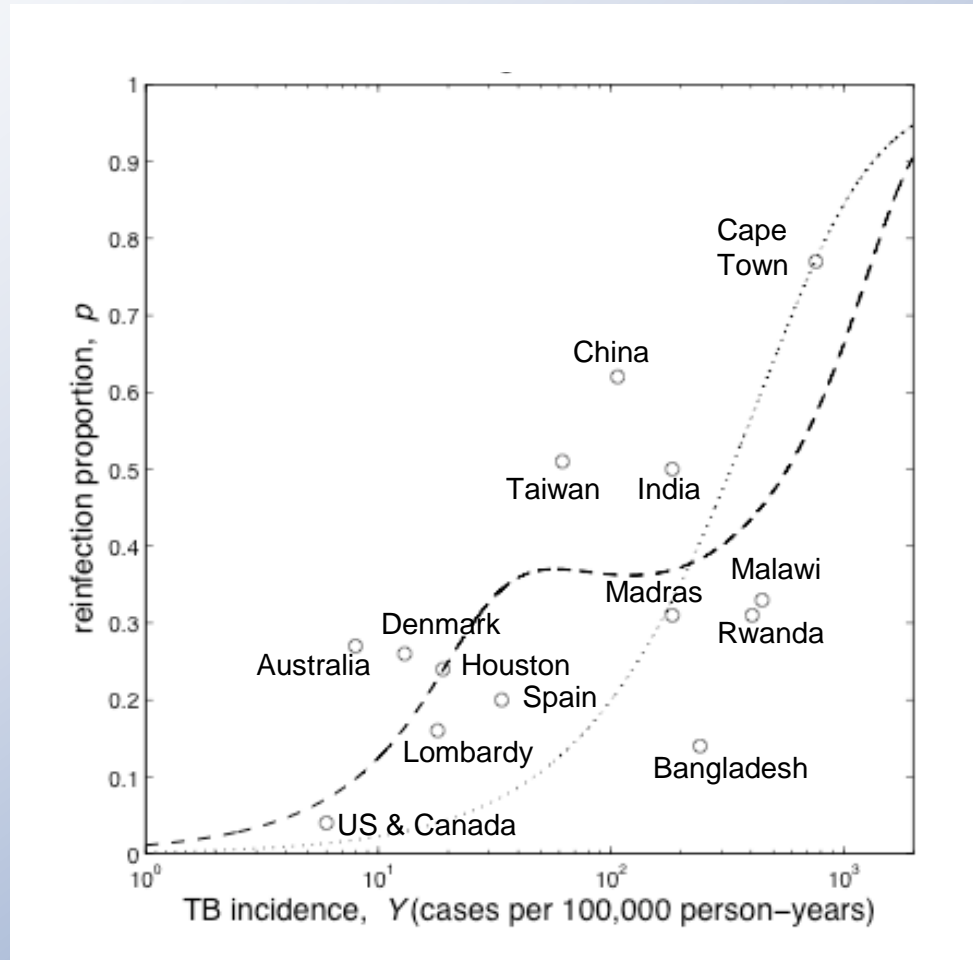


# Systematic literature review

Region	TB incidence per 100,000	Reinfection proportion, $p$	Reference
US & Canada	6*	0.04 (3/75)	Jasmer <i>et al.</i> 2004 [18]
Australia	8*	0.27 (4/15)	Dobler <i>et al.</i> 2009 [19]
Denmark	13*	0.26 (19/73)	Bang <i>et al.</i> 2010 [20]
Lombardy	18	0.16 (5/32)	Bandera <i>et al.</i> 2001 [21]
Houston	19	0.24 (6/25)	El Sahly <i>et al.</i> 2004 [22]
Spain	34*	0.20 (8/40)	Martin <i>et al.</i> 2011 [23]
Taiwan	62	0.51 (25/49)	Wang <i>et al.</i> 2007 [3]
China	107*	0.62 (32/52)	Shen <i>et al.</i> 2006 [24]
Madras	184*	0.31 (9/29)	Sahadevan <i>et al.</i> 1995 [25]
India	184*	0.50 (24/48)	Narayanan <i>et al.</i> 2010 [26]
Bangladesh	242*	0.14 (5/35)	Shamputa <i>et al.</i> 2007 [27]
Rwanda	405*	0.31 (4/13)	Umubyeyi <i>et al.</i> 2007 [28]
Malawi	447*	0.33 (13/39)	Crampin <i>et al.</i> 2010 [29]
Cape Town	761	0.77 (24/31)	Verver <i>et al.</i> 2005 [4]

\* WHO estimates for TB incidence in 2000.

# Fitting model to data



# Fitting model to data

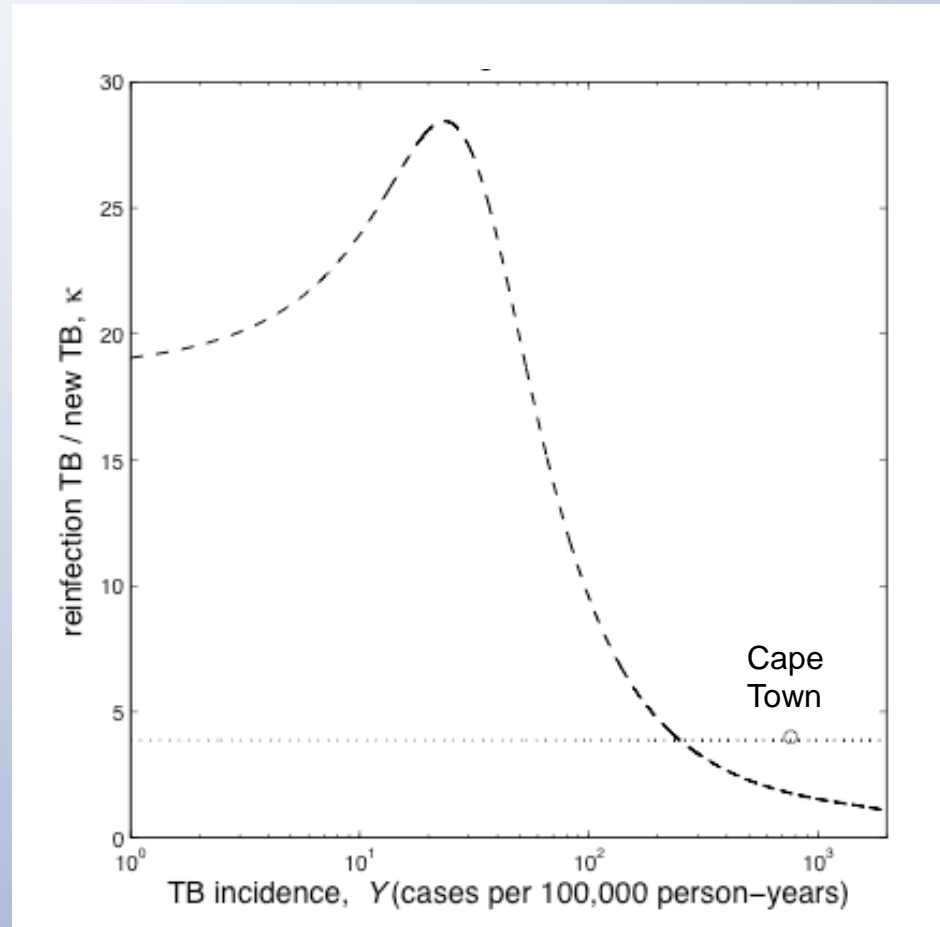
Symbol	Definition	Value
$\mu$	birth and death rate	1/70 yr <sup>-1</sup>
$\phi$	proportion progressing from primary infection to disease	0.05
$\delta$	rate of progression from primary infection	12 yr <sup>-1</sup>
$\tau$	rate at which infectious individuals are detected and treated	2 yr <sup>-1</sup>
$\omega$	rate of endogenous reactivation	0.01 yr <sup>-1</sup>
$\sigma$	reinfection factor	estimated
$\gamma$	proportion low-risk group	estimated
$\alpha$	low-risk factor	estimated

Parameter	Heterogeneous model	Homogeneous model
$\gamma$	0.98 [0.95, 1.00] <sup>*</sup>	NA
$\alpha$	0.15 [0.00, 0.56] <sup>*</sup>	NA
$\sigma$	0.51 [0.00, 2.37] <sup>*</sup>	3.87 [1.61, 7.79] <sup>*</sup>
Residual sum of squares	0.30	0.74
Standard error estimate	0.16	0.24
F test	8.12 (0.007) <sup>**</sup>	NA
Log-likelihood test	12.70 (0.002) <sup>**</sup>	NA

\* Mode [95% confidence interval]. \*\* Score (p-value).



# Prediction



## Conclusions:

Host heterogeneity improves model fit to data linking reinfection proportion in TB recurrences with TB incidence;

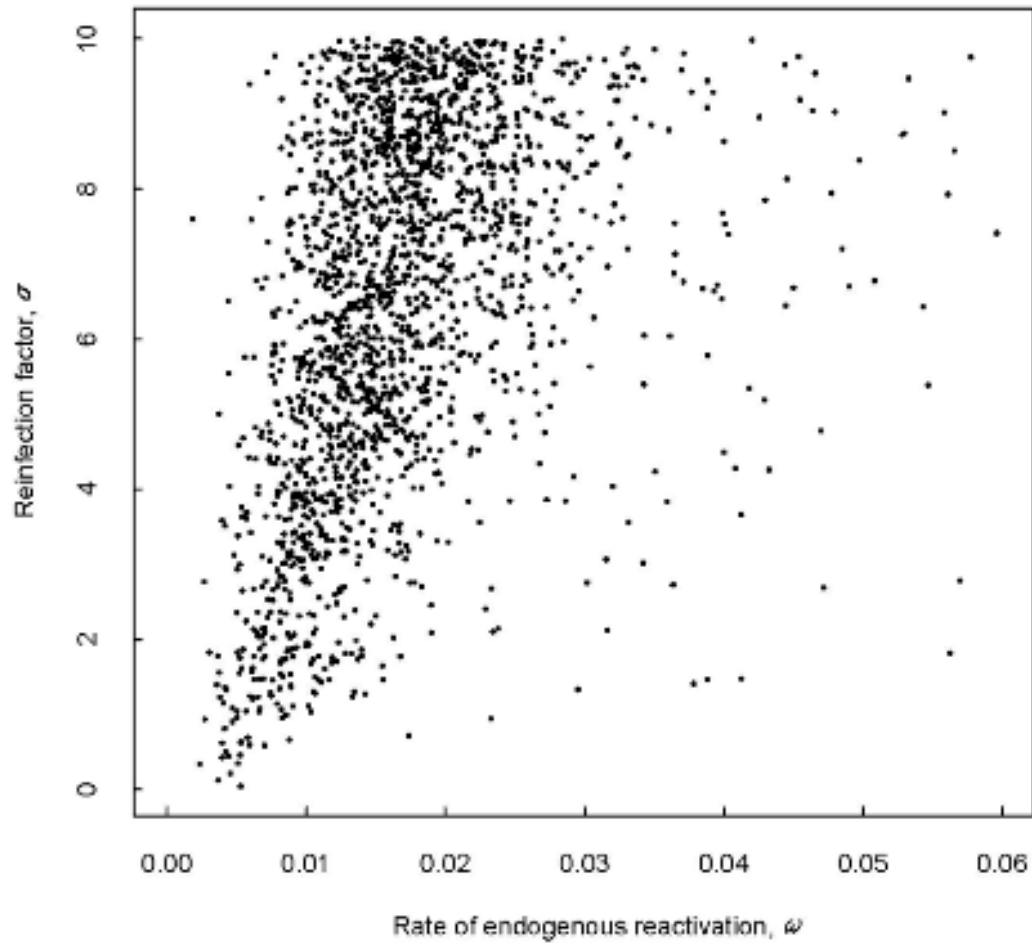
At the individual level, the model predicts that *the rate of reinfection TB is lower than the rate of new TB*;

At the population level, the model predicts that *the rate of reinfection TB is higher than the rate of new TB*, more so under low and moderate transmission;

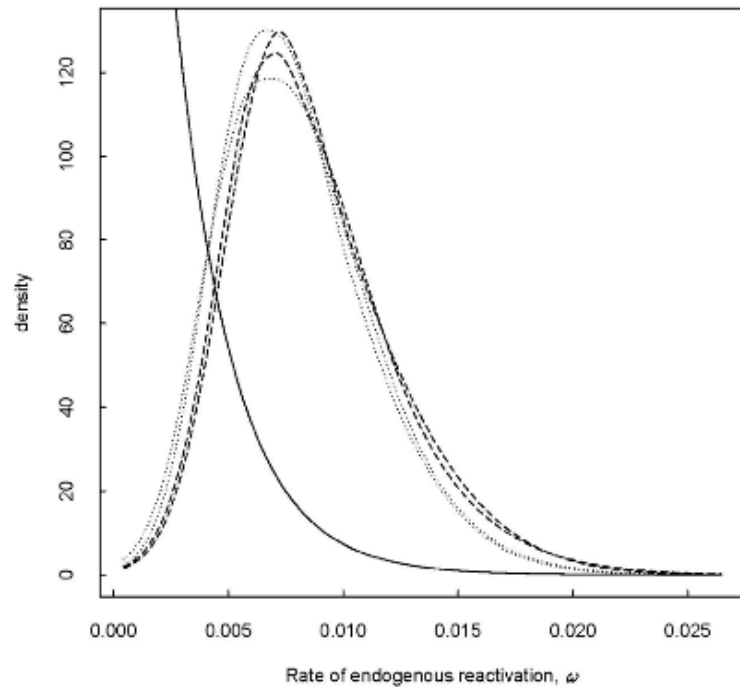
Host heterogeneity reconciles the two predictions above;

Testing and refinement of these predictions require direct measurement of the ratio “reinfection TB / new TB”, at individual and population levels.

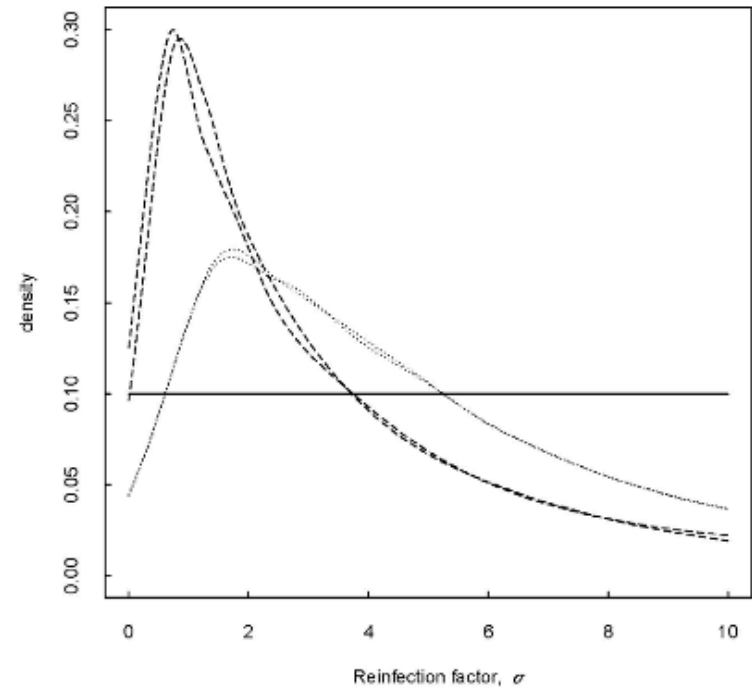
# Supplementary Material



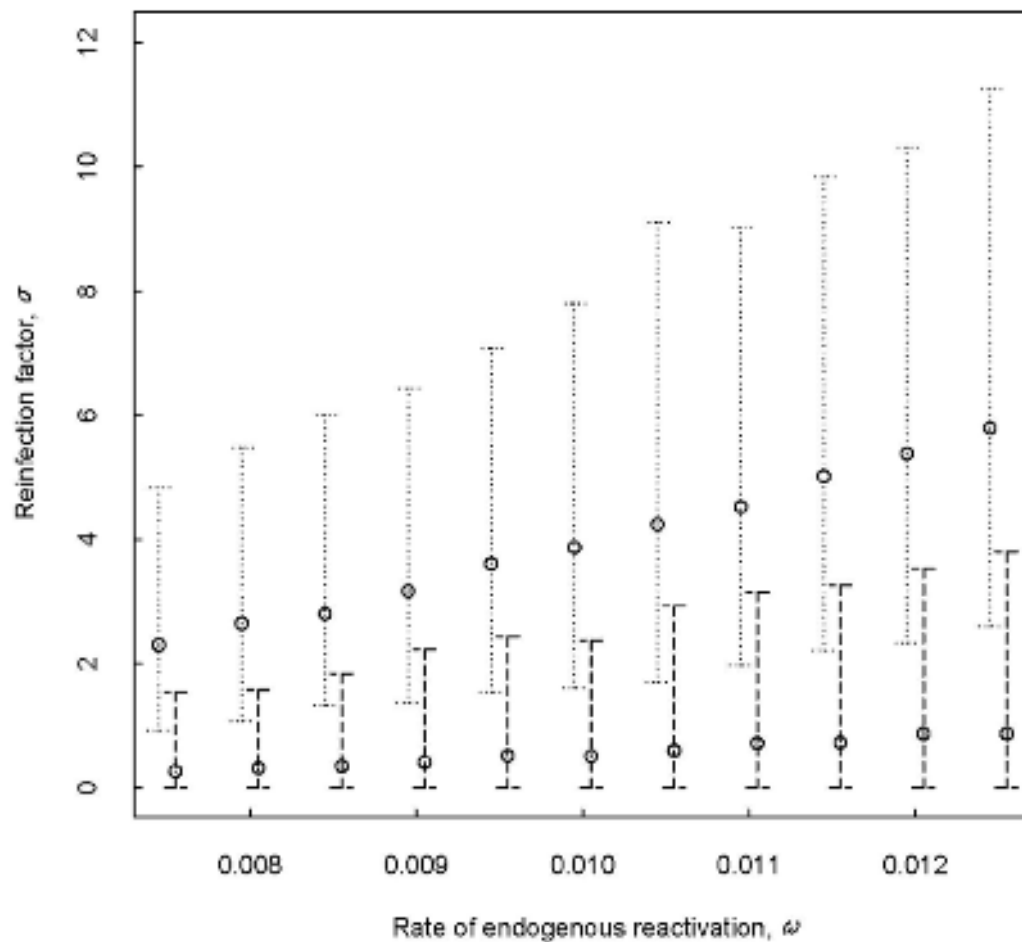
**Figure S1.** Plot of the trace of  $\sigma$  against the trace of  $\omega$  from a MCMC method assuming the homogeneous model with uninformative prior distributions.



**Figure S2.** Estimation of  $\omega$ : prior distribution in full line; posterior distributions for both replicates of homogeneous model in dotted line; posterior distribution for both replicates of heterogeneous model in dashes line.



**Figure S3.** Estimation of  $\sigma$ : prior distribution in full line; posterior distributions for both replicates of homogeneous model in dotted line; posterior distribution for both replicates of heterogeneous model in dashes line.



**Figure S4.** Sensitivity analysis on the fixed parameter  $\omega$  regarding the estimation of  $\sigma$  and its 95% confidence intervals: analysis assuming a homogeneous model in dotted line; analysis assuming a heterogeneous model in dashed line.

**Table S1.** Prior distributions used in the MCMC runs.

Parameter	Distribution
$\gamma$	Uniform(0,1)
$\alpha$	Uniform(0,1)
$\sigma$	Uniform(0,1)
$\omega$	Exponential(1/0.0025)
Standard error of estimate (SEE)	Uniform(0,1)

**Table S2.** Estimated parameters using MCMC for both homogeneous and heterogeneous model. The 95% credible intervals are presented in square brackets.

Parameter	Heterogeneous model	Homogeneous model
$\gamma$	0.98 [0.67, 1.00]	NA
	0.98 [0.67, 1.00]	NA
$\alpha$	0.35 [0.13, 1.00]	NA
	0.38 [0.12, 1.00]	NA
$\sigma$	0.85 [0.00, 7.99]	1.71 [0.03, 8.83]
	0.74 [0.00, 8.09]	1.74 [0.02, 8.80]
$\omega$	0.01 [0.00, 0.02]	0.01 [0.00, 0.02]
	0.01 [0.00, 0.02]	0.23 [0.12, 0.39]
SEE	0.23 [0.12, 0.39]	0.25 [0.17, 0.42]
	0.23 [0.12, 0.40]	0.25 [0.17, 0.42]

**Table S3.** Estimated parameters ( $\omega = 0.01$ ).

Parameter	Heterogeneous model	Homogeneous model
$\gamma$	0.98 [0.95, 1.00]	NA
$\alpha$	0.15 [0.00, 0.56]	NA
$\sigma$	0.51 [0.00, 2.37]	3.87 [1.61, 7.79]
RSS	0.30	0.74
SEE	0.16	0.24
F test	8.12 (0.007)	NA
Log-likelihood test	12.70 (0.002)	NA