What is TB

Topics

- The organism
- Transmission
- The disease spectrum in humans

Q1. Mtb complex is:

a) The set of mycobacteria that are pathogenic to humans.
b) The subset of mycobacteria that are slow growers.
c) The belief that mycobacteria are following you at night.
d) The set of organisms that cause clinical tuberculosis in humans.
e) The set of seven different *Mycobacteria tuberculosis* lineages that occur in humans.

Infection with Mtb occurs via:

a) Multiple routes including water, aerosol, food and fomites.
b) Inhalation of aerosols
c) Exposure to Mtb living in the soil.
d) Handling infectious body fluids (sputum, blood, urine).
e) Sexual contact

TB infection is followed by:

a) A brief non-specific illness which resolves within weeks.
b) A cell-mediated immune response within 2-8 weeks.
c) Active TB disease in 5% of TST converters.
d) Long lasting immunity to future TB infection.
e) Lifetime persistence of viable TB bacilli in host tissue/cells.

Extra-pulmonary TB

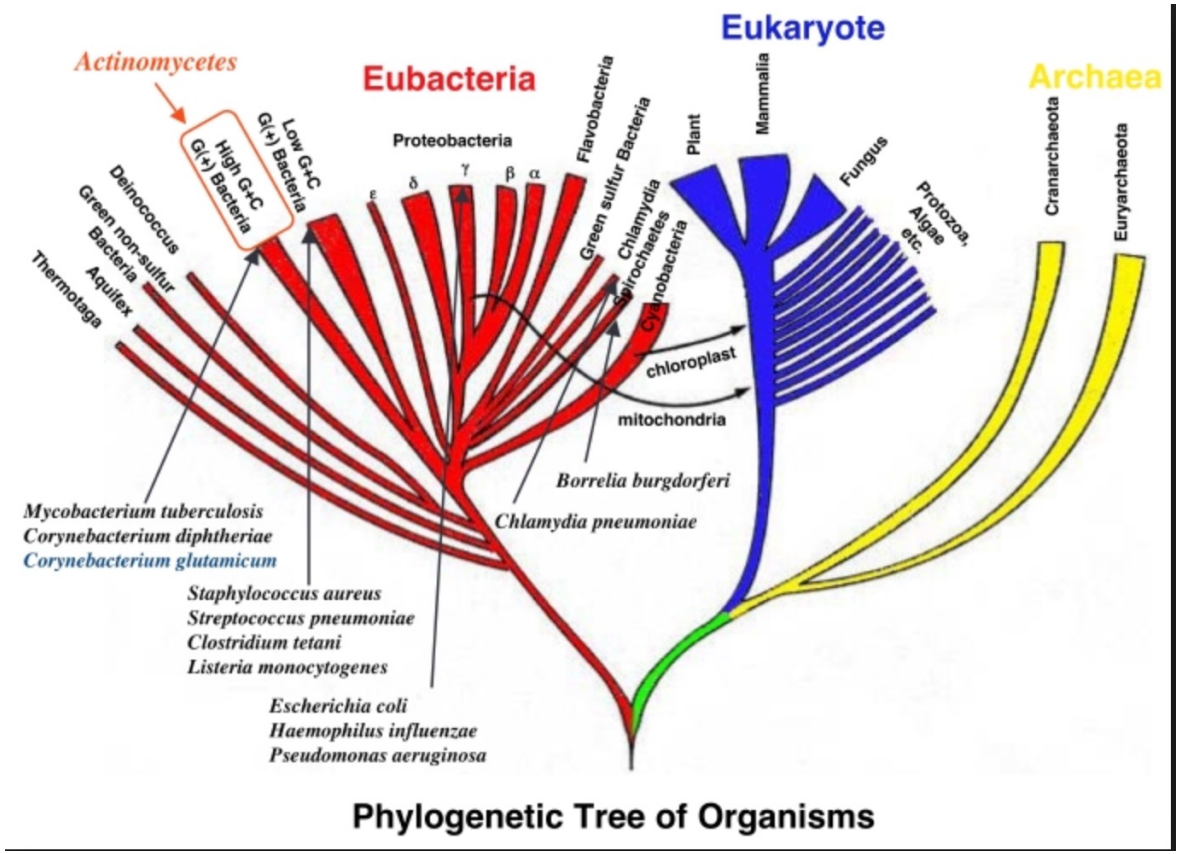
a) Is more common in children than adults.
b) Is more common among women than men.
c) Is more common among people living with HIV.
d) Is due to M. bovis infection rather than M. tb.
e) Most frequently involves lymph nodes.
f) Is the cause of Pott’s disease.
g) Can coincide with pulmonary TB.

Reactivation TB

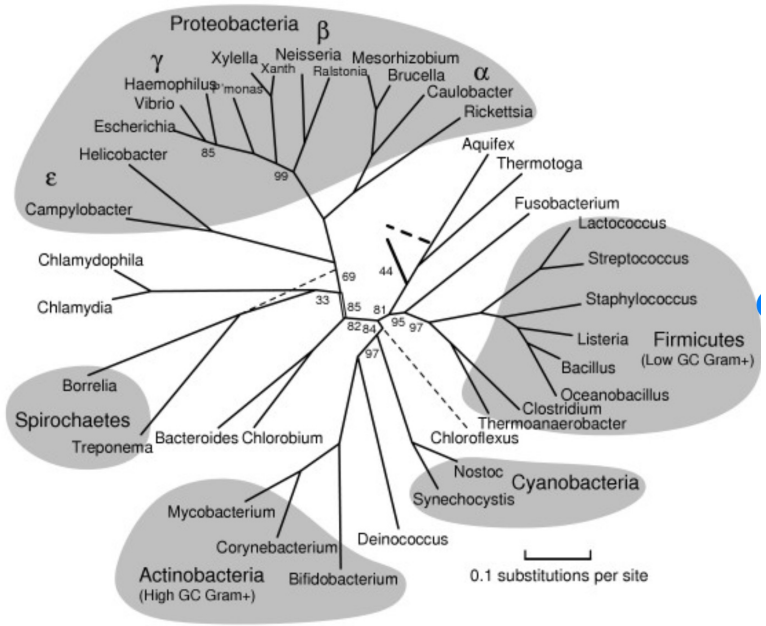
a) Occurs only in people who are immunosuppressed.
b) Is more common in the elderly.
c) Can be differentiated from primary TB on the basis of clinical appearance.
d) Is more likely to be drug resistant than primary TB.

Strains from different TB lineages

a) Vary in their ability to be transmitted.
b) Vary in their ability to cause disease.
c) Have different mutation rates.
d) Evoke different immune responses in humans.

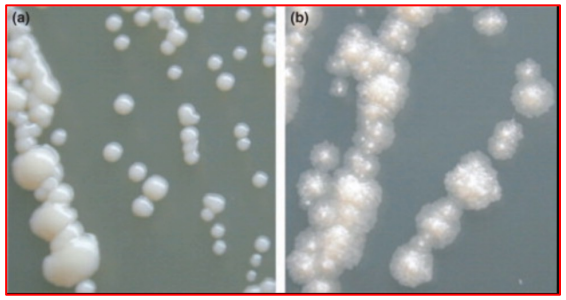


Phylogenetic Tree of Organisms

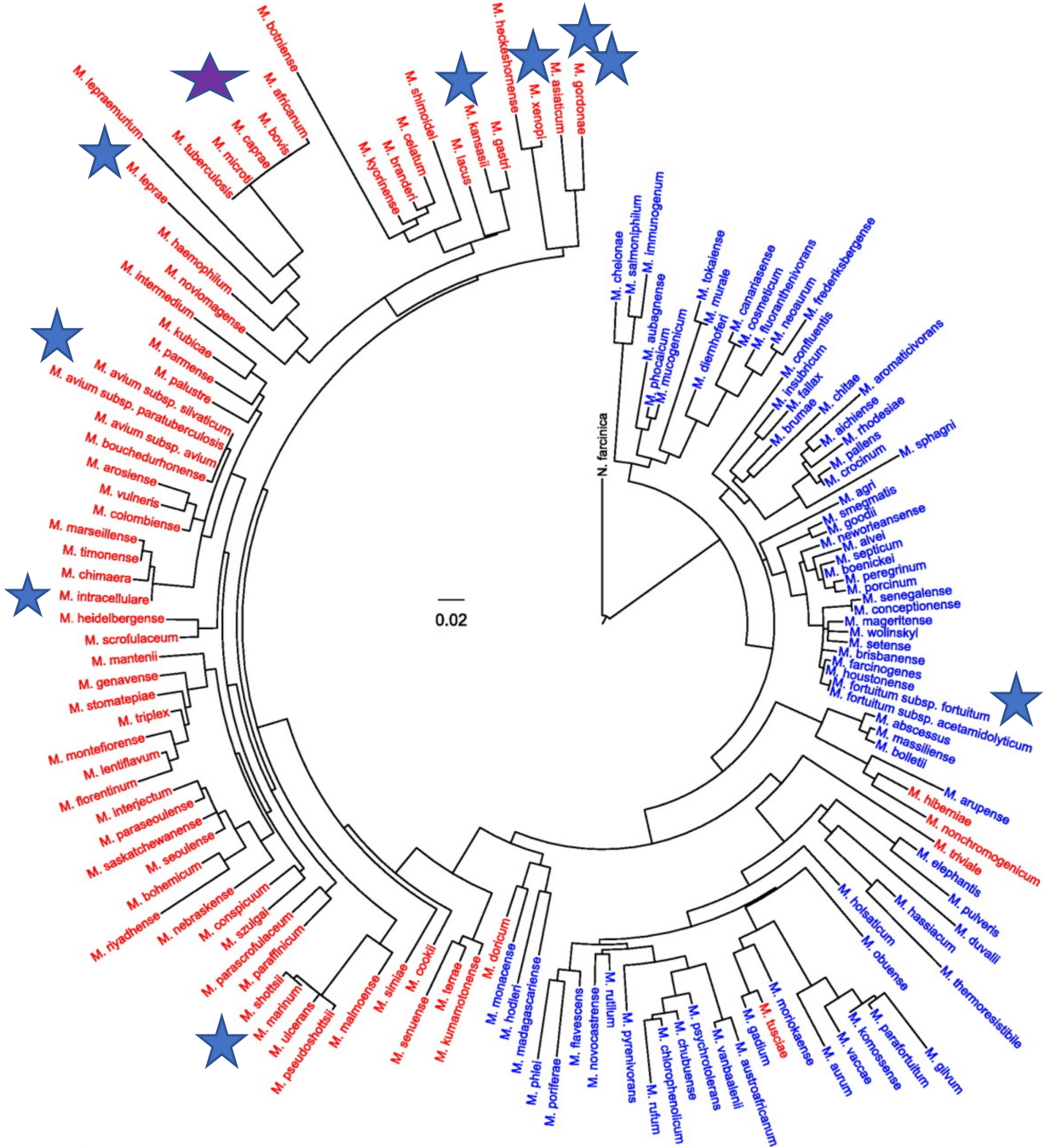


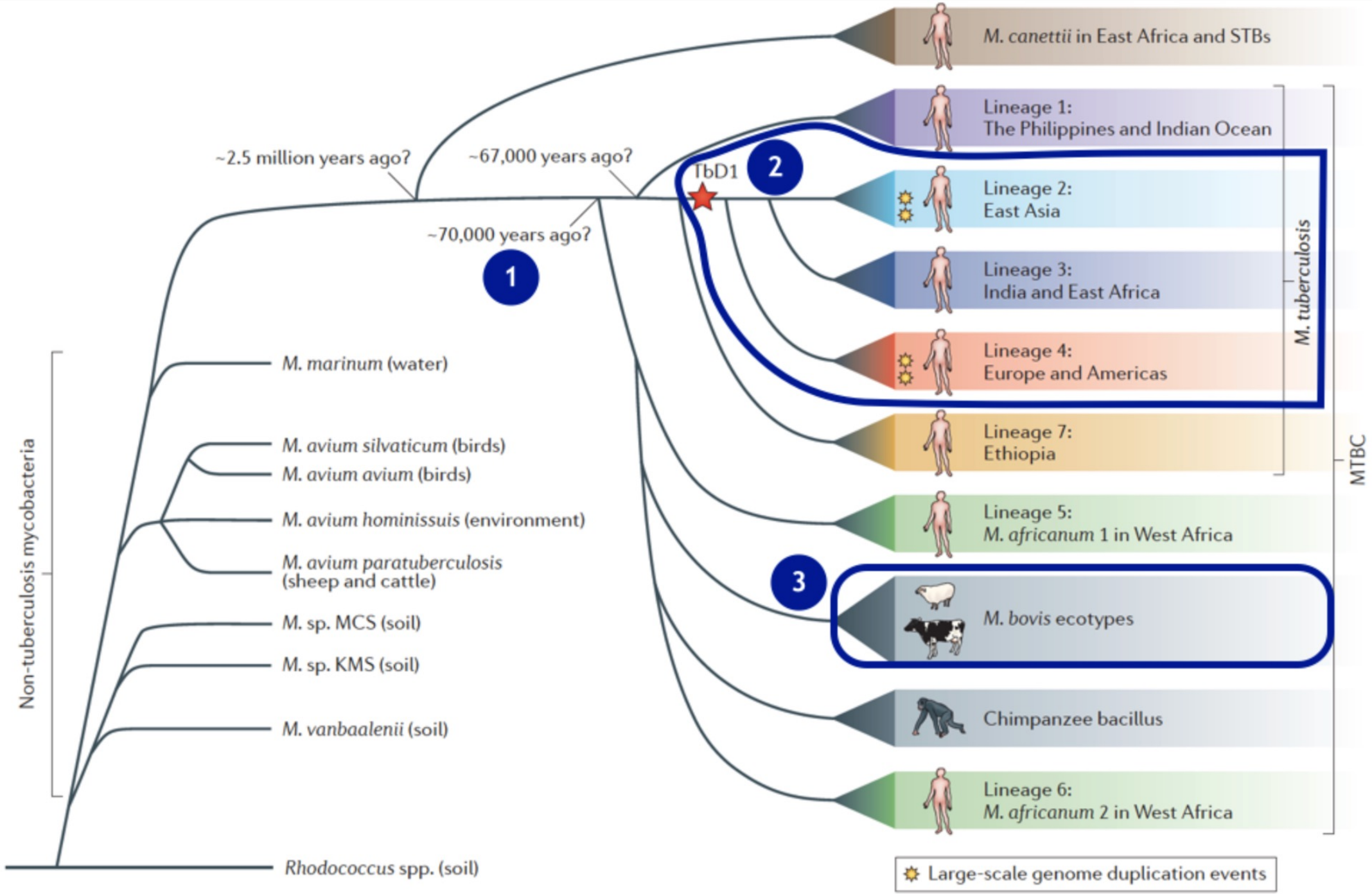
Mycobacteria

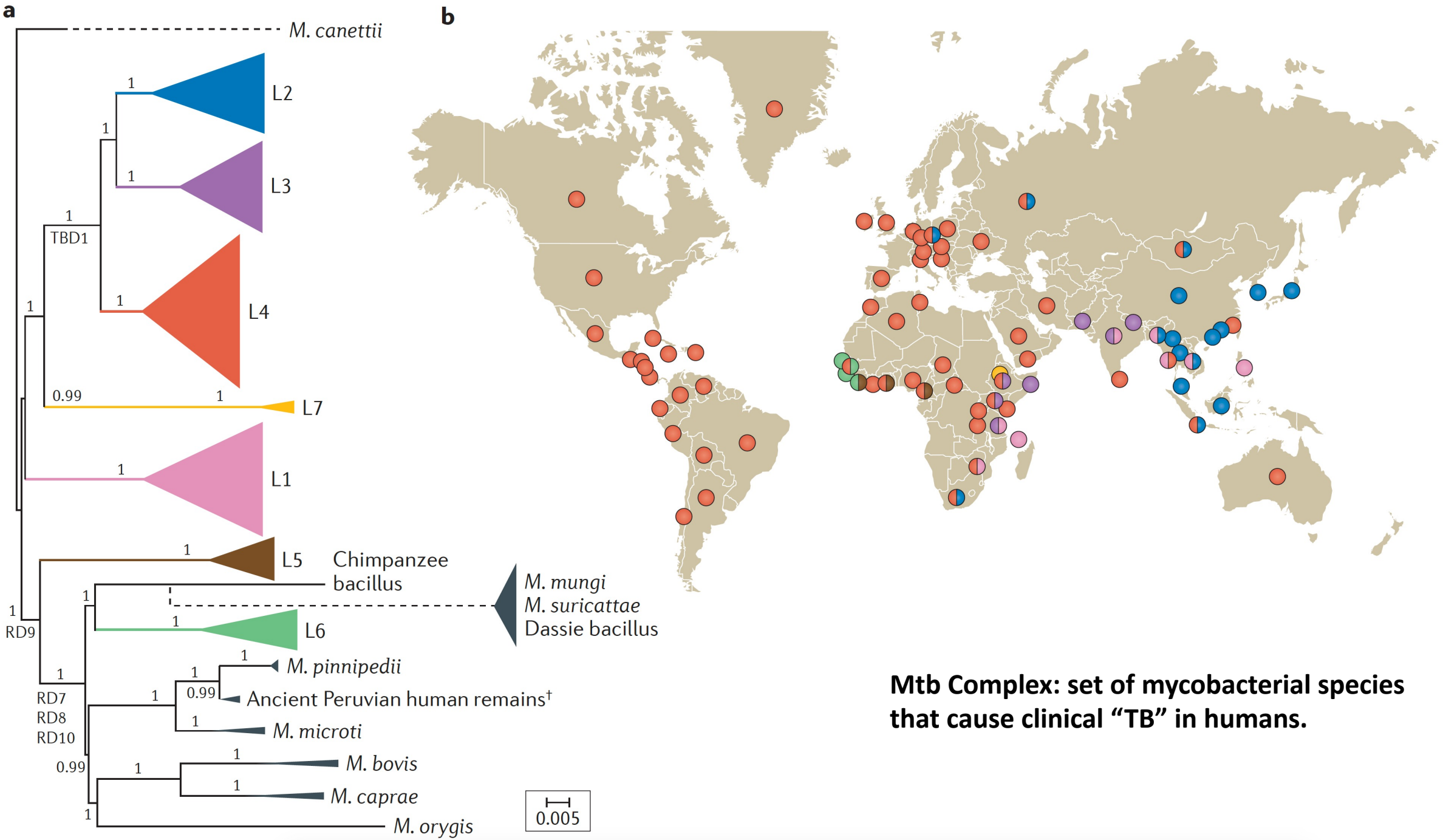
- 170 species, mostly environmental
- Slow and fast growers
- Rough and smooth colonies
- Pathogenic and non-pathogenic
- Human restricted, animals and human



Red: slow growers
Blue: fast growers




~2.5 million years ago?
~67,000 years ago?
~70,000 years ago?
TbD1
1
2
3
M. canettii in East Africa and STBs
Lineage 1:
The Philippines and Indian Ocean
Lineage 2:
East Asia
Lineage 3:
India and East Africa
Lineage 4:
Europe and Americas
Lineage 7:
Ethiopia
Lineage 5:
M. africanum 1 in West Africa
M. bovis ecotypes
Chimpanzee bacillus
Lineage 6:
M. africanum 2 in West Africa
M. tuberculosis
MTBC
Non-tuberculosis mycobacteria
M. marinum (water)
M. avium silvaticum (birds)
M. avium avium (birds)
M. avium hominissuis (environment)
M. avium paratuberculosis
(sheep and cattle)
M. sp. MCS (soil)
M. sp. KMS (soil)
M. vanbaalenii (soil)
Rhodococcus spp. (soil)
Large-scale genome duplication events



Mtb Complex: set of mycobacterial species that cause clinical "TB" in humans.

NTMs

Table 5
Major clinical syndromes associated with nontuberculous mycobacterial infections[a].

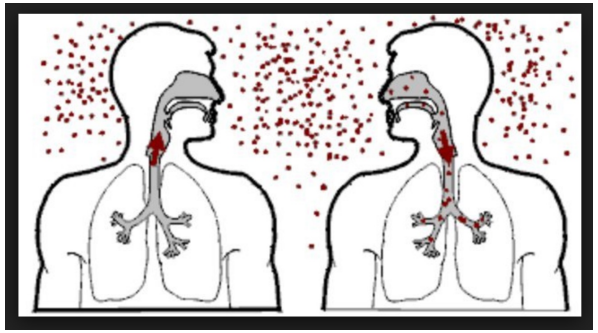
Clinical disease	Etiologic species[b]			
	Common[c]		Unusual[c]	
Chronic bronchopulmonary disease	*M. avium* complex *M. kansasii* *M. abscessus*	*M. malmoense* *M. xenopi*	*M. simiae* *M. szulgai* *M. fortuitum* *M. celatum* *M. gordonae*	*M. asiaticum* *M. shimodii* *M. smegmatis* *M. haemophilum*
Lymphadenitis	*M. avium* complex *M. scrofulaceum* *M. malmoense*		*M. fortuitum* *M. chelonae* *M. kansasii* *M. abscessus* *M. haemophilum*	*M. lentiflavum* *M. interjectum* *M. heidelbergense* *M. bohemicum*
Skin and soft tissue disease	*M. ulcerans* *M. marinum*	*M. chelonae* *M. abscessus* *M. fortuitum*	*M. kansasii* *M. haemophilum* *M. malmoense*	*M. smegmatis*
Otitis media	*M. abscessus*	*M. chelonae*		
Skeletal infection • Tenosynovitis	*M. marinum* *M. avium* complex		*M. fortuitum* *M. abscessus* *M. chelonae* *M. kansasii* *M. haemophilum* *M. scrofulaceum*	*M. smegmatis* *M. nonchromogenicum* *M. malmoense* *M. xenopi* *M. szulgai*
• Osteomyelitis	*M. fortuitum*	*M. abscessus*	*M. xenopi* *M. marinum*	*M. kansasii*
Foreign body-related infections • Catheter-related infections	*M. fortuitum* *M. abscessus* *M. chelonae*		*M. mucogenicum* *M. neoaurum* *M. aurum*	*M. avium* *M. smegmatis*
• Prosthetic valves	*M. fortuitum*	*M. chelonae*	*M. gordonae*	
Surgical site infections	*M. fortuitum*	*M. chelonae*	*M. abscessus*	*M. simiae*

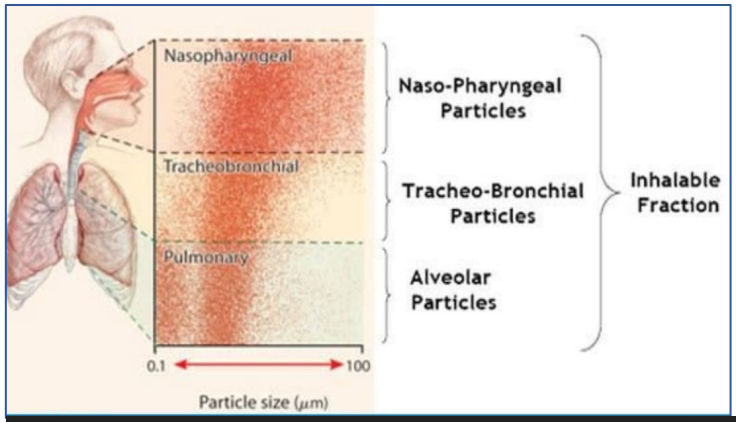
[a] Adapted from references [20, 74]; [b] The growing number of species associated with specific diseases precludes completeness of this list; [c] Classification as common or uncommon is adopted from references [20, 74] modified by more recent literature. It represents the judgment of the authors

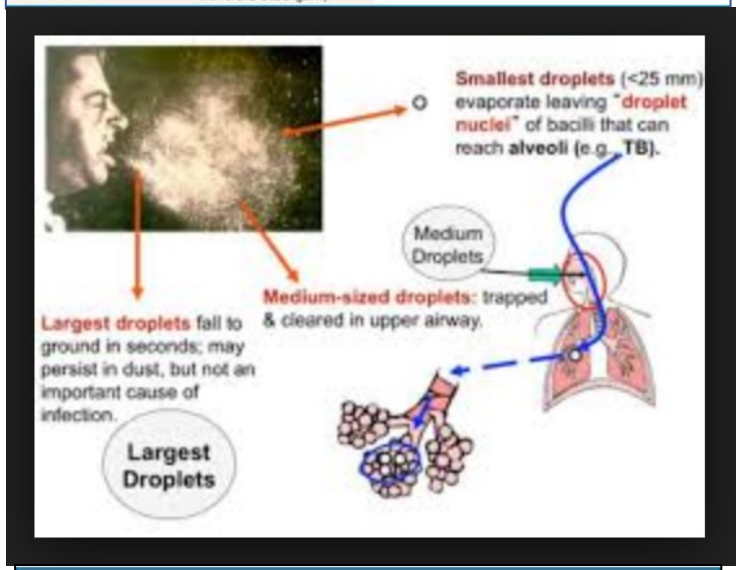
Some important points

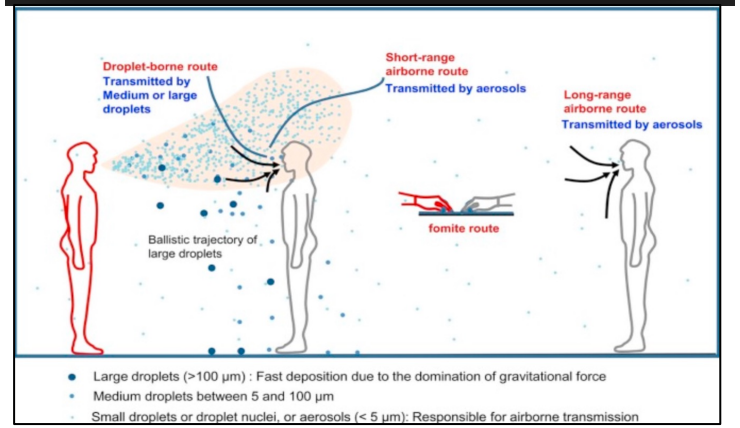
- M. bovis and other Mtb complex members probably “evolved” from Mtb, rather than vice versa.
- Evolution in mycobacteria proceeds by genomic deletions.
- Evidence for differences in lineages sparse.
- Generalist versus Specialist paradigm.

Mtb transmission via aerosol

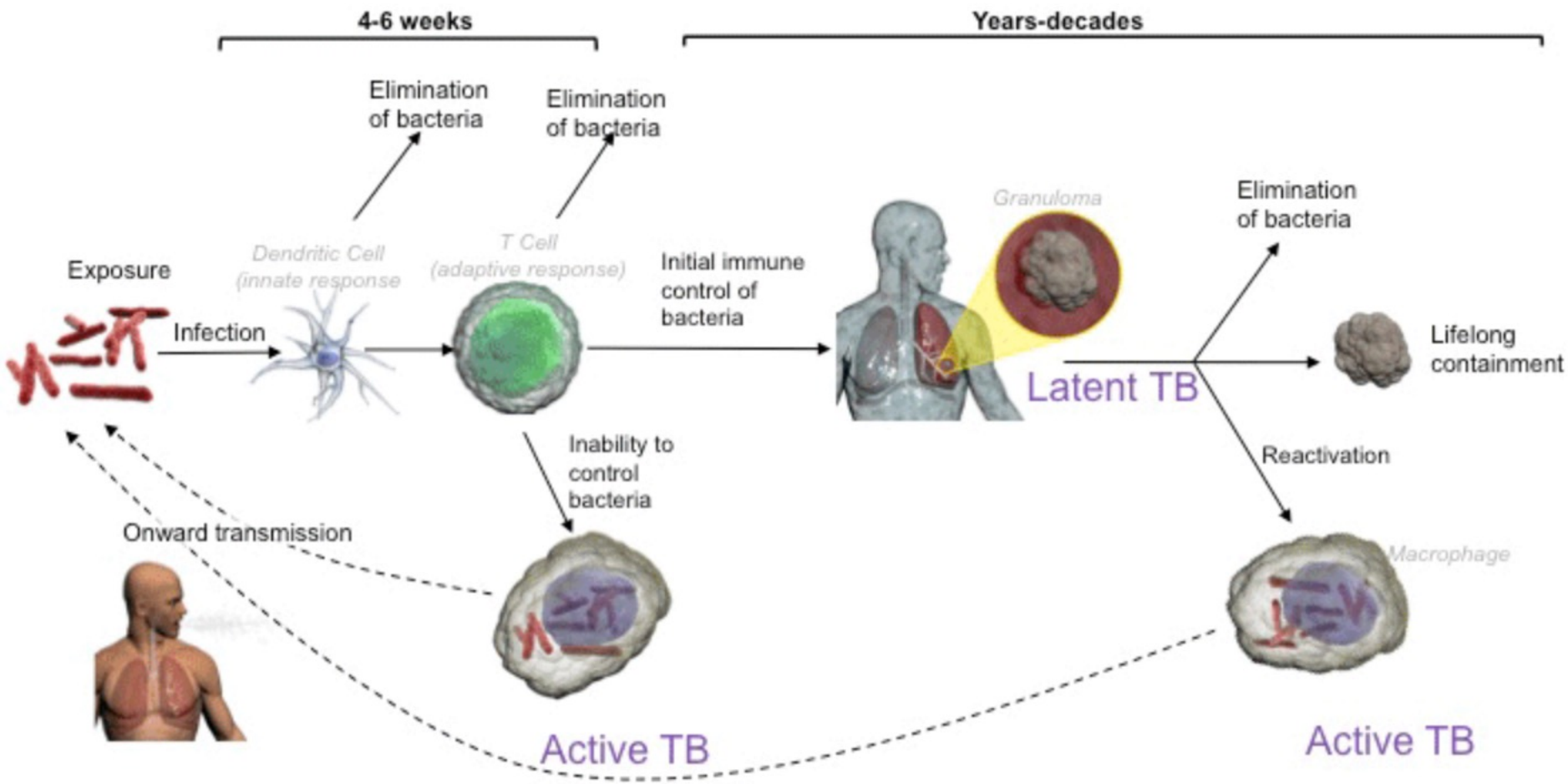








Natural history of TB infection



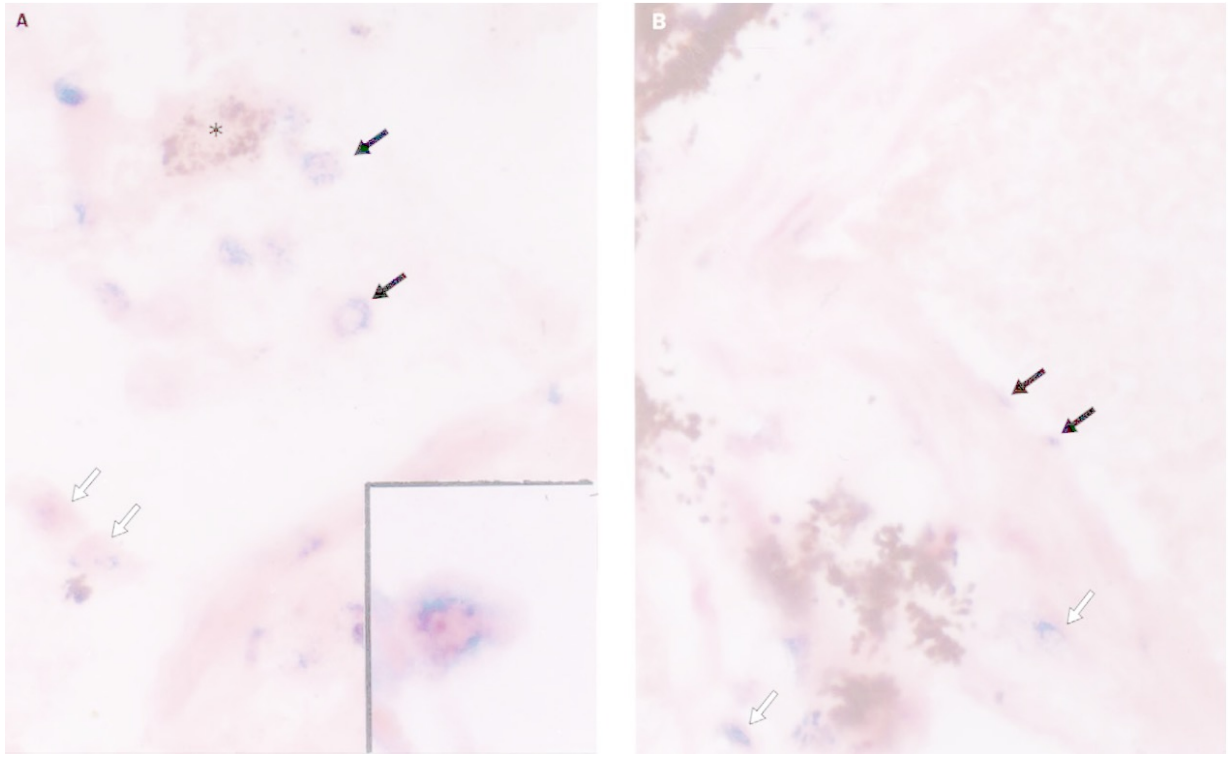
Evidence of latent TB: Autopsy studies

Dr. Eugene Opie
TB pioneer in 1920s
DM “hero”

In 126 people dying from causes other than TB, Opie recovered viable TB bacilli in 26%.

Persistence of DNA from *Mycobacterium tuberculosis* in superficially normal lung tissue during latent infection

5/13 Ethiopians and 10/34 Mexicans who died from causes other than TB were PCR +. All positive controls +, all negative controls -.



Hernández-Pando R, Jeyanathan M, Mengistu G, Aguilar D, Orozco H, Harboe M,Rook GA, Bjune G. Lancet. 2000 Dec 23-30;356(9248):2133-

Stead proposed "unified concept of TB pathogenesis" in 1967.

SPECIAL ARTICLE ARCHIVE

Pathogenesis of the Sporadic Case of Tuberculosis

William W. Stead, M.D.†

N Engl J Med 1967; 277:1008-1012 | November 9, 1967 | DOI: 10.1056/NEJM196711092771906

This article has no abstract; the first 100 words appear below.

PROBABLY every physician has been surprised by the sporadic appearance of pulmonary and other forms of tuberculosis in a previously healthy older person in whom recent exposure to an open case of the infection appeared highly unlikely. Occasionally, active tuberculosis is discovered at autopsy as the cause of an unexplained illness in a person with no apparent source of infection in the environment. When the disease is extrapulmonary (kidney, spine and so forth) it is usually explained as a late progression of a dormant infection. But when it lies within the lung, it is common to invoke reinfection (or superinfection) . . .

AMERICAN REVIEW
OF RESPIRATORY DISEASE
Clinical and Laboratory Studies of Tuberculosis and Respiratory Disease

VOLUME 95 *May 1967* NUMBER 5

PATHOGENESIS OF A FIRST EPISODE OF CHRONIC PULMONARY TUBERCULOSIS IN MAN: RECRUDESCENCE OF RESIDUALS OF THE PRIMARY INFECTION OR EXOGENOUS REINFECTION?

WILLIAM W. STEAD[1]

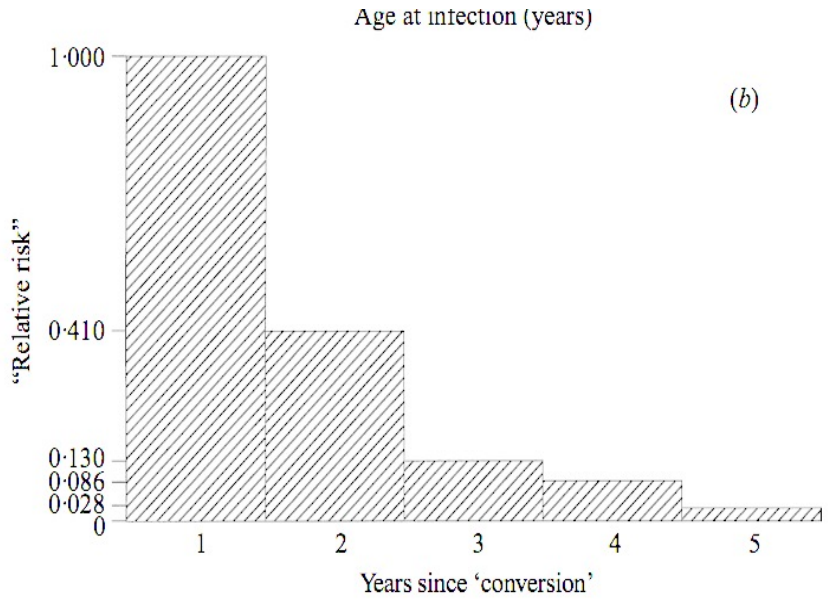
(Received for publication December 5, 1966)

INTRODUCTION

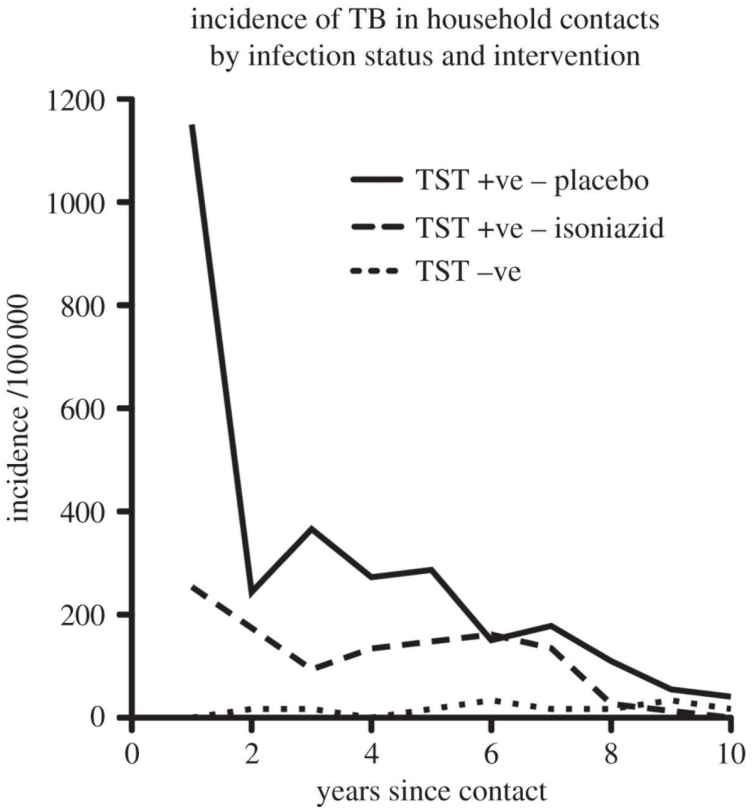
The purpose of this paper is to examine the evidence concerning the practical and important questions: (*1*) Is a person who reacts to tuberculin reinfectable under natural circumstances? (*2*) Does exogenous reinfection play a significant role in the pathogenesis of chronic pulmonary tuberculosis in man? (*3*) If not, by what mechanism does chronic tuberproof of actual reinfection by a newly acquired organism in a person known to have been infected previously.

The question to which the writer has addressed himself in the past several years concerns the pathogenesis of chronic pulmonary tuberculosis when it appears for the *first* time in previously healthy persons, whose only evidence of a prior infection was tuberculin

Decline in persistent TB risk over time since TB infection.



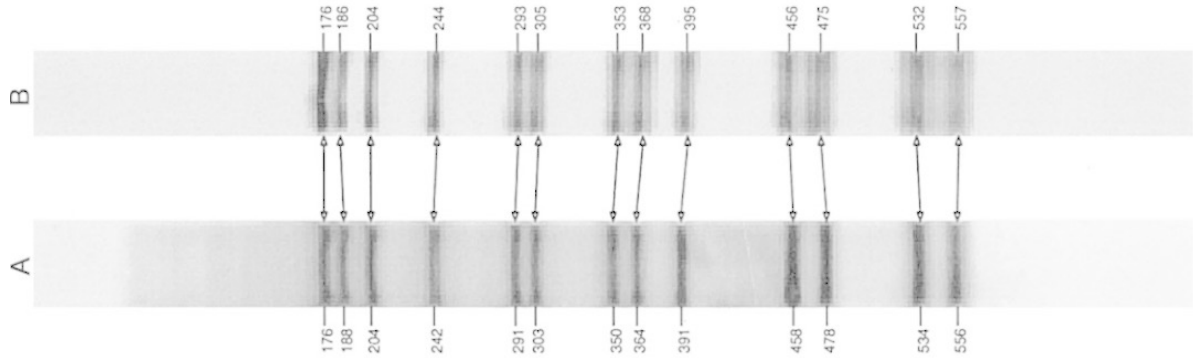
Data from UK MRC BCG trial in adolescents in 1950s



Data from Puerto Rico BCG trial published by Feregee.

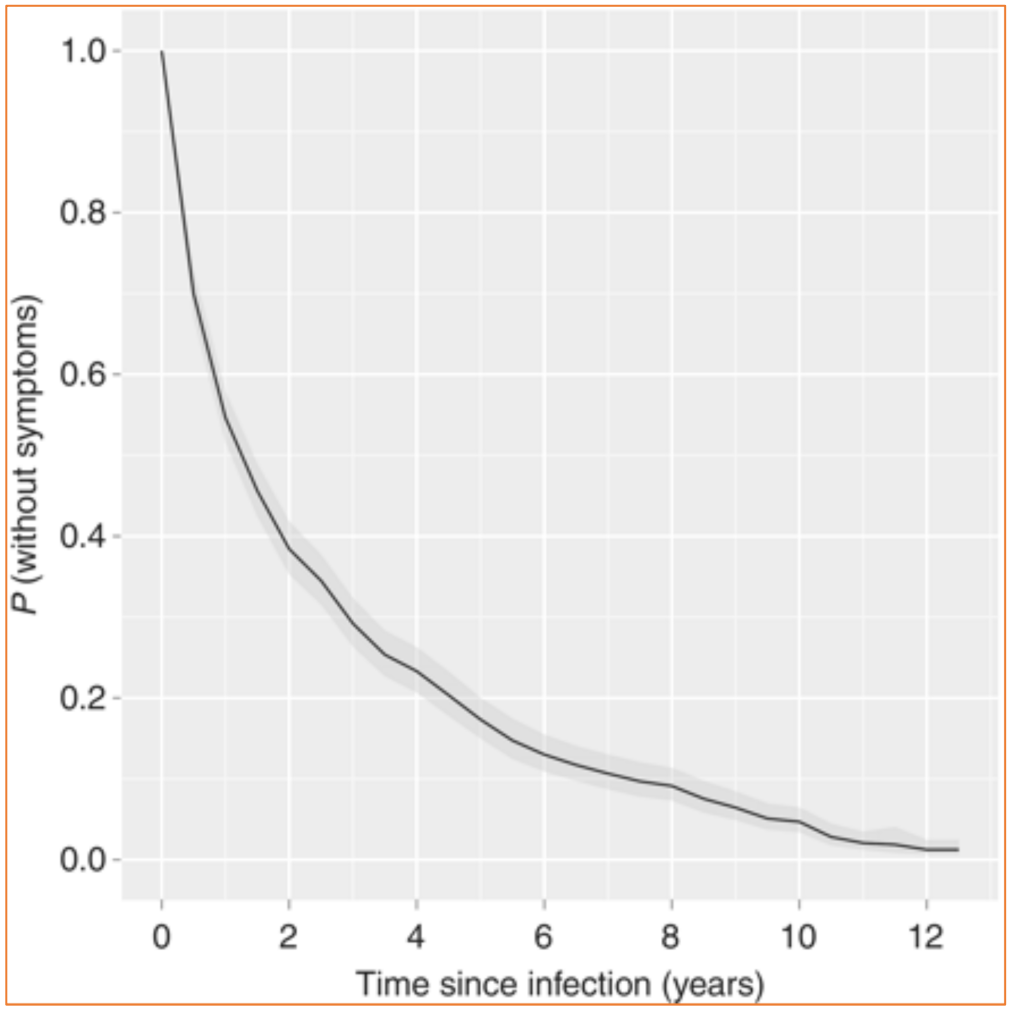
Molecular Evidence of Endogenous Reactivation of *Mycobacterium tuberculosis* after 33 Years of Latent Infection

Identical DNA RFLP patterns of Mtb isolates from a father in 1961 and his son in 1994. Son was 7 at the time the father had TB.



Lillebaek T, Dirksen A, Baess I, Strunge B, Thomsen VØ, Andersen AB. Molecular evidence of endogenous reactivation of Mycobacterium tuberculosis after 33 years of latent infection. J Infect Dis. 2002 Feb 1;185(3):401-4.

The incubation period distribution of tuberculosis estimated with a molecular epidemiological approach

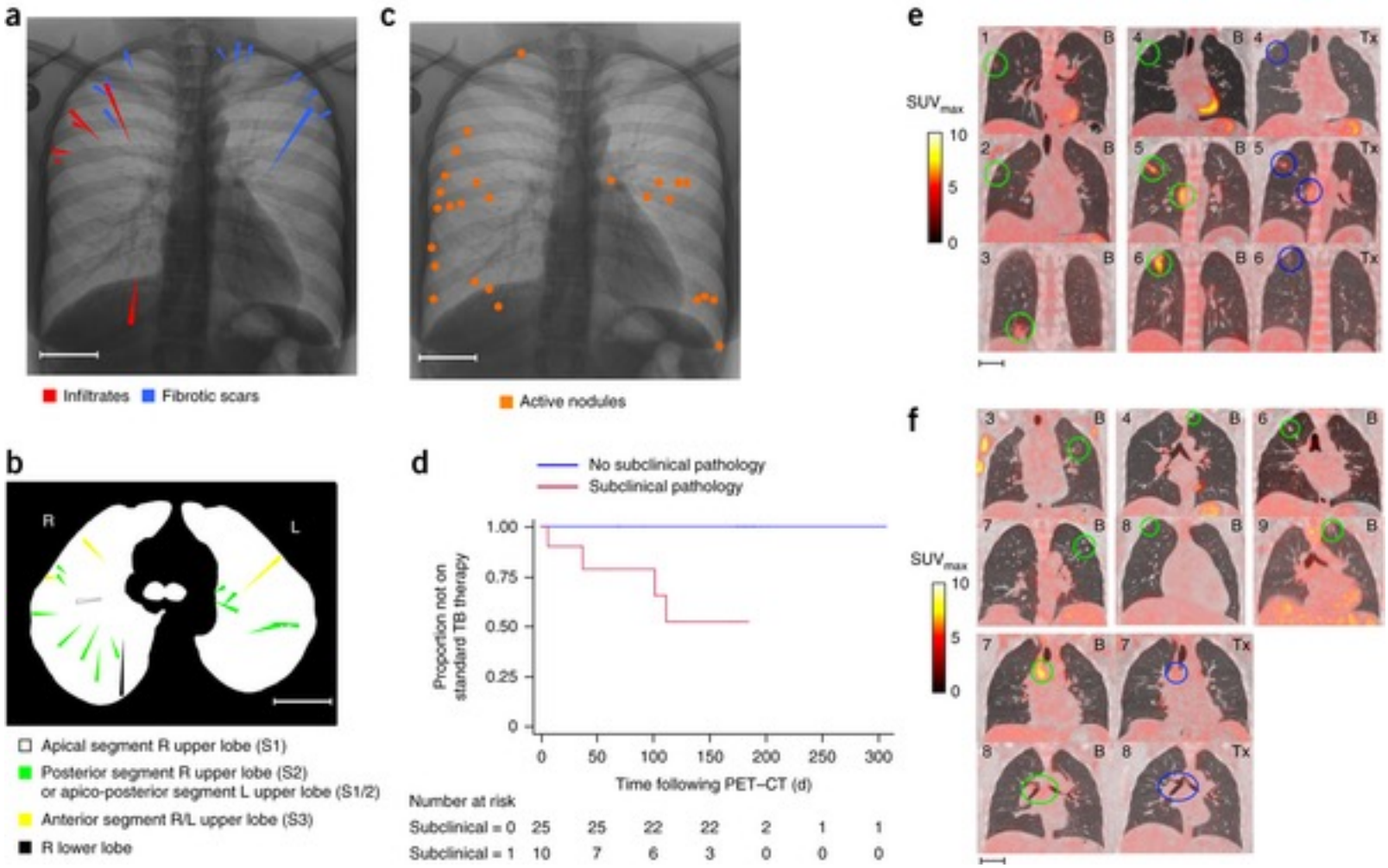


Incubation period in secondary cases from paired source and secondary cases defined by molecular and traditional epidemiologic links

Median 1.26 years
Range 0-12

Borgdorff MW, Sebek M, Geskus RB, Kremer K, Kalisvaart N, van Soolingen D. Int J Epidemiol. 2011 Aug;40(4):964-70.

PET scans of latent or “subclinical” TB



Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

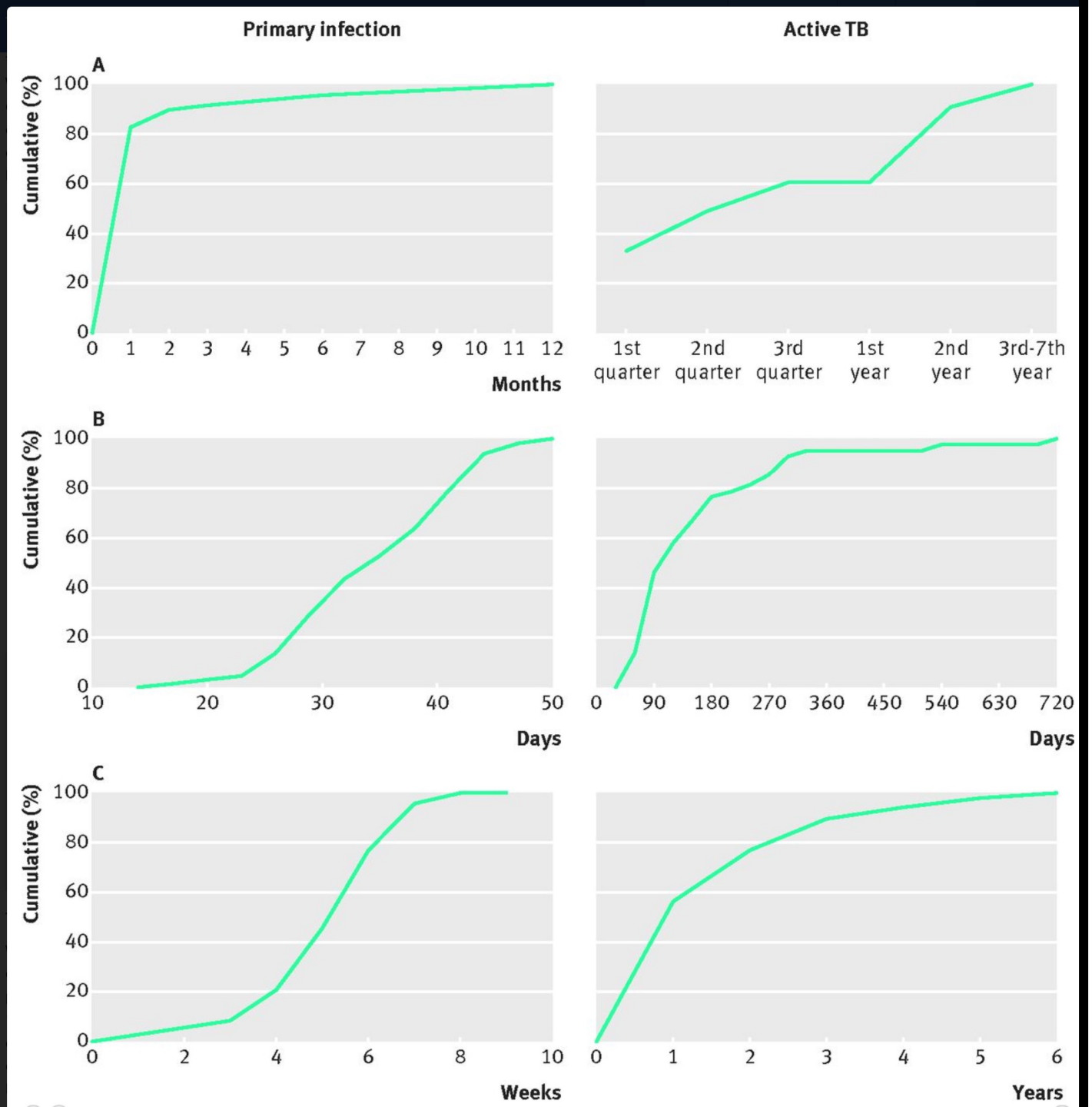
This Official Statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This Statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this Statement as it relates to infants and children were endorsed by the American Academy of Pediatrics (AAP), August 1999.

TABLE 2

INCIDENCE OF ACTIVE TUBERCULOSIS (TB) IN PERSONS WITH A POSITIVE TUBERCULIN TEST, BY SELECTED RISK FACTORS

Risk Factor	TB Cases/l ,000 Person-vears
Recent TB infection	
infection < 1 yr past	12.9 (6)*
Infection l-7 yr past	1.6
Human immunodeficiency virus	
(HIV) infection	35.0-l 62 (28)
Injection drug use	
HIV seropositive	76.0 (31)
HIV seronegative or unknown	10.0 (31)
Silicosis	68 (36)
Radiographic findings consistent with prior TB	2.0-l 3.6 (32-34)
Weight deviation from standard	
Underweight by ≥ 15%	2.6 (35)
Underweight by 1 0–14%	2.0
Underweight by 5–9%	2.2
Weight within 5% of standard	1.1
Overweight bv ≥ 5%	0.7

* Numbers in parentheses are reference numbers.

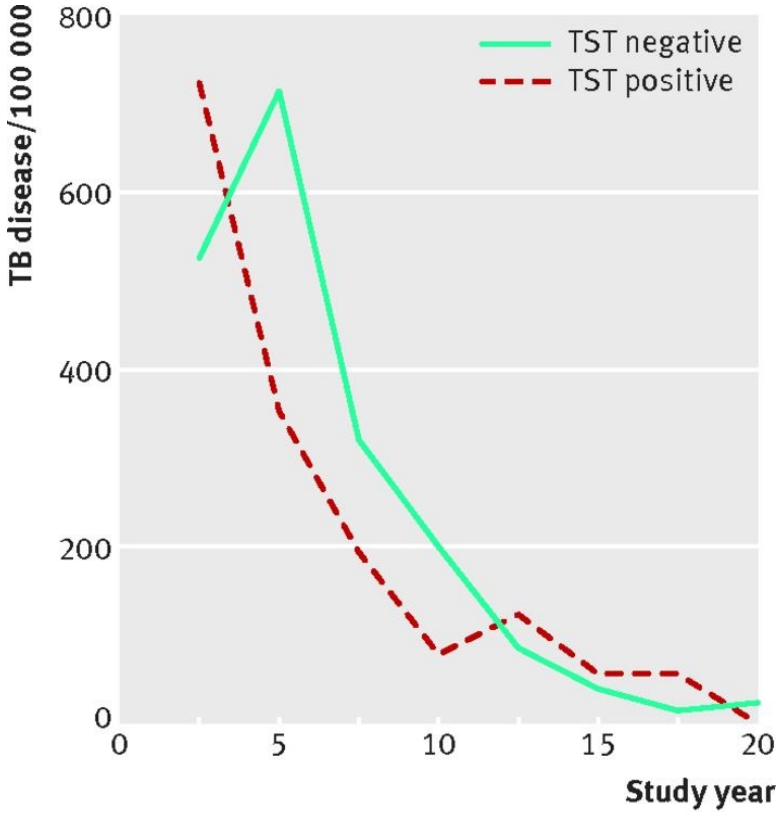


Tuberculous reactivity—Indirect evidence of present or past infection with *Mycobacterium tuberculosis* as inferred by a detectable adaptive immune response to *M tuberculosis* antigens (on tuberculin skin test or interferon gamma release assay) in an asymptomatic person

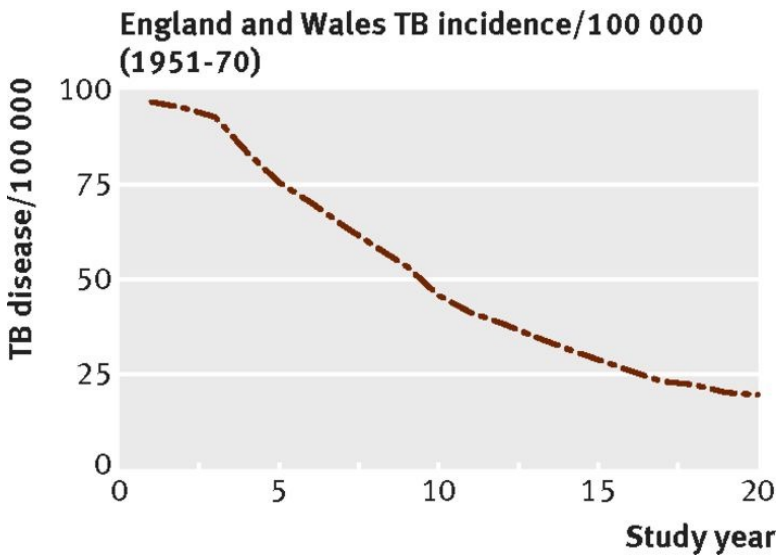
Primary infection—Evidence of new tuberculous infection, obtained with a tuberculin skin test conversion or a new positive interferon gamma release assay, which may be asymptomatic or accompanied by transient fever, erythema nodosum, elevated erythrocyte sedimentation rate or characteristic roentgenographic abnormalities

Active tuberculosis—Evidence of progressive disease of the lung and/or other organs generally accompanied by a positive culture for *M tuberculosis* and/or roentgenographic findings and/or histopathology consistent with TB

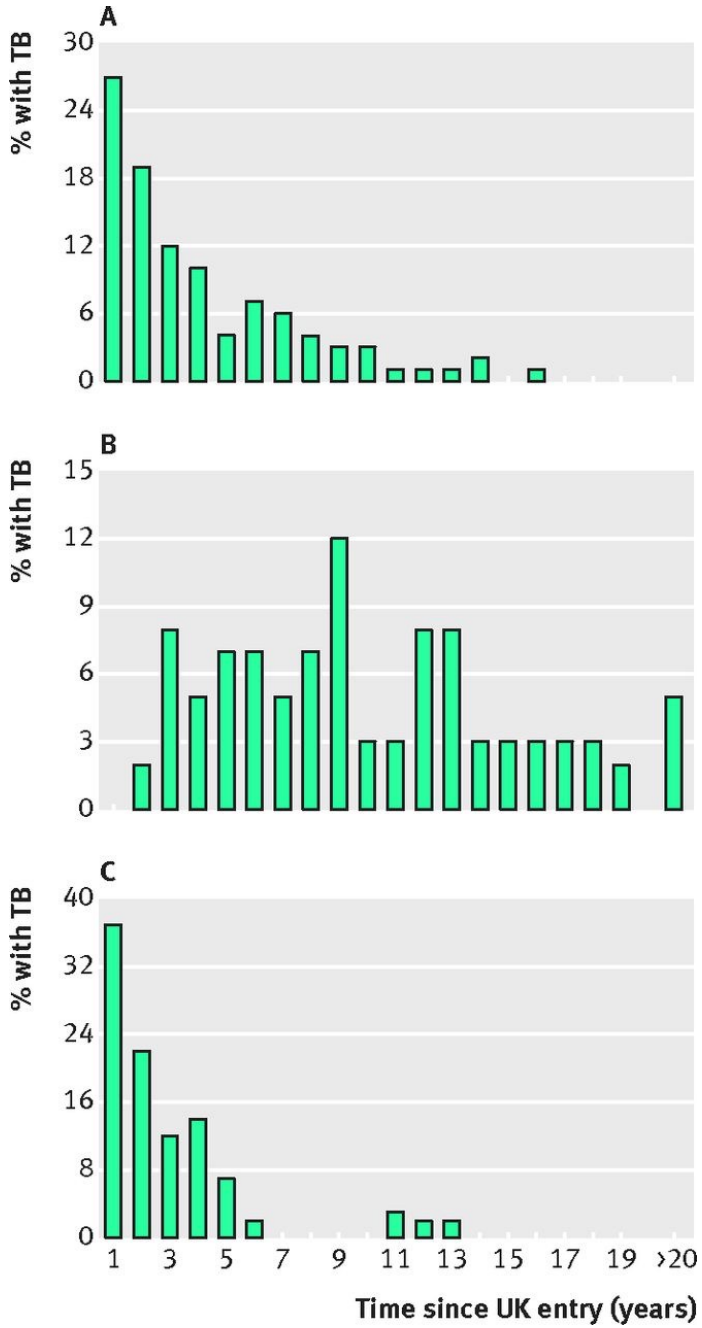
Three studies from pre-chemotherapeutic era that tracked contacts after a definitive exposure. Cited in Behr, 2018.



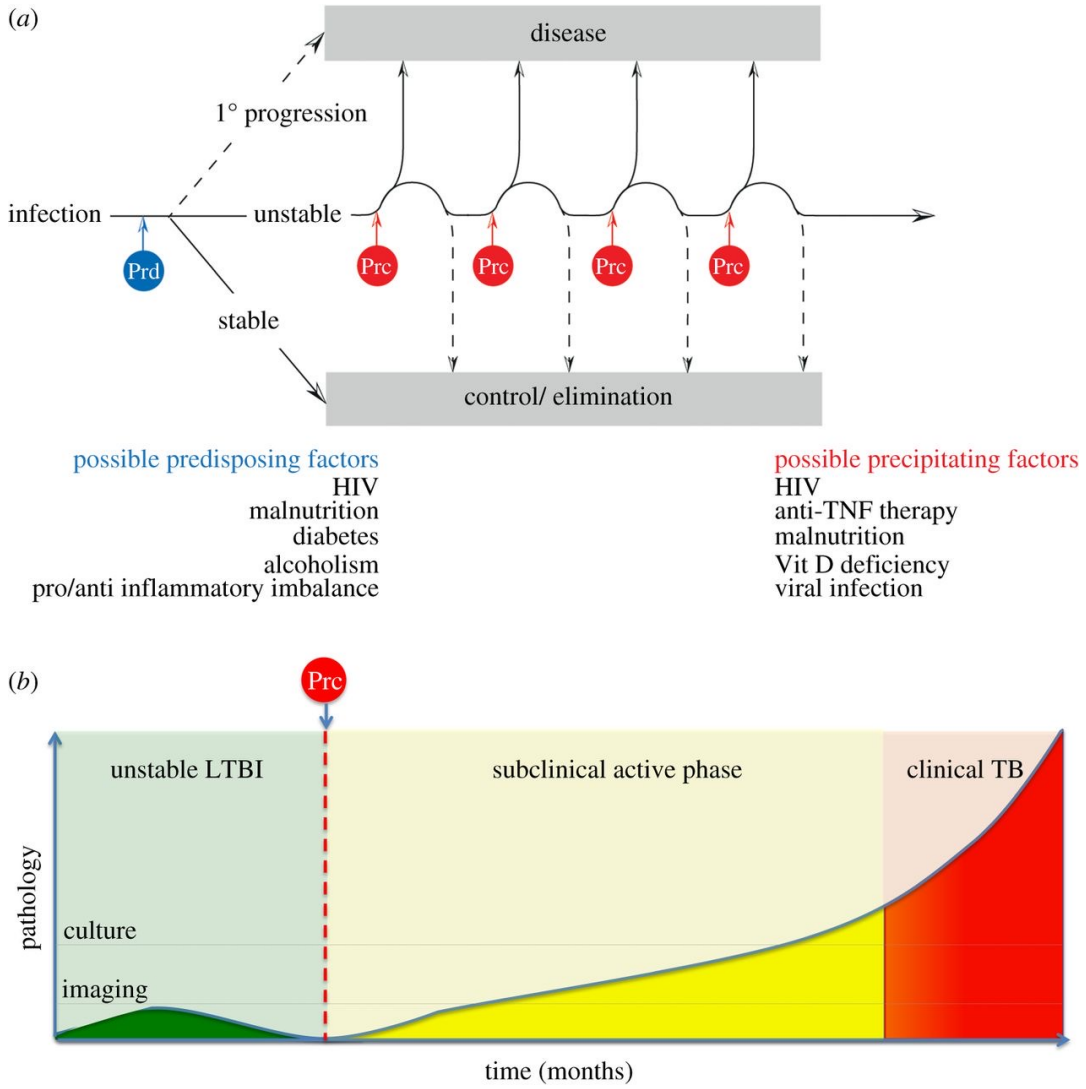
Long term rates in MRC adolescent study in Britain in the 1950s.



Asian immigrants to London: A is time since leaving home country, B is TB incidence over calendar time, C is time to TB after returning from travel to home country.

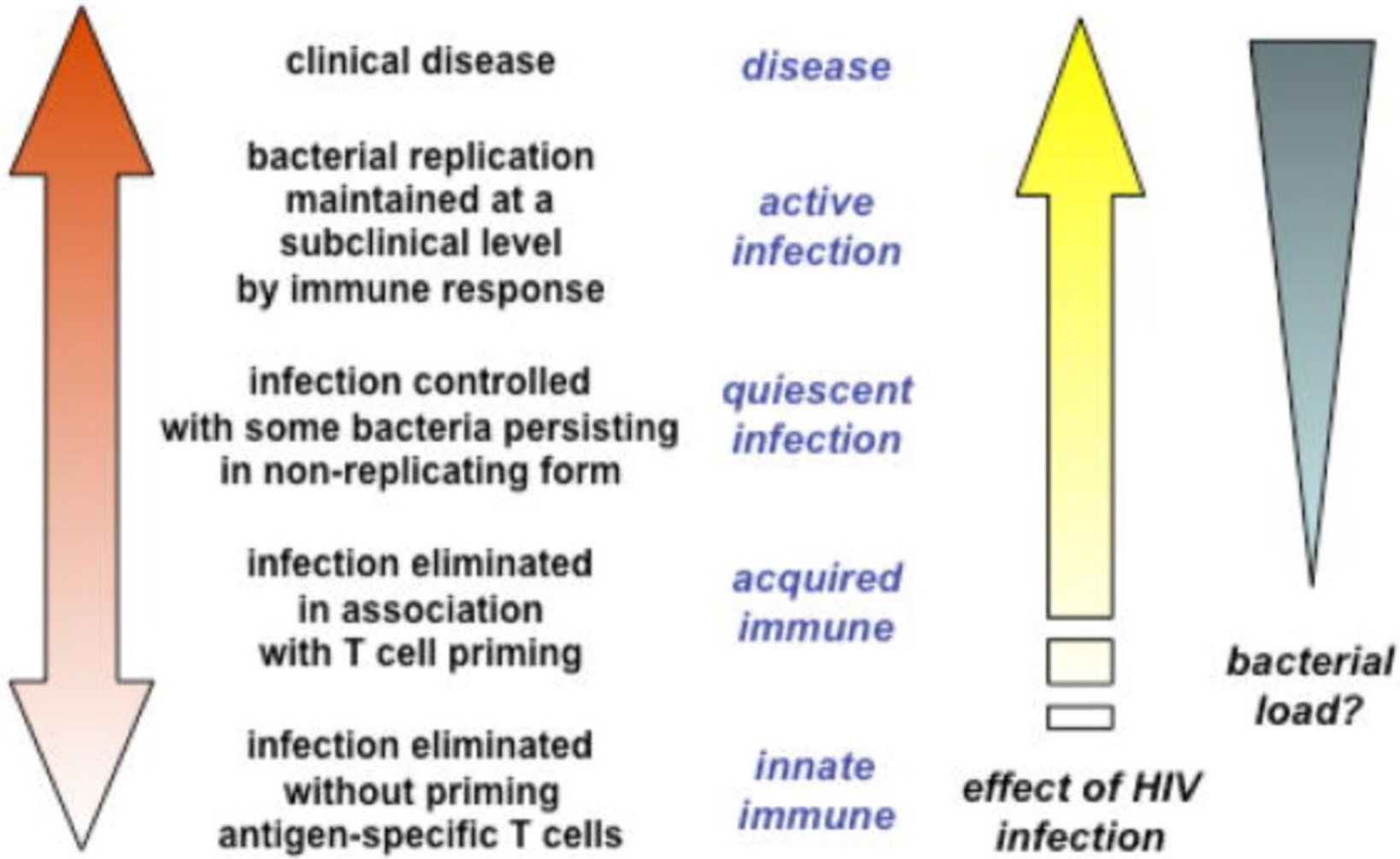


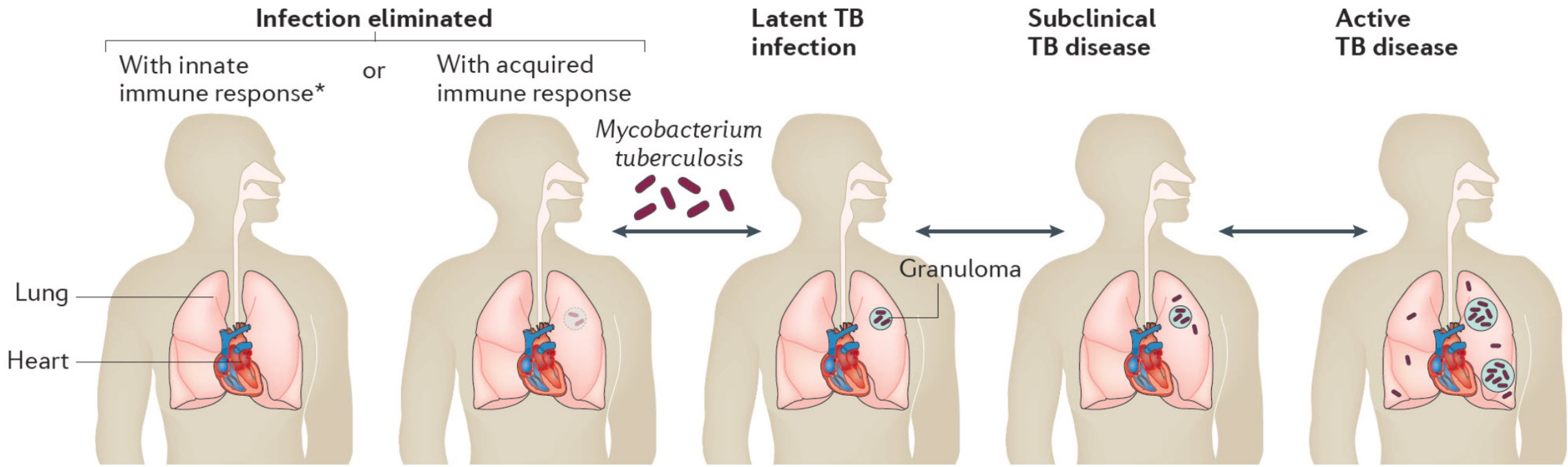
Following infection, there may be a critical period where fate of infection is determined with predisposing factors.



H. Esmail et al. Phil. Trans. R. Soc. B 2014;369:20130437

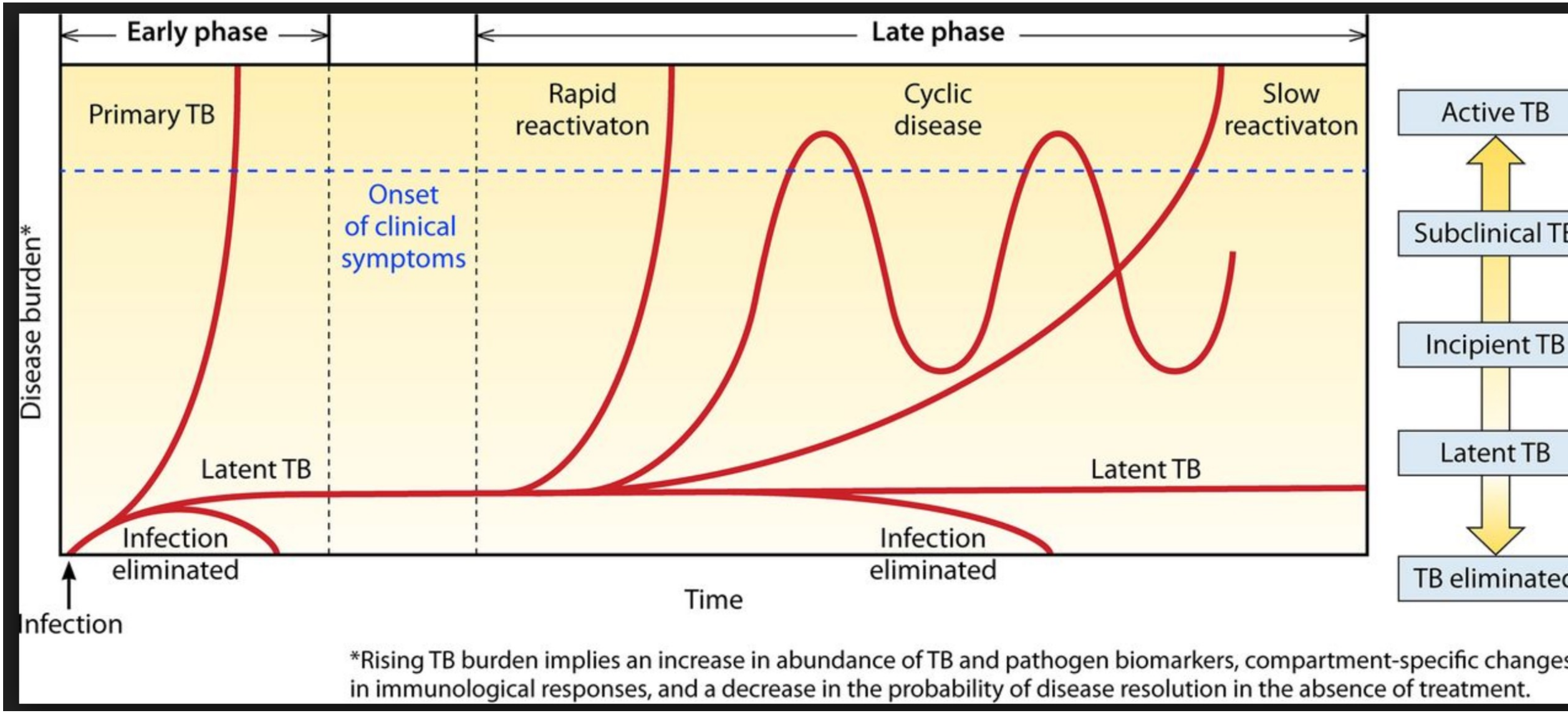
A spectrum of responses to tuberculosis infection





TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Incipient and subclinical disease



Disease progression

Quiescent infection	*Incipient disease*	*Subclinical disease*	*Active disease*
Immunological sensitization Bacterial replication controlled successfully	Low-level bacterial replication Asymptomatic without radiological or microbiological evidence of disease	Moderate bacterial replication Asymptomatic with radiological or microbiological evidence of disease	Moderate to high bacterial replication Clinical signs & symptoms Radiological and/or microbiological evidence of disease
	>12 months	3-6 months	0 months