Host Genetics of Tuberculosis

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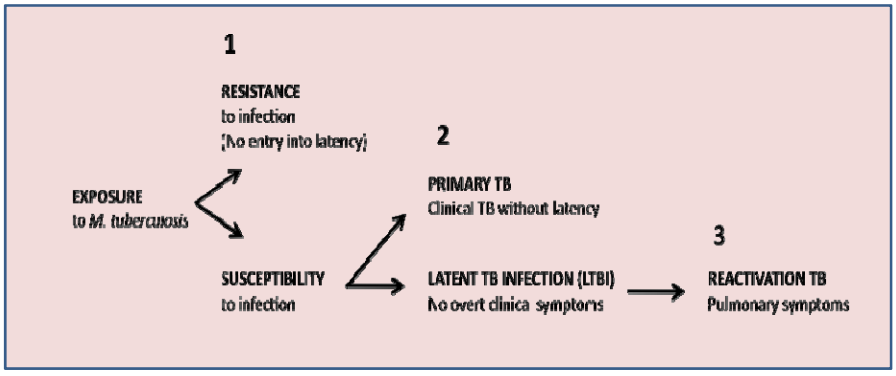
Tuberculosis Pathogenesis



Host Genetics of TB?

TB is an infectious disease caused by *Mycobacterium tuberculosis:*

No *M. tuberculosis* = No TB!

Is TB a genetic disease? NO!

Host Genetics of TB?

Phenylketonuria (PKU) is a metabolic disease that is caused by phenylalanine:

No phenylalanine = No PKU!

Is PKU a genetic disease? YES!

Host Genetics of TB?

"It is not the microbe that is transmitted from the parents to the offspring, but the predisposition to disease"

Louis Pasteur

In 'Etudes sur la maladie des vers à soie.
La pébrine et la flacherie (tome I)' Gauthier-Villars eds; 1870

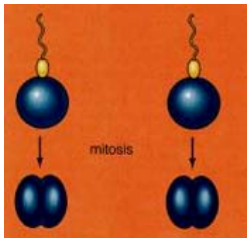
The Lübeck Accident

Virulence level	Number	Disease severity			
		death	serious disease	mild symptoms	no symptoms
1	1	-	-	-	1
2	93	6 = 6.5%	9 = 9.7%	78 = 83.8%	-
3	83	18 = 21.7%	34 = 41.0%	31 = 37.3%	-
4	74	53 = 71,6%	18 = 24.3%	3 = 4.1%	-
Totals	**251**	**77**	**61**	**112**	**1**

Moegling A. Die Epidemiologie der Lübecker Säuglingstuberkulose, Arbeiten a. d. Reichsges-Amt 69:1-24, 1931

Twin studies

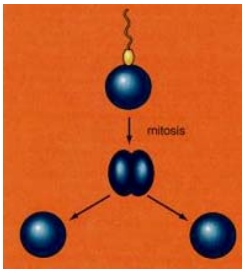
DZ TWINS



2 fertilizations

Share 50% of genetic background

MZ TWINS



1 fertilization

Share 100% of genetic background

Twin studies

Concordance

Monozygous twins	Dizygous twins	Reference
65%	25%	Diehl and Von Verschuer Beitr. Klin Kunsch 92: 275, 1936
62%	18%	Kallmann and Reisner, Am Rev Respir Dis 47, 549, 1942
32%	14%	Comstock, Am Rev Respir Dis 117, 621, 1978

Significant excess of concordance among monozygous twins demonstrates the importance of host genetic factors

Host genetics of tuberculosis

Only few TB susceptibility genes have been convincingly identified.

Why do we have difficulties in identifying host susceptibility genes?

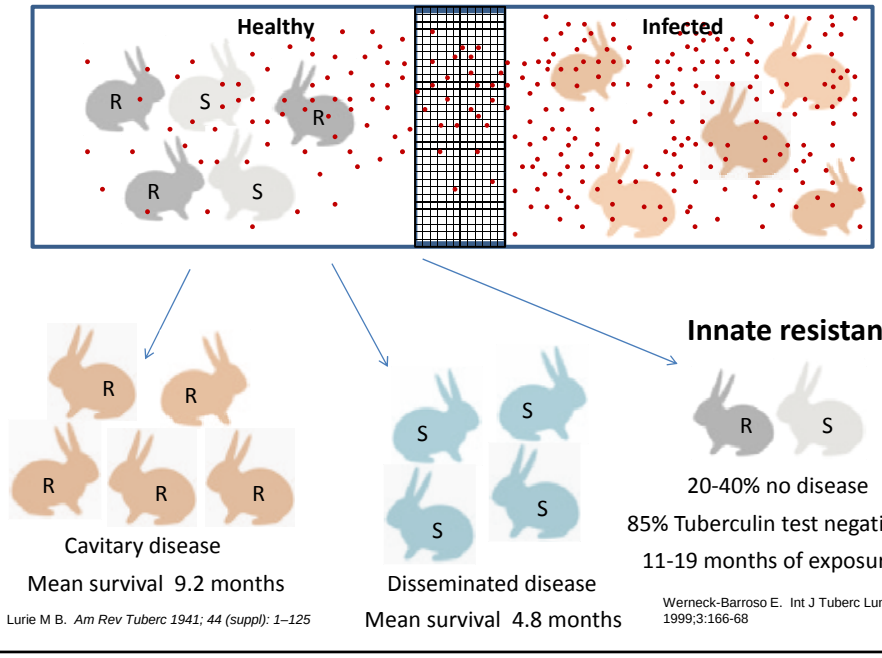
TB pathogenesis is more than "disease"

(i) age

(ii) host x pathogen interaction (*M. tuberculosis* strain)

(iii) gene x environment interactions (exposure history)

Max Lurie's Rabbits



Lurie M B. *Am Rev Tuberc 1941; 44 (suppl): 1–125*

Werneck-Barroso E. Int J Tuberc Lung Dis 1999;3:166-68

Latent *M. tuberculosis* infection

How do we measure infection?

No "gold standard"

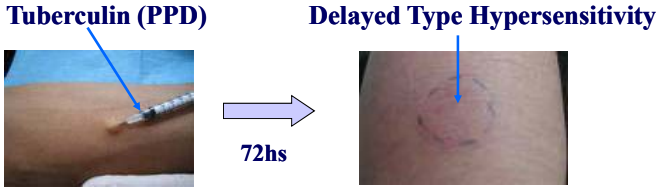
Three types of assays

In vivo **tuberculin skin test (TST)**

In vitro **production of antigen-specific IFNγ production (ELISA)**

In vitro **determination of frequency/number of antigen-specific T-cells (ELISpot/FACS)**

Tuberculin Skin Test



Detection of people infected by *M. tuberculosis*

Public Health
- **≥ 5 mm (Immuno-)**
- **≥ 10 mm (no BCG)**
- **≥ 15 mm (BCG)**

→ **Infection**

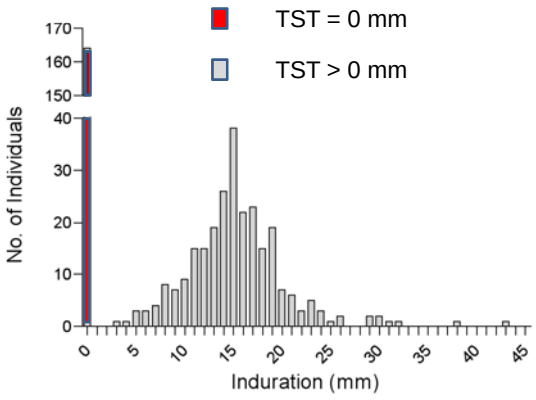
Intrinsically a quantitative measure

High heritability in endemic area (70 to 90%)

Study Setting: Cape Town, South Africa

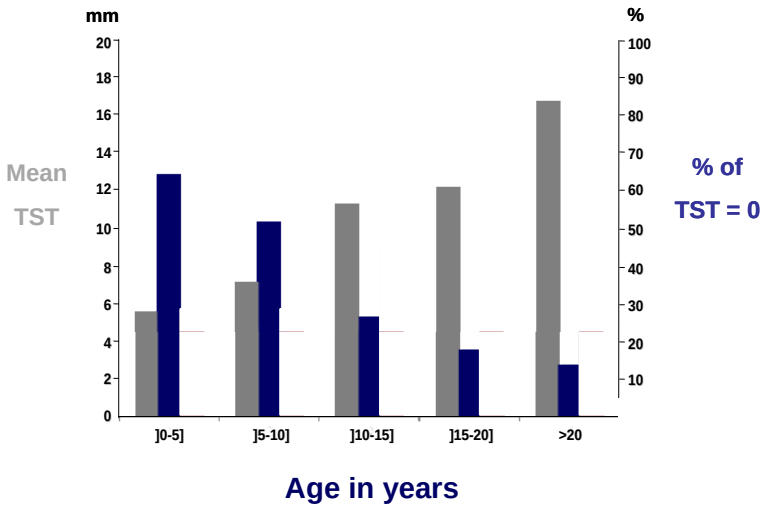
- **During subject enrolment period:**
- **Highest TB incidence worldwide**
- **Pediatric HIV < 1%**
- **BCG at birth**

TST reactivity is bi-modal



Gallant et al *Chest* 137:1071, 2010

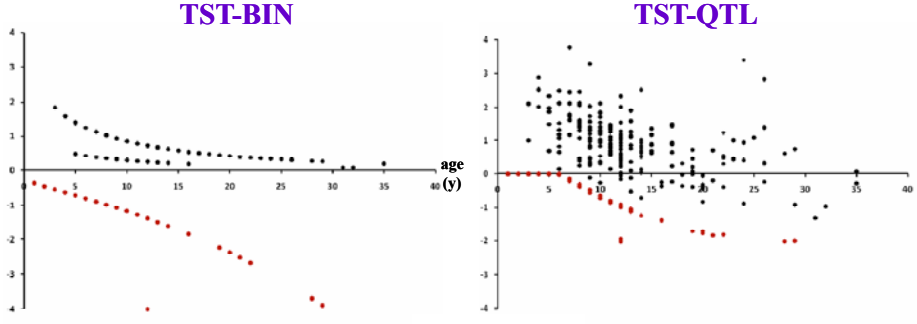
Age has a strong effect on TST



Two phenotypes – Two linkage analyses

TST= 0 vs. Non 0 | **TST in mm**

TST-BIN | **TST-QTL**



Pearson residuals

• TST 0 mm

• TST > 0 mm

Tobit residuals

Cobat et al. *J Exp Med* 206:2583, 2009

TST1* ⇒ T-cell-independent resistance to *M. tuberculosis

Linkage disequilibrium mappping

***TST2* ⇒ intensity of T-cell mediated DTH to tuberculin**

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