Impact of reduction of treatment duration in tuberculosis - back to basic questions

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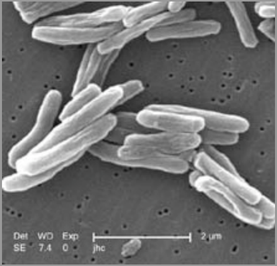
Tuberculosis

- infection with *Mycobacterium tuberculosis*
- Pulmonary Tuberculosis



Tuberculosis epidemiology

- 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)

[1] World Health Report 2007, Millennium Development Goal 6

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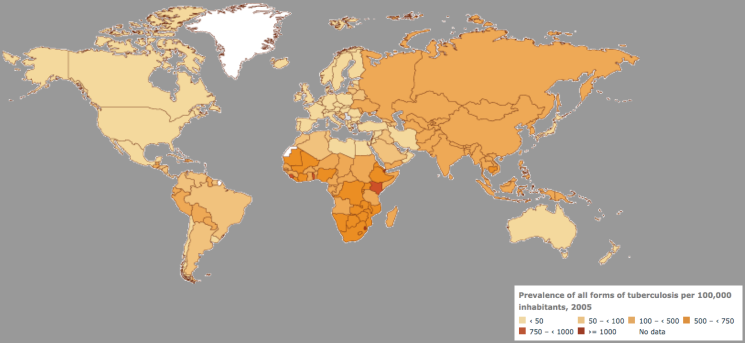
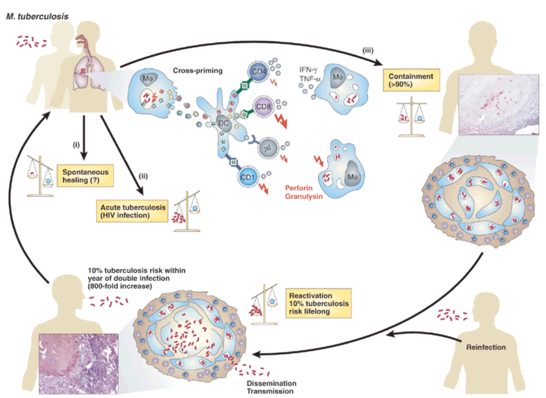


- 22 countries correspond more than 80% of all TB cases[1]

[1] World Health Report 2007, Millennium Development Goal 6

Tuberculosis infection and transmission

Transmission **Latency**

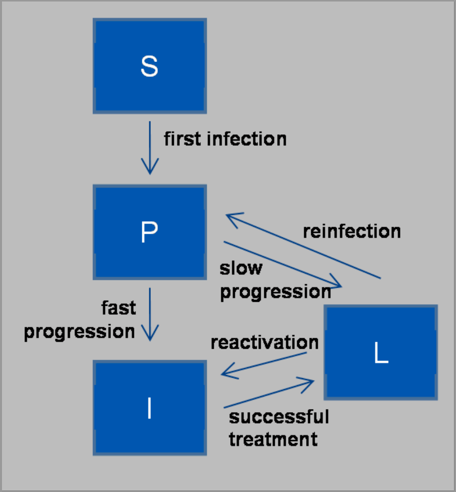


[2]

Reactivation **Reinfection**

[2]Kaufmann & McMichael, *Nature Medicine*, 2005

Epidemiological model for Tuberculosis



Motivation – TB treatment duration

- TB control programs recommend a treatment strategy that consists on a 6- to 8-month regimen

[3] Kruk et al. 2008

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- long **duration** of treatment seems to be related to a high treatment **default rate** (6% to 30%[3])

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- long **duration** of treatment seems to be related to a high treatment **default rate** (6% to 30%[3])
- Treatment default contributes to treatment **failure** and increases the risk of **resistant** TB

- efforts based on **new drugs** have been done to **reduce** the length of TB treatment

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- How reduction of treatment duration impacts on TB epidemiology

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- Relation with treatment default

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$$\Downarrow$$

under treatment class - T

- How reduction of treatment duration impacts on TB epidemiology

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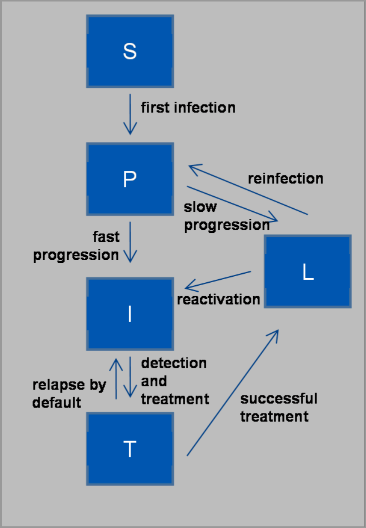
$$\Downarrow$$

under treatment class - T

relapse by default – $\phi_T \delta_T$

successful treatment – $(1-\phi_T)\delta_T$, where $1/\delta_T$ treatment duration



Literature review

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Prospects for Advancing Tuberculosis Control Efforts through Novel Therapies

Joshua A. Salomon[1,2*], James O. Lloyd-Smith[3,4], Wayne M. Getz[3], Stephen Resch[2], María S. Sánchez[3], Travis C. Porco[5], Martien W. Borgdorff[6,7]

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PNAS

Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

Laith J. Abu-Raddad[a,1], Lorenzo Sabatelli[a], Jerusha T. Achterberg[a,b,c], Jonathan D. Sugimoto[a,b], Ira M. Longini, Jr.[a,d], Christopher Dye[e], and M. Elizabeth Halloran[a,d,2]

[a]Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; Departments of [b]Epidemiology, [c]Anthropology, and [d]Biostatistics, University of Washington, Seattle, WA 98195; and [e]Office of HIV/AIDS, Tuberculosis, Malaria, and Neglected Tropical Diseases, World Health Organization, CH-1211 Geneva 27, Switzerland

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Under treatment...

Assumptions on under treatment class **T**:

- Model I – partially protected to reinfection (Abu-Raddad et al., 2009)

Under treatment...

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Under treatment...

Assumptions on under treatment class **T**:

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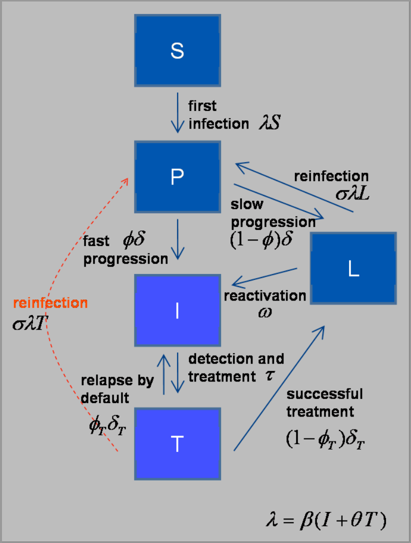
- Model II – infectious (Salomon at al., 2006)
- **Model III** – not infectious and protected from reinfection



$$\begin{cases} \frac{dS}{dt} &= \mu - \lambda S - \mu S \\ \frac{dP}{dt} &= \lambda S + \sigma \lambda L + \sigma_0 \lambda T - (\delta + \mu) P \\ \frac{dL}{dt} &= (1-\phi)\delta P + (1-\phi_T)\delta_T T - \sigma \lambda L - (\omega + \mu) L \\ \frac{dI}{dt} &= \phi \delta P + \omega L + \phi_T \delta_T T - (\tau + \mu) I \\ \frac{dT}{dt} &= \tau I - \sigma_0 \lambda T - (\delta_T + \mu) T \end{cases}, [4]$$

$$\lambda = \beta(I + \theta T)$$

symbol	definition	value
β	transmission coefficient	variable
θ	infectiousness of under treatment individuals	0 or 0.5
μ	death and birth rate	$1/70\ yr^{-1}$
δ	inverse of primary infection length	$12\ yr^{-1}$
ϕ	fraction of infected population developing active TB	0.05
	(the $1-\phi$ fraction remain persistent latent)	
σ	factor of exogenous reinfection for persistent latent	0.25
σ_0	factor of exogenous reinfection for under treatment	0 or σ
ω	rate of endogenous reactivation for persistent latent inf.	$0.0002\ yr^{-1}$
τ	rate at which infectious individuals enter treatment	$2\ yr^{-1}$
$\rightarrow \delta_T$	inverse of **treatment length**	$2\ yr^{-1}$ or variable
$\rightarrow \phi_T$	fraction of individuals that drop out treatment **(default)**	0.1 or variable
	(the $1-\phi_T$ fraction are successfully treated)	

[4] Gomes et al., 2007

Epidemiological consequences of reducing treatment duration – implementation and analysis

Treatment length $(1/\delta_T)$ from 6 to 2 months: $\delta_T^{BL} = 2 \quad \longrightarrow \quad \delta_T = 6$

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$$\Downarrow$$

Proportion Infectious

$$Inf = I + \theta T$$

Basic reproduction number

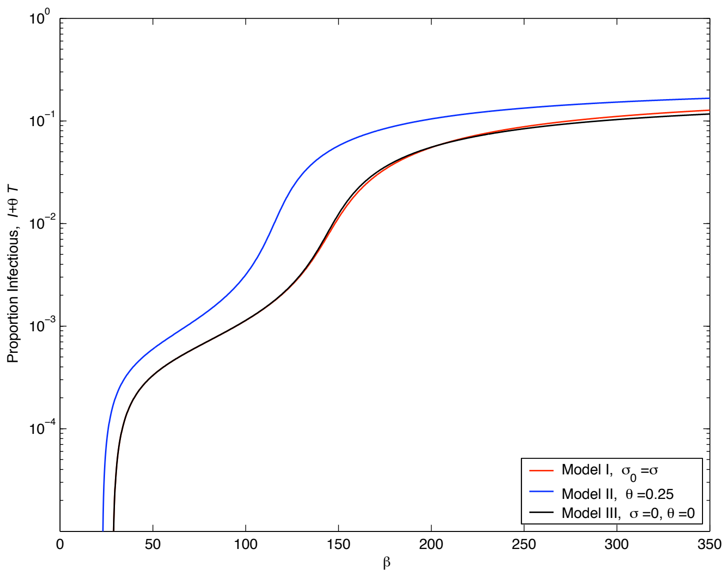
$$R_0$$

Efficacy of treatment regimen improvement

$$Eff = 1 - Inf / Inf_{BL}$$

where Inf_{BL} and Inf are the proportion infectious before and after treatment improvement.

Stability analysis



Efficacy of new interventions

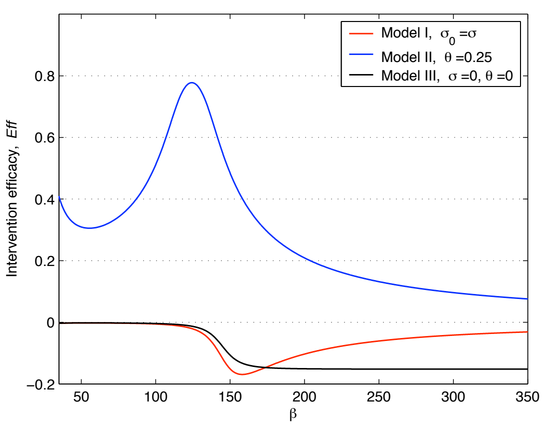
Efficacy function

$$Eff = 1 - \frac{Inf}{Inf_{BL}}$$

where Inf_{BL} and Inf are the proportion infectious before and after treatment improvement, at equilibrium.

- Eff defined for $\beta > \beta^*_{BL}$
- $Eff > 0 \Rightarrow$ intervention reduces proportion infectious
- $Eff < 0 \Rightarrow$ intervention increases proportion infectious

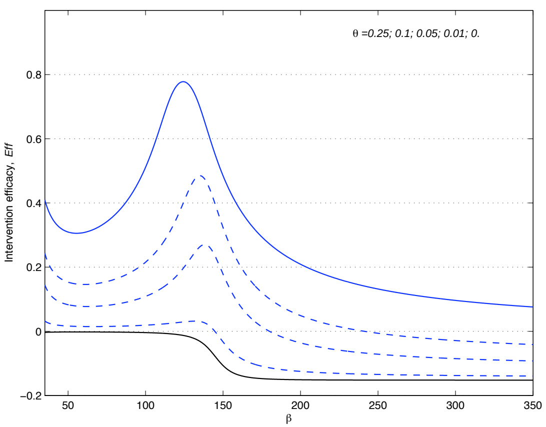
Efficacy of new interventions – not always positive...



Treatment duration $(1/\delta_T)$ from 6 to 2 months:

$$\delta_T^{BL} = 2 \longrightarrow \delta_T = 6$$

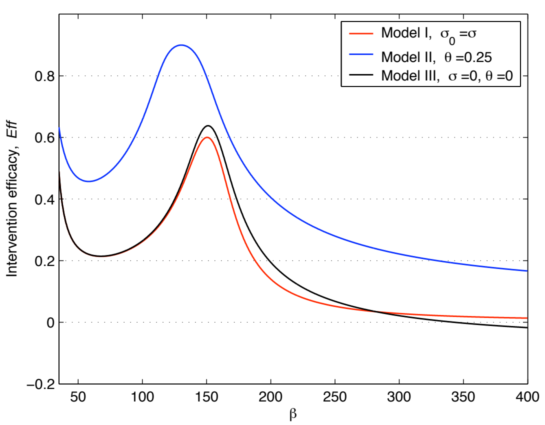
Efficacy of new interventions – depends highly on transmissibility of individuals under treatment...



Model II – Treatment duration $(1/\delta_T)$ from 6 to 2 months:

$$\delta_T^{BL} = 2 \longrightarrow \delta_T = 6$$

Efficacy of new interventions – must be a combined effort...



Treatment duration $(1/\delta_T)$ from 6 to 2 months and treatment default from 10% to 1%:

$$\delta_T^{BL} = 2 \longrightarrow \delta_T = 6; \qquad \phi_T^{BL} = 0.1 \longrightarrow \phi_T = 0.01$$

Basic reproduction number, R_0

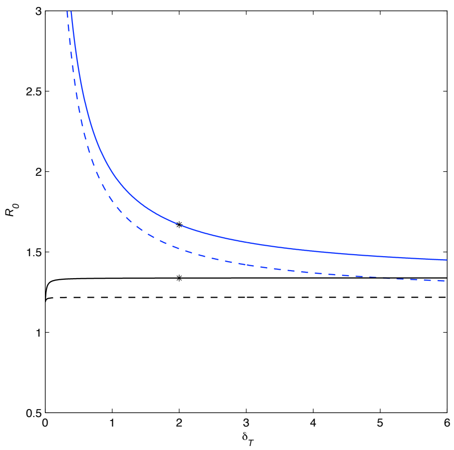
Model I – $R_0^I = \dfrac{\beta\delta(\omega+\phi\mu)(\mu+\delta_T)}{\mu(\delta+\mu)\left[(\mu+\omega)(\mu+\delta_T+\tau)+\tau\delta_T(1-\phi_T)\right]}$

Model II – $R_0^{II} = \dfrac{\beta\delta(\omega+\phi\mu)(\mu+\delta_T+\theta\tau)}{\mu(\delta+\mu)\left[(\mu+\omega)(\mu+\delta_T+\tau)+\tau\delta_T(1-\phi_T)\right]}$

$$= R_0^I + \frac{\beta\delta(\omega+\phi\mu)\theta\tau}{\mu(\delta+\mu)\left[(\mu+\omega)(\mu+\delta_T+\tau)+\tau\delta_T(1-\phi_T)\right]}$$

Model III – $R_0^{III} = R_0^I$

Impact on R_0



Change on R_0 while changing treatment rate $1/\delta_T$.
Improvment of treatment default from $\phi_T^{BL} = 0.1 \longrightarrow \phi_T = 0.01$.

Impact on R_0

$$\frac{\partial R_0}{\partial \phi_T} = \Gamma \delta_T (\mu + \delta_T + \theta\tau)$$

$$\frac{\partial R_0}{\partial \delta_T} = \Gamma \left[(\omega + \phi_T \mu) - (\mu + \omega + (1 - \phi_T)\tau)\theta \right]$$

where

$$\Gamma = \frac{\beta\delta(\omega + \phi\mu)\tau}{\mu(\delta + \mu)\left[(\mu + \omega)(\mu + \delta_T + \tau) + \tau\delta_T(1 - \phi_T)\right]^2}$$

Impact on R_0

$$\frac{\partial R_0}{\partial \phi_T} = \Gamma \delta_T (\mu + \delta_T + \theta\tau) \qquad \frac{\partial R_0}{\partial \phi_T} > 0$$

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for $\theta < \frac{\omega+\phi_T\mu}{\mu+\omega+(1-\phi_T)\tau}$

where

$$\Gamma = \frac{\beta\delta(\omega+\phi\mu)\tau}{\mu(\delta+\mu)\left[(\mu+\omega)(\mu+\delta_T+\tau)+\tau\delta_T(1-\phi_T)\right]^2}$$

Impact on R_0 – not always positive...

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- for Model I and **III** ($\theta = 0$) $\rightarrow$ negative impact

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$$\Downarrow$$

- for Model I and **III** $(\theta = 0) \rightarrow$ negative impact
- for Model II$\rightarrow$ negative impact for:
  - very low infectiousness of individuals under treatment (θ)
  - regions with very high proportion of default (ϕ_T)

Impact on R_0– must be a combined effort...

For Model I and **Model III** we must have a combined intervention:

$$\phi_T(\delta_T)$$

then

$$\frac{dR_0}{d\delta_T} = \Gamma\left[\omega + \mu\phi_T + (\mu + \delta_T)\delta_T\phi'_T\right].$$

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$$\Downarrow$$

$$\phi'_T < -\frac{\omega + \mu\phi_T}{(\mu + \delta_T)\delta_T}, \ \forall \delta_T > 0.$$

... back to basic questions

Epidemiological consequences of reducing treatment duration:

... back to basic questions

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$$\Downarrow$$

better characterize the group of individuals under treatment

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- Gabriela Gomes
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