

# High rates of reinfection tuberculosis: the selection hypothesis

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# Tuberculosis

## Modeling tuberculosis

P Rodrigues

### Introduction

#### Tuberculosis

Epidemiology  
Infection and transmission

### Motivation

Reactivation vs  
Reinfection  
Increased  
reinfection

### The Model

SIRI results  
TB model

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### Discussion

- infection with *Mycobacterium tuberculosis*
- Pulmonary Tuberculosis (TB)



# Tuberculosis epidemiology

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- infects two billion people (one-third of the world's population)
- nine million new cases of active disease per year
- two million deaths per year (mostly in developing countries)

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- infects two billion people (one-third of the world's population)
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- ↑ **incidence** is increasing, largely due to an association with human immunodeficiency virus (HIV)

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  - nine million new cases of active disease per year
  - two million deaths per year (mostly in developing countries)
- ↑ **incidence** is increasing, largely due to an association with human immunodeficiency virus (HIV)
- ↓ **treatment efficacy** is decreasing due to the emergence of drug resistant strains

# Tuberculosis epidemiology

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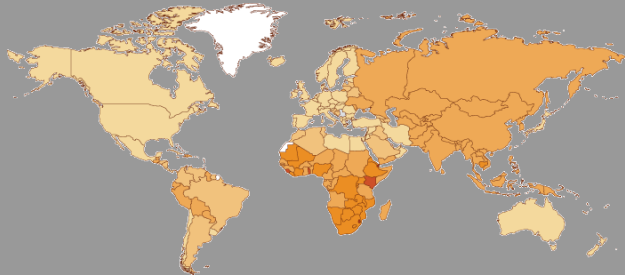
## Results

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Prevalence of all forms of tuberculosis per 100,000 inhabitants, 2005



<sup>1</sup>World Health Report 2007, Millennium Development Goal 6

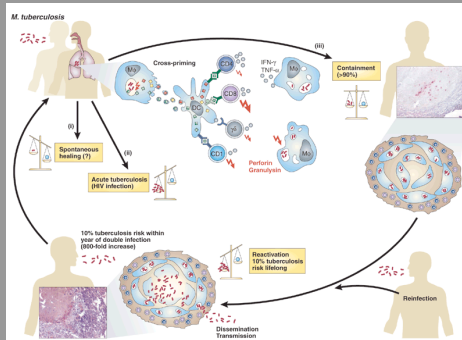
# Tuberculosis infection and transmission

Modeling tuberculosis

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Transmission

Latency



Reactivation

Reinfection

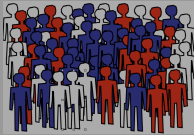
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<sup>2</sup>Kaufmann & McMichael, *Nature Medicine*, 2005

# Epidemiological model for Tuberculosis

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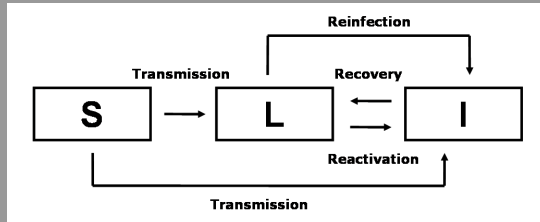
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# Reactivation vs Reinfection

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## Reactivation

- old infections
- immunocompromized immune system
- is thought to be common
- linear process ( $\omega R$ )

## Reinfection

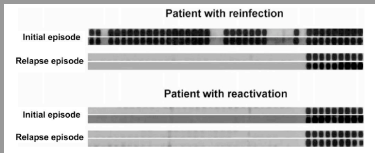
- recent infections
- partial immunity
- is thought to be rare
- nonlinear process ( $\sigma\beta IR$ )

Important consequences to TB control

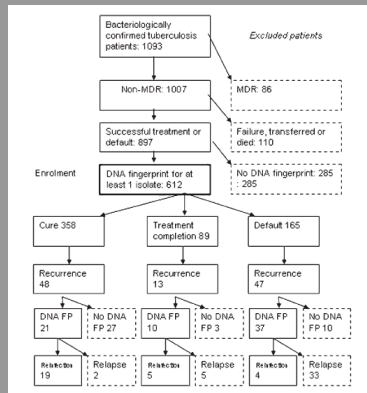
# Reactivation vs Reinfection

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Distinction between reactivation and reinfection by fingerprinting.<sup>a</sup>



Molecular epidemiology study (population study).<sup>b</sup>

<sup>a</sup>Wang *et al*, 2007

<sup>b</sup>Verver, S. *et al.*, 2005

# Impact of reinfection in TB transmission

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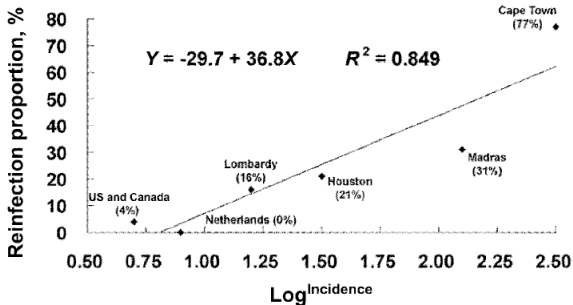
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Relation between reinfection proportion in recurrent cases and TB incidence ( $\log$ )<sup>3</sup>

<sup>3</sup>Wang *et al.* *JID*, 2007

# Increased reinfection

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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>1</sup> Gian D. van der Spuy, Martien W. Borgdorff, Donald A. Enarson, Marcel A. Behr, and Paul D. van Helden

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<sup>4</sup>Verver, S. *et al.* *Am J Respir Crit Care Med.*, 2005

<sup>5</sup>Uys, P. *et al.*, *J R Soc Interface*, 2009

# Increased reinfection

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Individual risk

TB increases the risk of new TB episodes<sup>5</sup>

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<sup>4</sup>Verver, S. *et al.* *Am J Respir Crit Care Med.*, 2005

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# Increased reinfection

## Modeling tuberculosis

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

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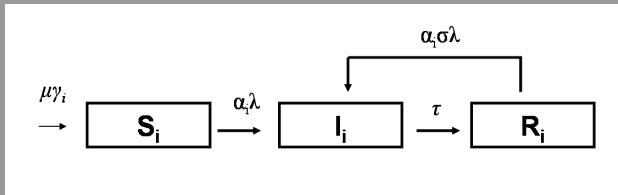
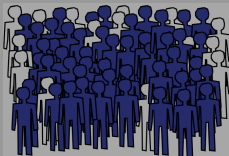
Population phenomenon

**Selection hypothesis** – selection by infection of the more susceptible individuals in the population

<sup>4</sup>Verver, S. *et al.* *Am J Respir Crit Care Med.*, 2005

<sup>5</sup>Uys, P. *et al.*, *J R Soc Interface*, 2009

# Preliminary results – SIRI model with heterogeneity to susceptibility to infection<sup>6</sup>



<sup>6</sup>Rodrigues, P. *et al* JTB 2009

# Preliminary results – SIRI model with heterogeneity to susceptibility to infection<sup>6</sup>

Modeling tuberculosis

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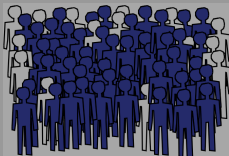
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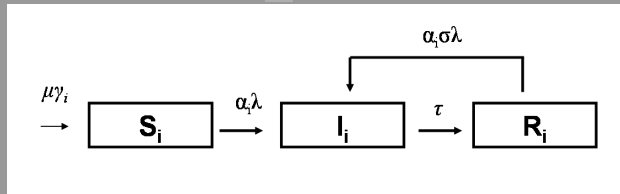
Results

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selection by  
infection



- Heterogeneity decreases disease prevalence

<sup>6</sup>Rodrigues, P. *et al* JTB 2009

# Preliminary results – SIRI model with heterogeneity to susceptibility to infection<sup>6</sup>

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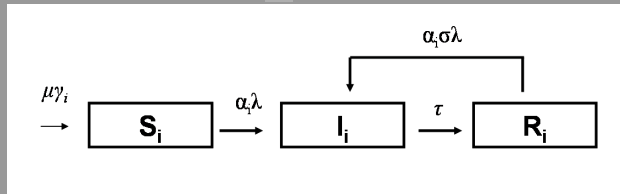
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- Heterogeneity decreases disease prevalence
- Rate of reinfection unexpectedly high under partial immunity

<sup>6</sup>Rodrigues, P. *et al* JTB 2009

# Objectives

## Modeling tuberculosis

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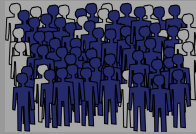
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### Discussion

- Built a **mechanistic model** for which is possible to discriminate reactivation from reinfection
- Include **heterogeneity in susceptibility to infection** – reconcile partial immunity with the observed increased reinfection by the selection hypothesis
- Confront both homogeneous and heterogeneous versions of the model with available **data** on incidence and proportion of reinfection in recurrent cases

# TB model with heterogeneity in susceptibility to infection



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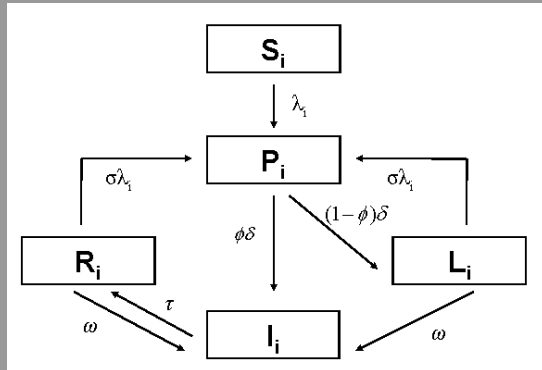
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# Model equations

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$$\begin{cases} S'_i &= \mu\gamma_i - (\lambda_i + \mu)S_i \\ P'_i &= \lambda_i S_i + \sigma\lambda_i(L_i + R_i) - (\delta + \mu)P_i \\ I'_i &= \phi\delta P_i + \omega L_i + \omega R_i - (\tau + \mu)I_i \\ L'_i &= (1 - \phi)\delta P_i - (\sigma\lambda_i + \omega + \mu)L_i \\ R'_i &= \tau I_i - (\sigma\lambda_i + \omega + \mu)R_i. \end{cases}$$

In each susceptibility group  $i = 1, 2$ :

- Force of infection  $\lambda_i = \alpha_i \beta I$
- Reinfection  $\sigma\lambda_i = \sigma\alpha_i \beta I$

Constant population:  $\gamma = \gamma_1 = 1 - \gamma_2$

Normalized susceptibility factors:  $\gamma\alpha_1 + (1 - \gamma)\alpha_2 = 1$

# Individual risk vs. population effect

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## Homogeneous model

- possible increased risk  $\sigma\lambda$ ,  
 $\sigma > 0$
- homogeneous  
susceptibility to infection  
( $\alpha_1 = 1$ )
- no risk group ( $\gamma = 1$ )

vs.

## Heterogeneous model

- partial immunity,  $\sigma\lambda$   
 $\sigma < 1$
- heterogeneous  
susceptibility to infection  
( $\alpha_1 < 1$ )
- risk group ( $\gamma < 1$ )

# Parameter estimation

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Data for each region:<sup>3</sup>

- Local incidence
- Proportion of reinfection in recurrent cases

Parameter estimation:<sup>7</sup>

- Global:  $\gamma, \alpha_1, \omega \in \sigma$
- Local:  $\lambda$  ou  $\lambda_j, j = 1, \dots, 6$  (local force of infection)

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<sup>3</sup>Wang *et al.* *JID*, 2007

<sup>7</sup>White, *et al.* *Math Biosci*, 2007

# Global Parameters $\sigma, \omega, \gamma$ and $\alpha_1$

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Symbol	Definition	Homogeneous	Heterogeneous
		Model	Model
$\sigma$	reinfection factor	6.56	0.617
$\omega$	rate of endogenous reactivations	0.00425	0.00779
$\gamma$	proportion low-risk group	1 (imposed)	0.937
$\alpha_1$	low risk factor	1(imposed)	0.0690
$\alpha_2$	high risk factor	1(imposed)	14.8

Homogeneous model:

- $\sigma > 1$  – increased individual risk

Heterogeneous model:

- $\sigma < 1$  – partial protection (**selection hypothesis**)
- $\approx 6\%$  risk group with very high susceptibility to infection

# Model results for Incidence vs proportion of reinfection

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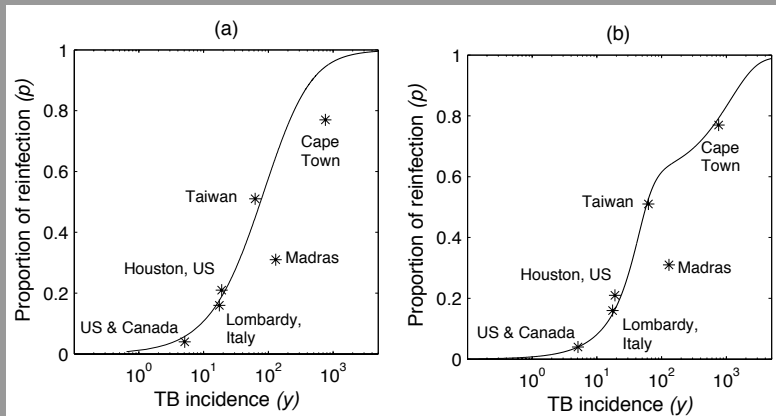
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# Local Parameters $\lambda$ or $\lambda_{2,j}$

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	US & Canada	Lombardy, Italy	Houston, US	Taiwan	Madras, India	Cape Town, South Africa
	Homogeneous			model		
$\Lambda$	0.00014733	0.00050992	0.00062570	0.0018278	0.001006	1 0.023296
$\beta$	5.8231	5.8323	5.8352	5.8631	5.8451	6.1224
$R_0$	1.0013	1.0029	1.0034	1.0082	1.0051	1.0527
	Heterogeneous			model		
$\Lambda_2$	0.0012664	0.0053642	0.0059830	0.045075	0.016876	2.0896
$\beta$	3.6691	4.4998	4.6211	10.604	6.5942	40.275
$R_0$	1.0802	1.3247	1.3604	3.1218	1.9413	11.856

Homogeneous model:

- $R_0$  very close to one

Heterogeneous model:

- Wider range of  $R_0$

# Model results for Incidence vs $R_0$

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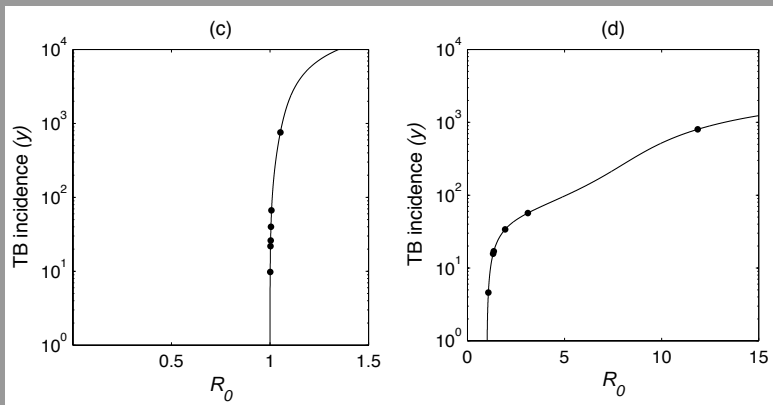
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# Additional information

Ratio between TB by reinfection among recovered and first TB:

$$\rho = \frac{reINF / (R_1 + R_2)}{newINF / (S_1 + S_2)}$$

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<sup>4</sup>Verver, S. *et al. Am J Respir Crit Care Med.*, 2005



# Additional information

Ratio between TB by reinfection among recovered and first TB:

$$\rho = \frac{reINF / (R_1 + R_2)}{newINF / (S_1 + S_2)}$$

## Data

Cape Town, measured  $\rho \in [4, 7]$ <sup>4</sup>

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<sup>4</sup>Verver, S. *et al.* *Am J Respir Crit Care Med.*, 2005

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Data

Cape Town, measured  $\rho \in [4, 7]$ <sup>4</sup>

Model results

	Homogeneous Model (prediction)	Heterogeneous Model (prediction)
Rate new TB* $newINF / (S_1 + S_2)$	1095	579
Rate reinfection TB* $reINF / (R_1 + R_2)$	7180	3114
$\rho$	6.6	5.4

\*Cases per 100,000 person-years.

<sup>4</sup>Verver, S. et al. *Am J Respir Crit Care Med.*, 2005

# Model results for $\rho$

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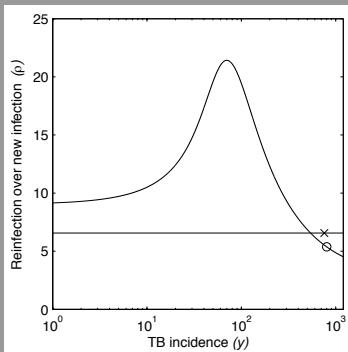
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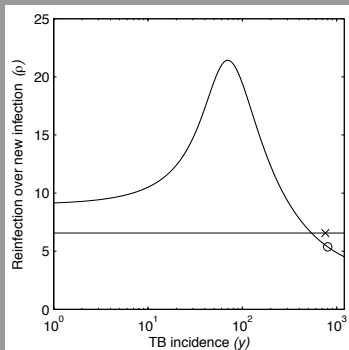
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- Homogeneous model – constant ratio  $\rho = \sigma$
- **Selection hypothesis** – ratio varies with incidence

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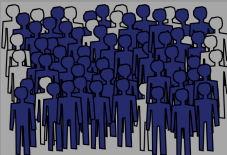
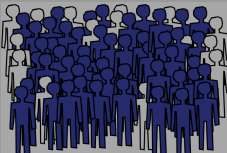
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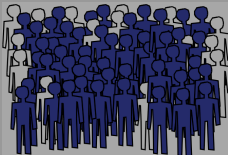
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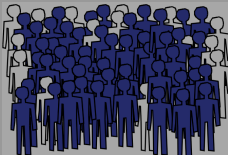
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weak  
transmission  
→



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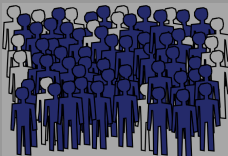
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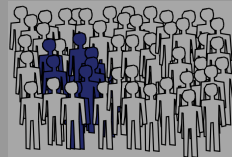
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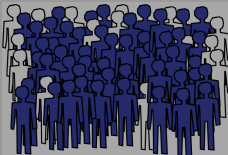
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## Results

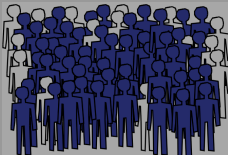
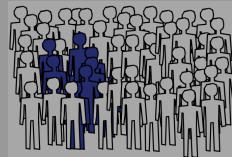
- Global parameters
- Local parameters

## Validation criteria

## Discussion



weak transmission  
→



strong transmission  
→

# Modeling tuberculosis

P Rodrigues

## Introduction

- Tuberculosis
- Epidemiology
- Infection and transmission

## Motivation

- Reactivation vs Reinfection
- Increased reinfection

## The Model

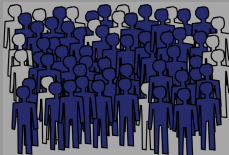
- SIRI results
- TB model

## Results

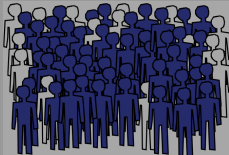
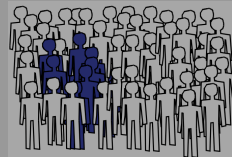
- Global parameters
- Local parameters

## Validation criteria

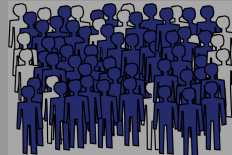
## Discussion



weak transmission  
→



strong transmission  
→



# Alternative validation criteria, $\rho$

## Modeling tuberculosis

P Rodrigues

### Introduction

Tuberculosis  
Epidemiology  
Infection and transmission

### Motivation

Reactivation vs  
Reinfection  
Increased reinfection

### The Model

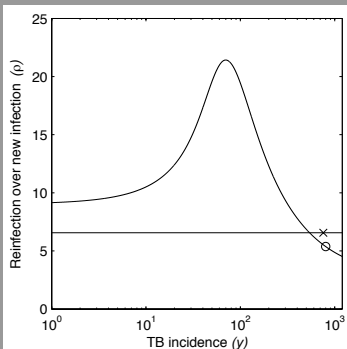
SIRI results  
TB model

### Results

Global parameters  
Local parameters

Validation criteria

### Discussion



Ratio between TB by reinfection among recovered and first TB:

$$\rho = \frac{reINF / (R_1 + R_2)}{newINF / (S_1 + S_2)}$$

# Discussion

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SIRI results  
TB model

### Results

Global  
parameters  
Local  
parameters  
Validation  
criteria

### Discussion

- Selection hypothesis reconciles the epidemiological observations with the consensual view that infection confers some degree of protection that reduces the individual susceptibility to reinfection
- Local  $R_0$  calculated from estimated local forces of infection are closer to published data for the case of the heterogeneous model
- Alternative validation model allows a better model discrimination

# Acknowledgments

## Modeling tuberculosis

P Rodrigues

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