

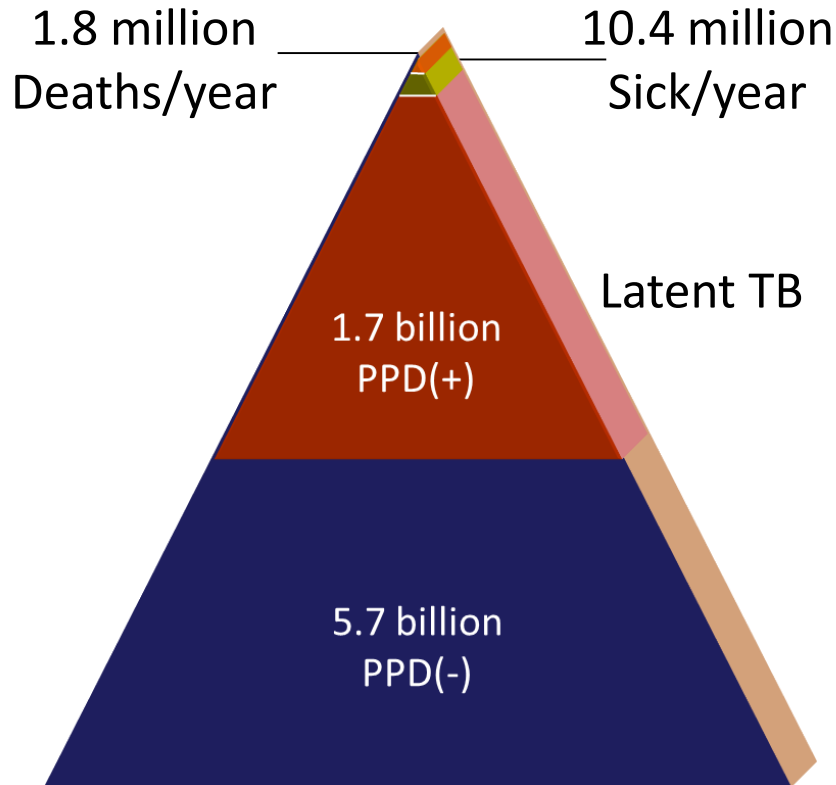
The biology of latency: considerations for modelers

Shuyi Ma
TB MAC Meeting
September 14, 2018

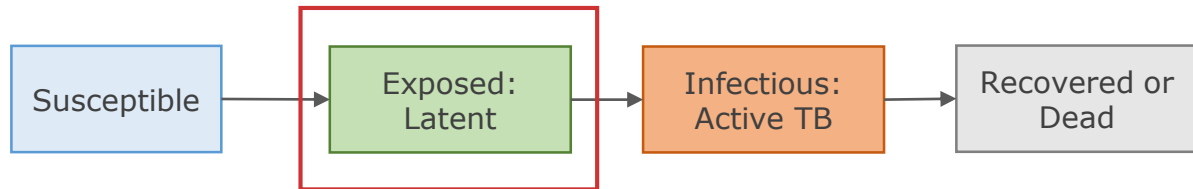


Center for Infectious
Disease Research

Tuberculosis poses a global health challenge



Historically assumed trajectory of TB disease progression



Assumption: Broadly treating latent TB will improve control of the pandemic.

Assumption: During latency, the bacteria are dormant.



- During latency, the bacteria are dormant.

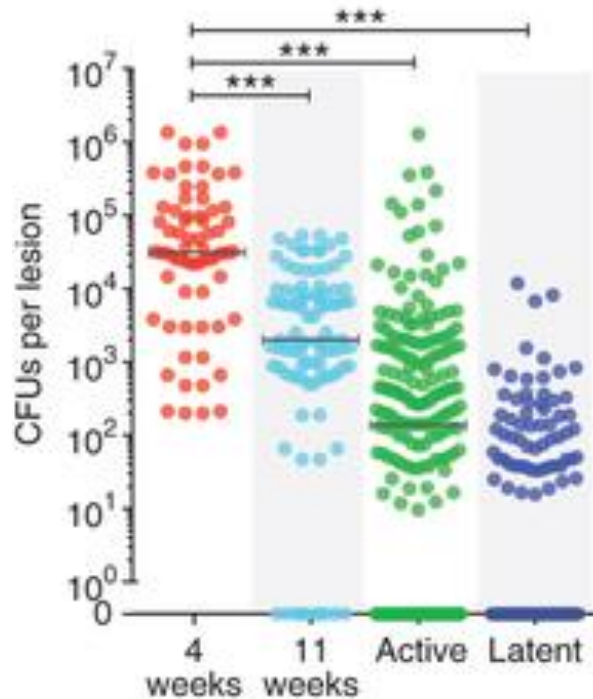
Are bacteria different in latency?

- Broadly treating latent TB will improve control of the pandemic.

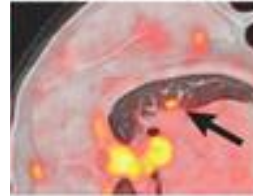
Primate experiments show overlapping, heterogeneous behavior in latent, active TB



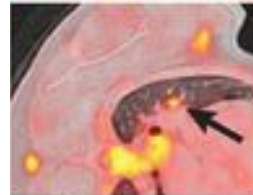
Primate lesions



Right upper lobe progression and regression



30 weeks



32 weeks

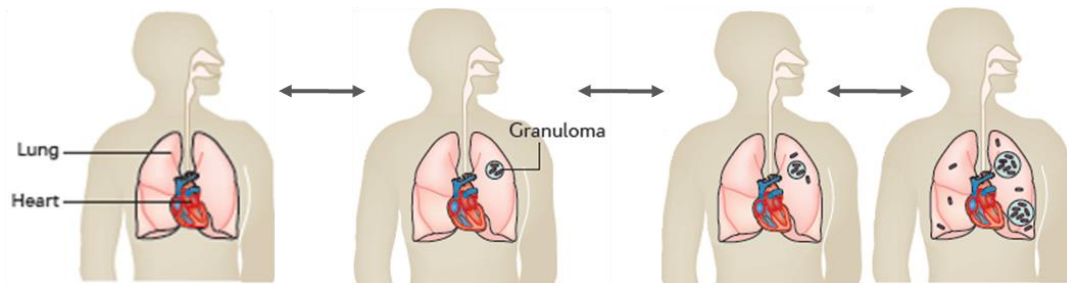


36 weeks



40 weeks

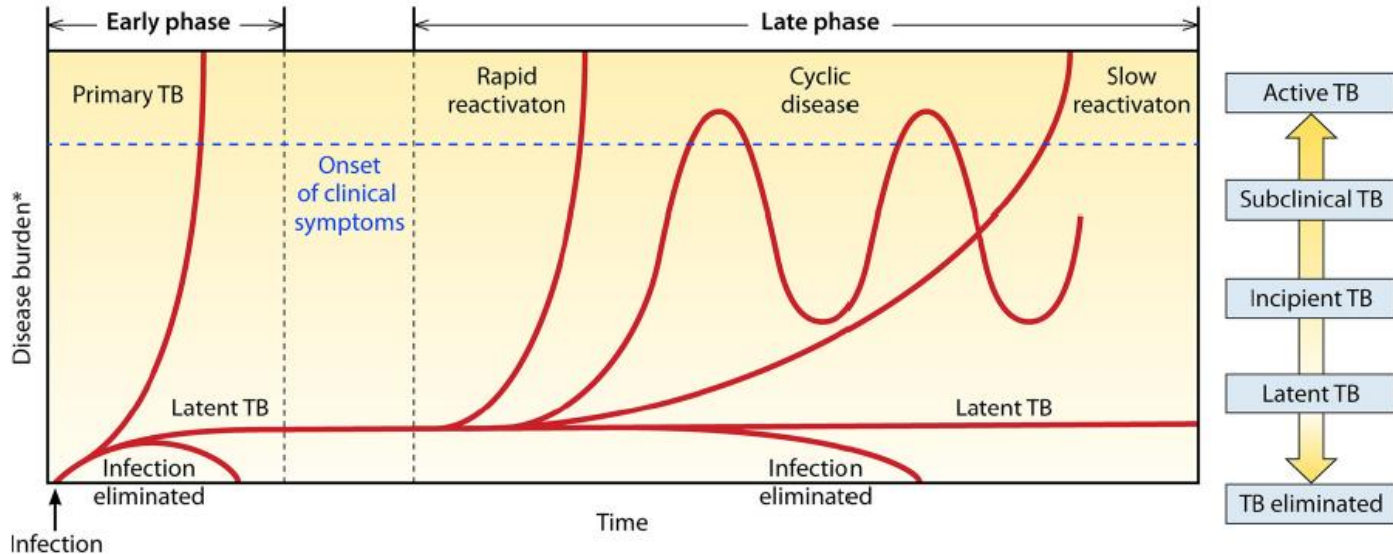
Spectrum of TB progression



	Eliminated Infection	Latent Infection	Incipient Infection	Subclinical Disease	Active Disease
MTB Exposure	x	x	x	x	x
Viable MTB		x	x	x	x
Progressing MTB			x	x	x
Evidence of MTB (Radiologic, Microbiologic)				x	x
TB Disease Symptoms					x



Spectrum TB progression





- ~~During latency, the bacteria are dormant.~~

Bacterial heterogeneity contributes to spectrum of progression

- Broadly treating latent TB will improve control of the pandemic.



- During latency, the bacteria are dormant.
- Broadly treating latent TB will improve control of the pandemic.

How beneficial is prophylactic therapy?

Clinical data suggest broadly treating latent TB does not always improve control



ORIGINAL ARTICLE

A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control

Gavin J. Churchyard, M.B., B.Ch., Ph.D., Katherine L. Fielding, Ph.D., James J. Lewis, Ph.D., Leonie Coetzee, D.Soc.Sc., Elizabeth L. Corbett, M.B., B.Chir., Ph.D., Peter Godfrey-Faussett, F.R.C.P., Richard J. Hayes, D.Sc., Richard E. Chaisson, M.D., and Alison D. Grant, M.B., B.S., Ph.D., for the Thibela TB Study Team

N Engl J Med 2014; 370:301-310 | [January 23, 2014](#) | DOI: 10.1056/NEJMoa1214289

~30,000 S. African gold miners.

Very high TB rate (~2%).

Widespread INH prophylaxis (IPT) for 6+ months.

Conclusions

“Mass screening and treatment for latent tuberculosis had no significant effect on tuberculosis control....”

Clinical data suggest latent TB can offer protection



[Epidemics](#). 2016 Mar;14:54-61. doi: 10.1016/j.epidem.2015.10.001. Epub 2015 Oct 20.

Tuberculosis in Cape Town: An age-structured transmission model.

[Blaser N¹](#), [Zahnd C¹](#), [Hermans S²](#), [Salazar-Vizcaya L¹](#), [Estill J¹](#), [Morrow C³](#), [Egger M⁴](#), [Keiser O⁵](#), [Wood R⁶](#).

[Clin Infect Dis](#). 2012 Mar;54(6):784-91. doi: 10.1093/cid/cir951. Epub 2012 Jan 19.

Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis.

[Andrews JR¹](#), [Noubary F](#), [Walensky RP](#), [Cerdeira R](#), [Losina E](#), [Horsburgh CR](#).

[J Infect Dis](#). 2011 Jun 1;203(11):1582-9. doi: 10.1093/infdis/jir162.

Epidemiologic inference from the distribution of tuberculosis cases in households in Lima, Peru.

[Brooks-Pollock E¹](#), [Becerra MC](#), [Goldstein E](#), [Cohen T](#), [Murray MB](#).

[Epidemiol Infect](#). 1997 Oct;119(2):183-201.

The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection.

[Vynnycky E¹](#), [Fine PE](#).

[Tubercle](#). 1982 Dec;63(4):255-68.

The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands.

[Sutherland I](#), [Svandová E](#), [Radhakrishna S](#).

Conclusions

Latent TB infection offered 16-79% risk reduction of reinfection

Latent TB reduces reinfection bacterial load in mice



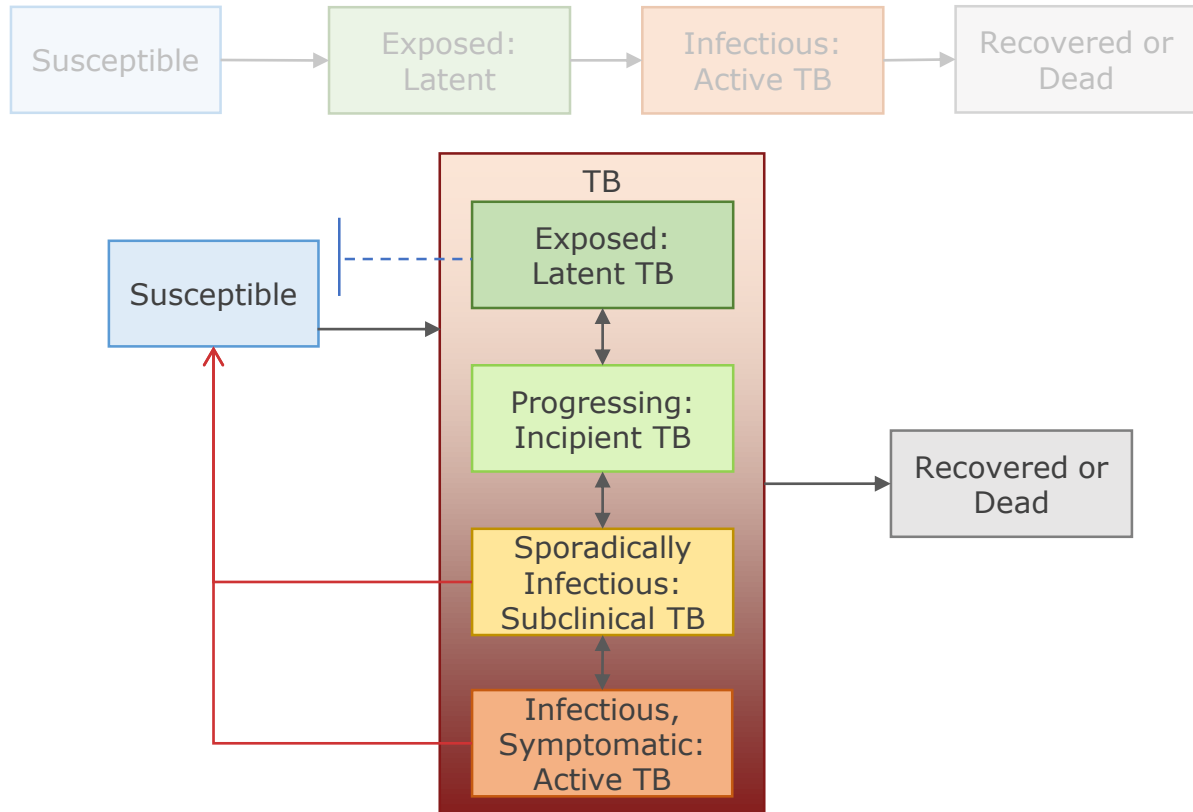
Assumptions about latent TB



- During latency, the bacteria are dormant.
- Broadly treating latent TB will improve control of the pandemic.

Targeted therapy may be more beneficial

Conclusions



Acknowledgments



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