Tuberculosis

Pathophysiology and Transmission

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July 2023
Tuberculosis Clinical Intensive Course

DISCLOSURE

The following planner/speaker has reported a relevant financial relationship with a commercial interest:

- Gilead Sciences
- Abbott/Alere
- LumiraDx
- InBios International
- Cepheid
- Alveo Technologies
- Abbvie

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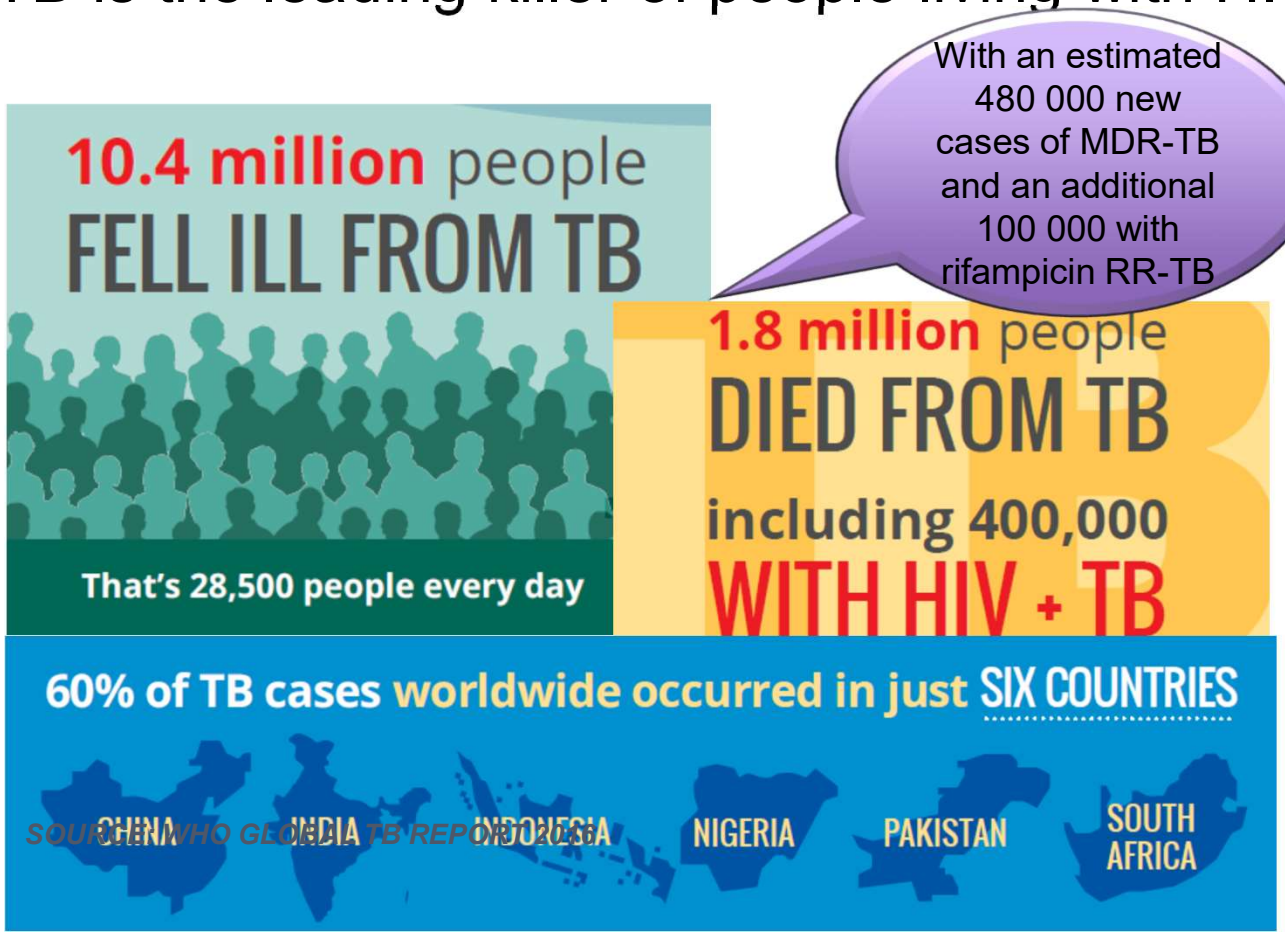
Global Health Facts

1. TB is among the Top 10 causes of death
2. TB is the leading infectious cause of mortality
3. TB is the leading killer of people living with HIV



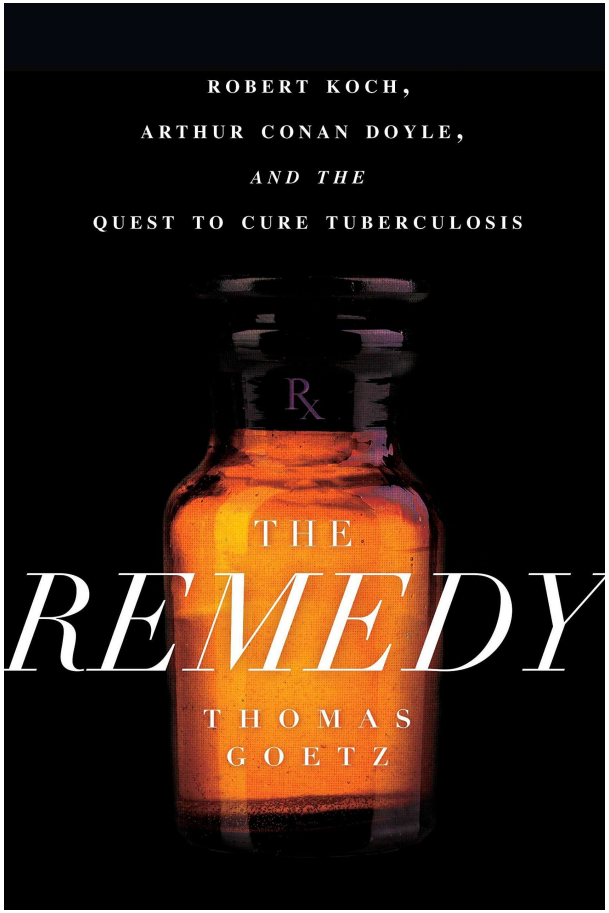
WHO, Global TB Report 2017

Outline

- Historical Context of Tuberculosis (TB)
- *Mycobacterium spp.* and *M. tuberculosis*
- TB Pathophysiology
- TB Transmission
- Clinical Summary

Who identified M. tuberculosis as the bacterium that causes tuberculosis disease, known at the time a "Consumption"?

1. Louis Pasteur
2. Robert Koch
3. Arthur Conan Doyle
4. Albert Calmette and Camille Guérin



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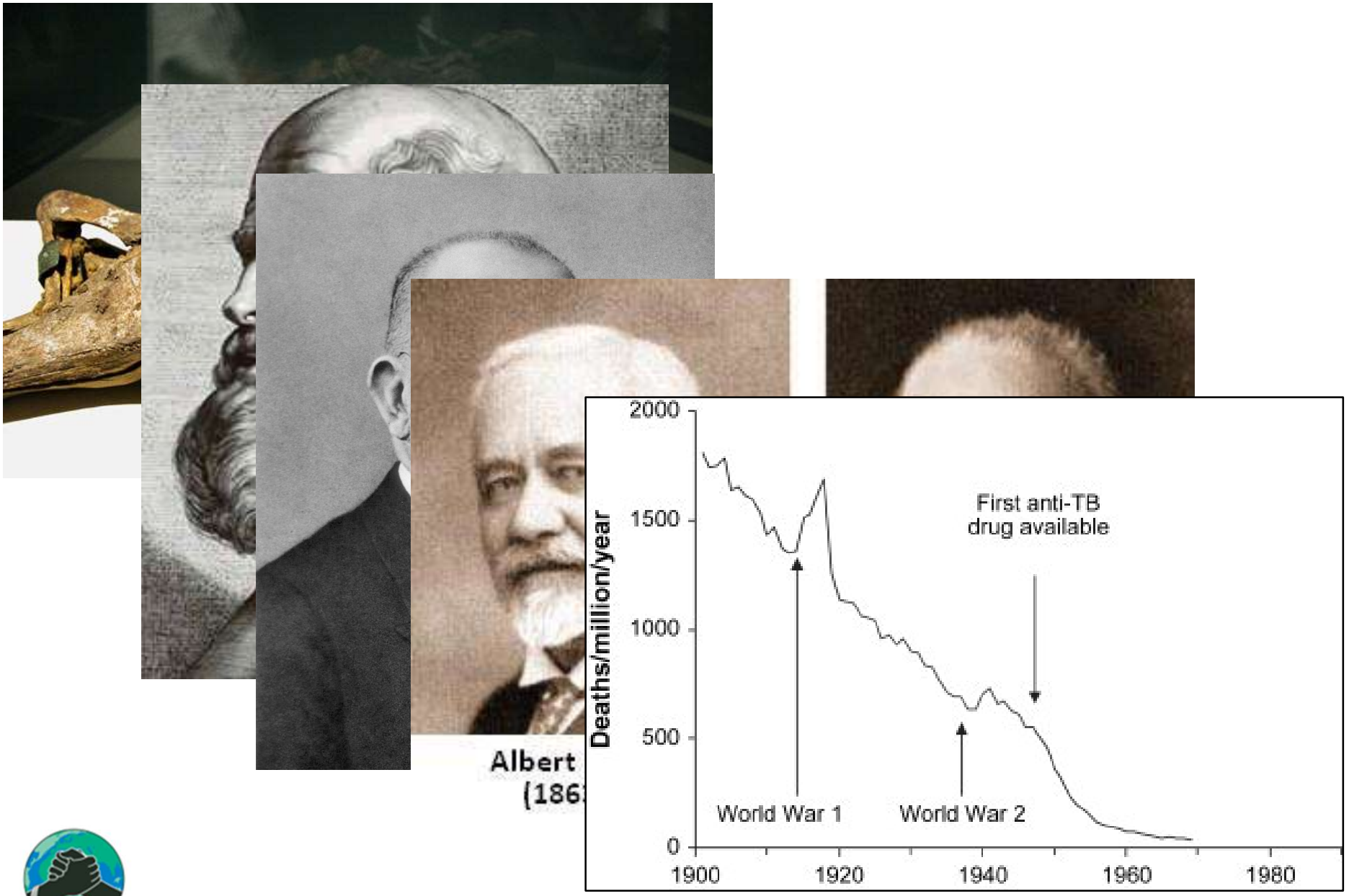

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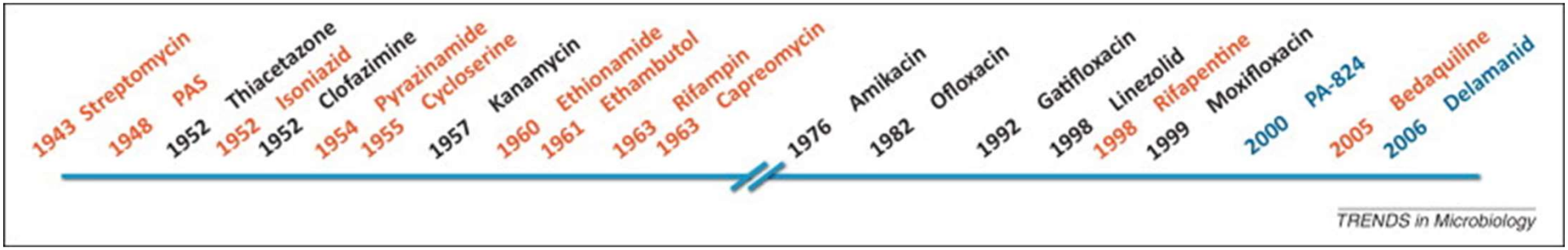
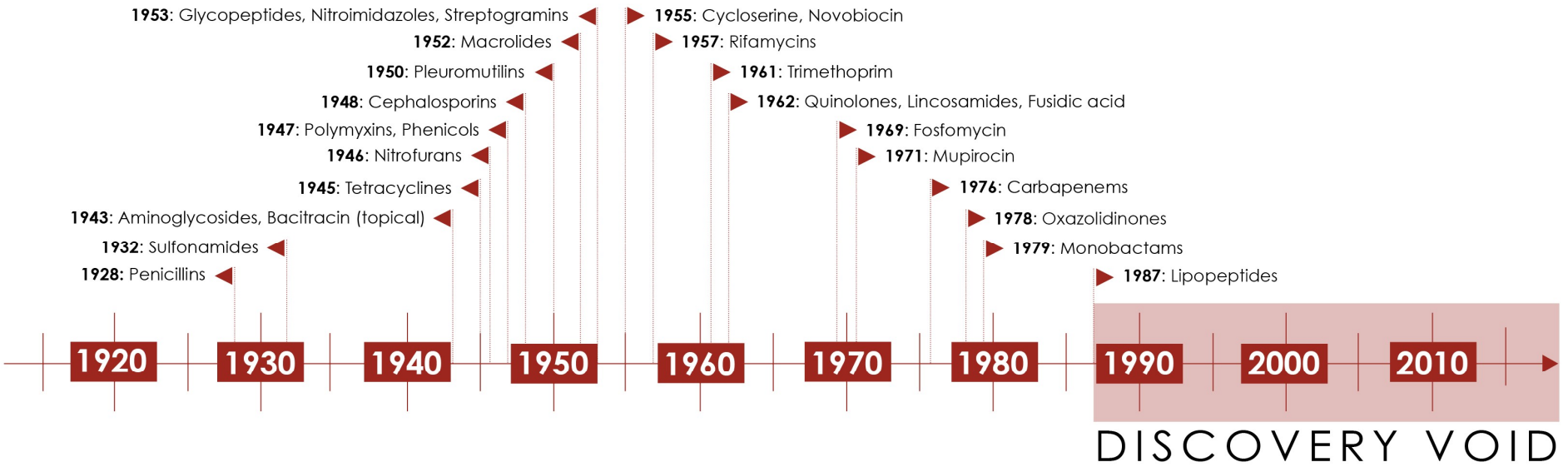
History of TB Medications





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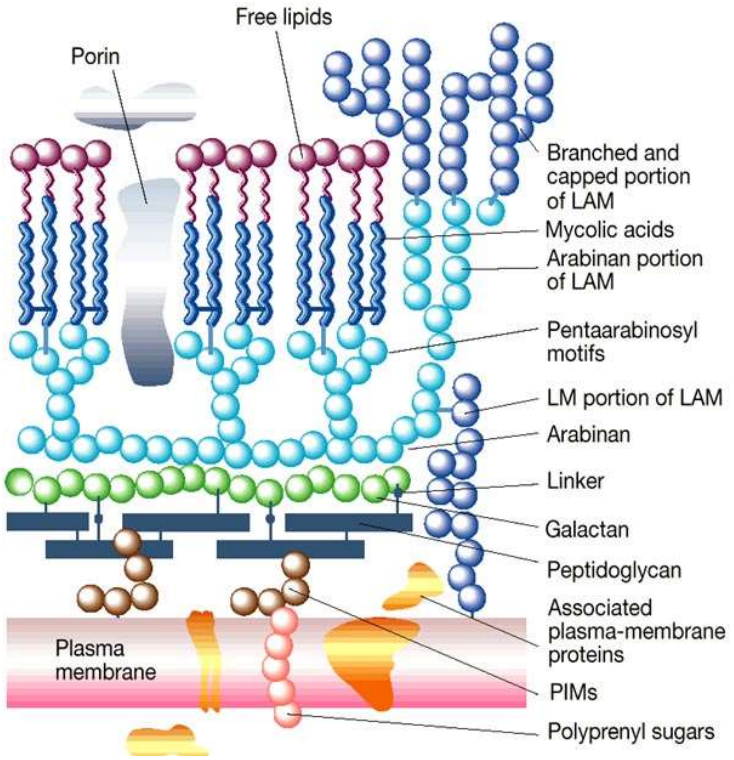
Mycobacterium spp.

- Family: Mycobactericiaea
- Highly aerobic bacillus
- Mycolic cell wall (“waxy”) with 5 layers:
    1. Capsule
    2. Mycolic acids
    3. Lipo-arabinogalactan (LAM)
    4. Peptidoglycan
    5. Plasma membrane
- Acid-fast Ziehl-Neelsen stain positive
- Non-TB Mycobacterium are ubiquitous in the environment with no person-to-person transmission, but can cause human disease
- *M. leprae* is an exception - can be transmitted through nasal secretions; humans and armadillos are only known reservoir



Non-TB *Mycobacterium spp.*

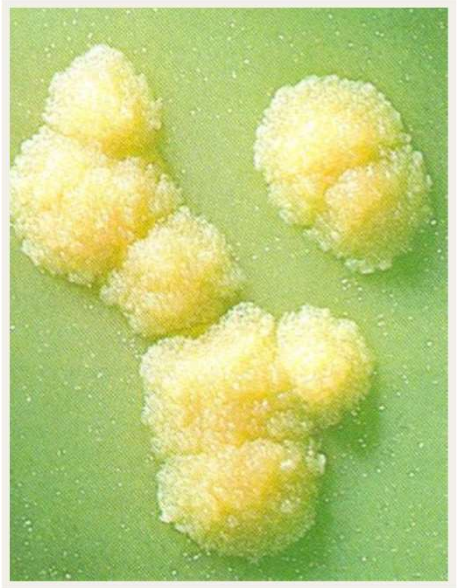
- Classification of Non-TB *Mycobacterium spp.*
  - Group 1 (photochromogens) – M. kansasii, M. marinum
  - Group 2 (scotochromogens) – M. gordonae, M. scrofulaceum
  - Group 3 (non-photochromogens) – MAC, M. terrae, M. ulcerans, M. xenopi, M. simine, M. malmuense, M. szulgai, M. asiaticum
  - Group 4 – Rapid Growers – M. fortuitum, M. chelonae, M. abscessus
- Non-TB *Mycobacterium spp.* by Organ
  - Pulmonary – MAC ("Lady Windemere's Syndrome"), M. kansasii (most similar to TB), M. abscessus, M. xenopi
  - Lymph – MAC, M. scrofulaceum, M. bovis
  - Cutaneous – M. marinum, M. fortuitum, M. chelonae, M. abscessus, M. haemophilum
  - Disseminated – M. fortuitum, M. chelonae, M. abscessus, MAC, M. haemophilum

Mycobacterium tuberculosis complex

***M. tuberculosis* complex** refers to genetically related group of Mycobacterium species that can cause tuberculosis disease in humans or others

Seven species of *M. tuberculosis* complex:

1. *M. tuberculosis* (humans - global)
2. *M. canettii* (humans in horn of Africa)
3. *M. africanum* (humans in West Africa)
4. *M. bovis* (cow, antelope; humans by dairy)
5. *M. microti* (vole)
6. *M. pinnipedii* (seal)
7. *M. caprae* (goat, cattle)



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How many species of Mycobacterium tuberculosis complex cause disease in humans?

1. 1
2. 4
3. 7
4. 10

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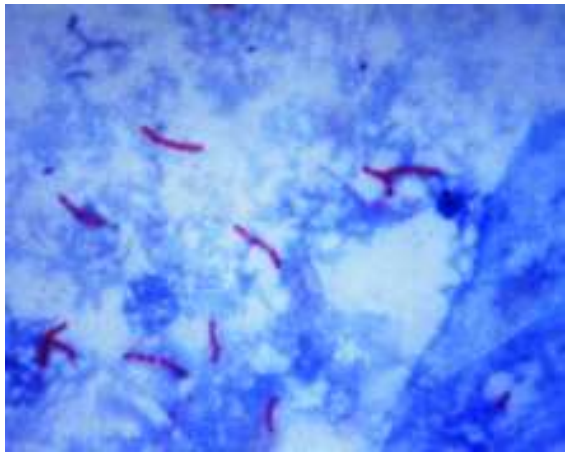
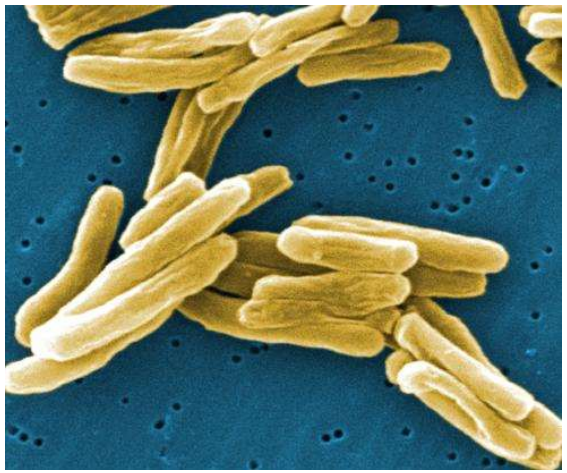
Mycobacterium tuberculosis complex

- Aerobic, non-motile, rod shaped bacilli
- Facultative intracellular pathogen
- Slow-growing (multiplies in 18-24 hrs)
- Thick lipid cell wall
- Acid-fast bacillus (AFB); requires special stains
- Remains dormant for decades (resists dehydration, oxidative stress, low pH)
- Resistant to most common antibiotics

AFB stain





Scanning EM

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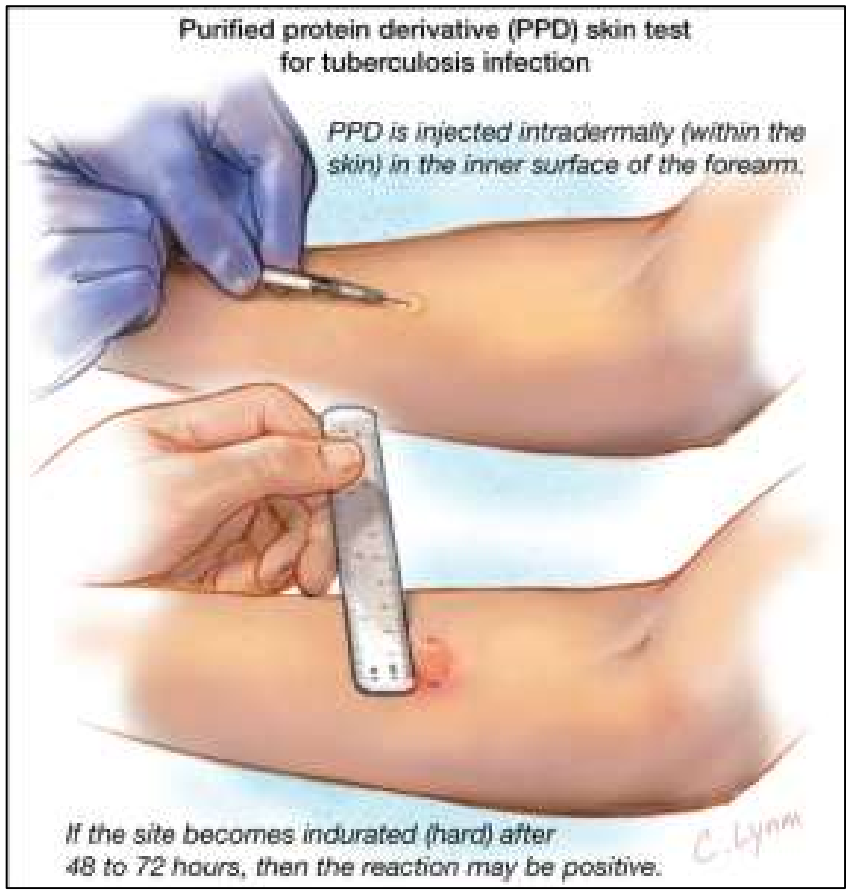
Latent TB Infection

- Asymptomatic people
- Mantoux PPD skin test (TST) or interferon-gamma release assay (IGRA)
- Risk factors for exposure:
  - High local TB prevalence
  - Close household contact
  - Institutional settings (hospitals, prisons, shelters)
  - Social contact (public transit)
  - Urbanization
  - Age
  - Low socioeconomic status



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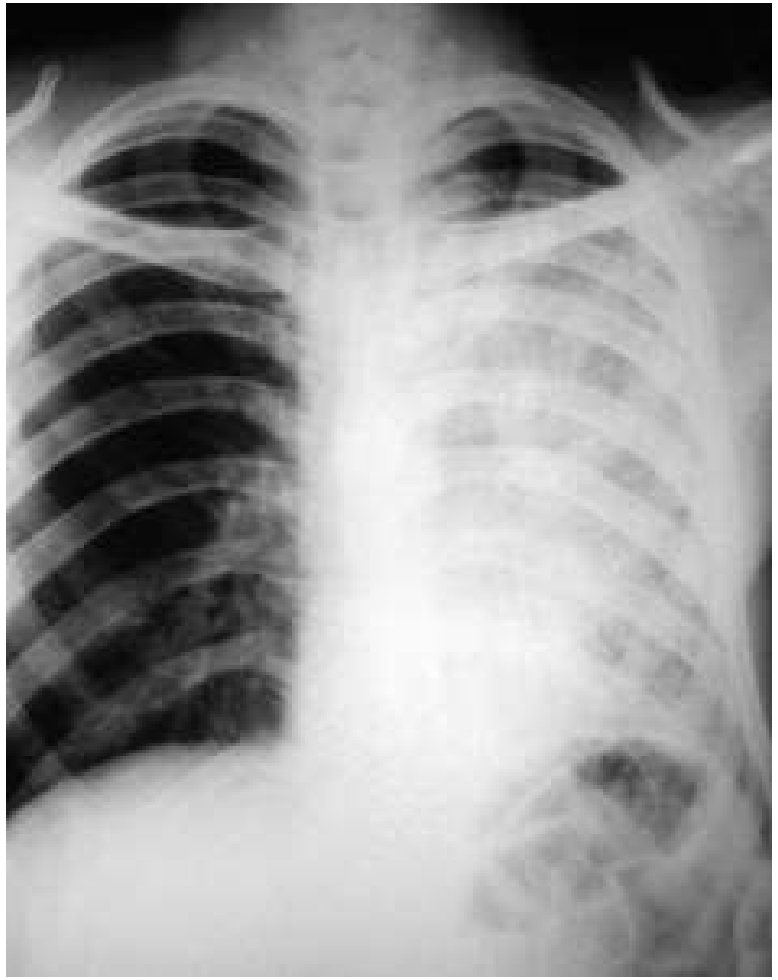
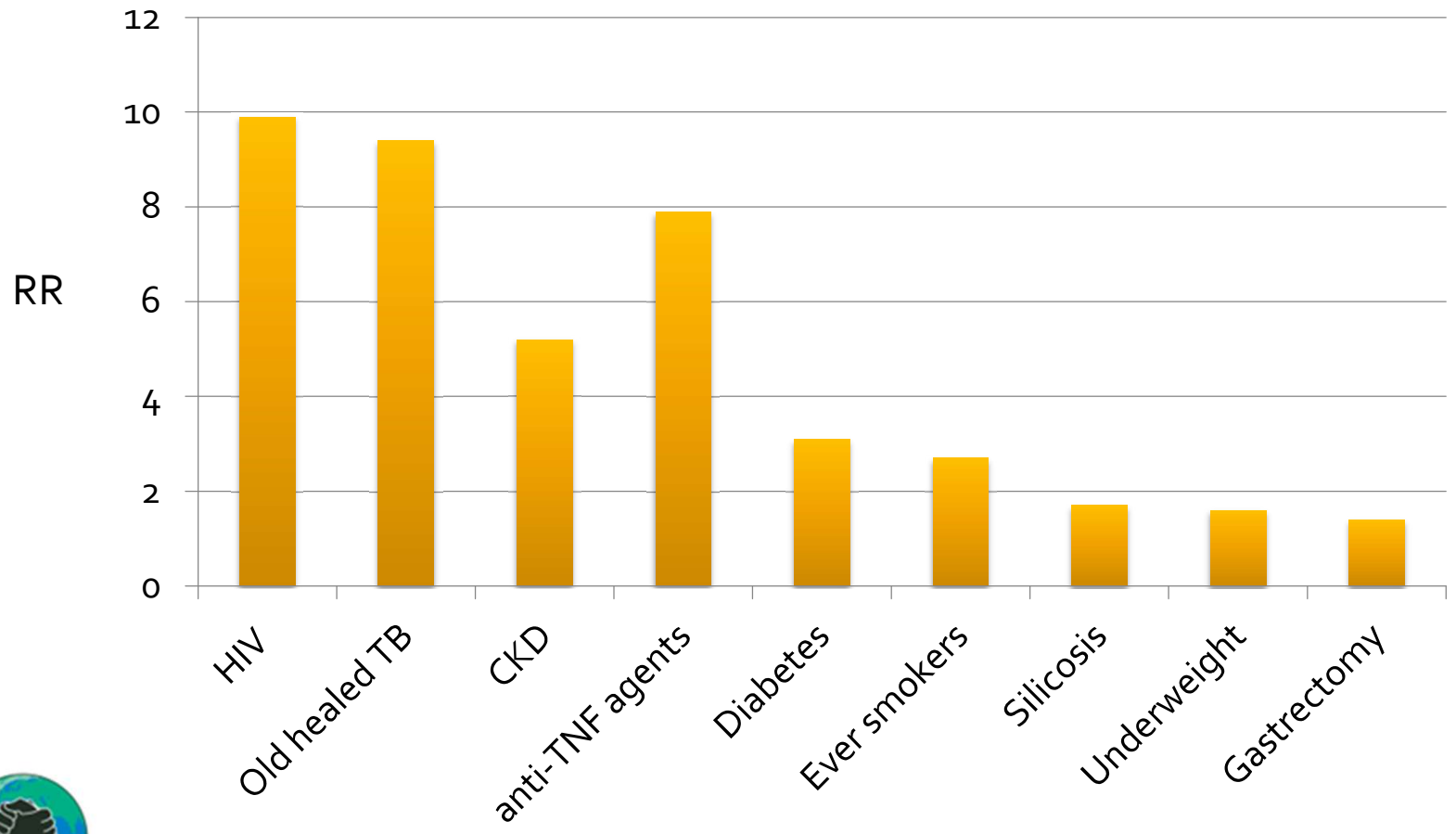
Active TB Disease

- Clinical Features:
  - Cough
  - Fever
  - Night sweats
  - Weight loss
  - Hemoptysis
- Diagnosed by symptoms, chest x-ray, sputum microscopy or culture
- Risk factors for active disease:
  - Proximity to contact case
  - HIV-infected
  - Immunosuppression
  - Diabetes
  - Smoking
  - Existing lung damage
  - Poor nutrition and/or low BMI
  - Host age, sex, genetics, bacterial factors



Wellcome Trust, 2012.

Relative risk of TB reactivation



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Horsburgh CR, Jr. NEJM 2004;350:2060-7

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What percentage of new TB infections (after exposure) lead to a primary active TB disease?

1. 5%
2. 20%
3. 30%
4. 50%

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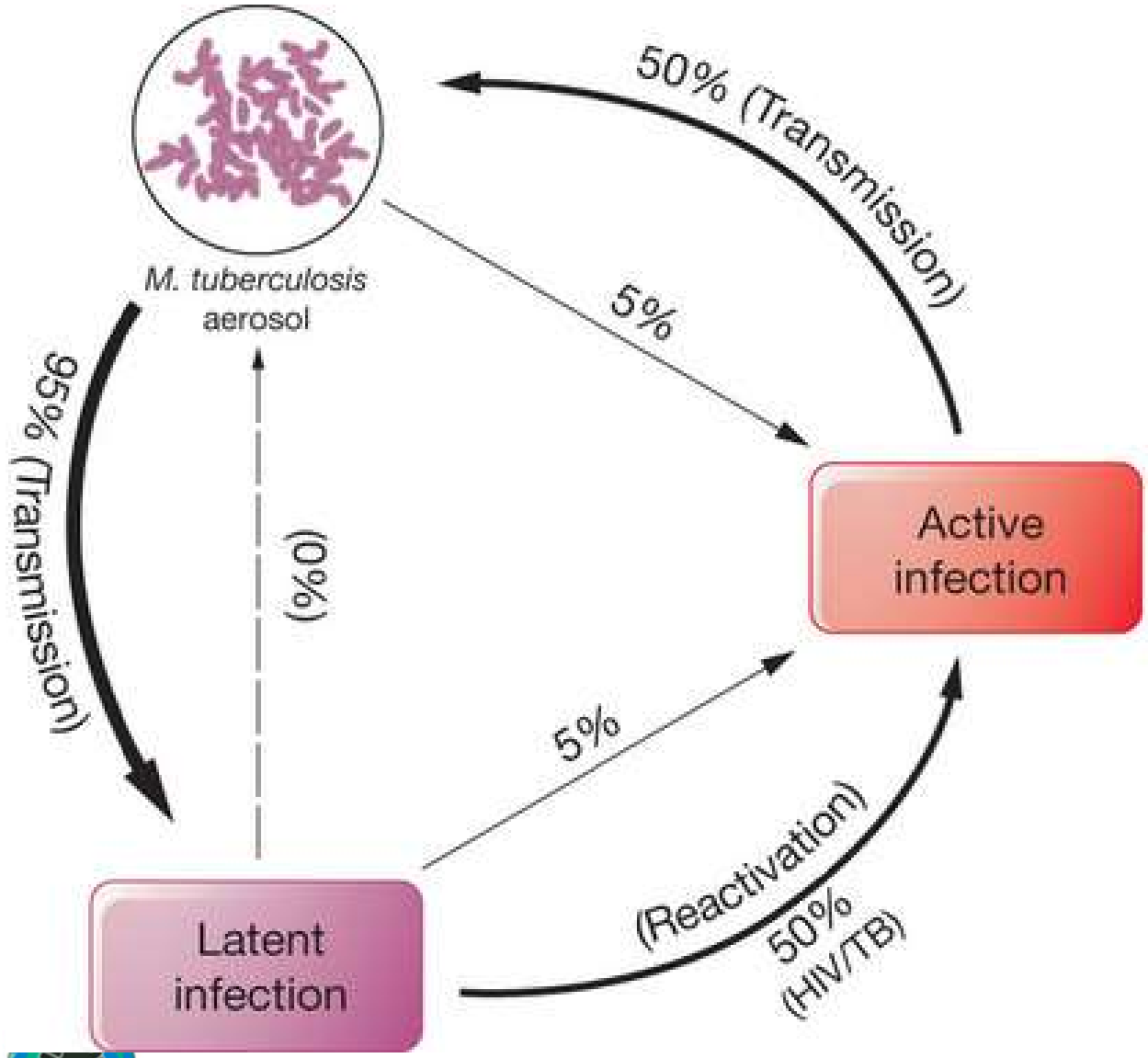

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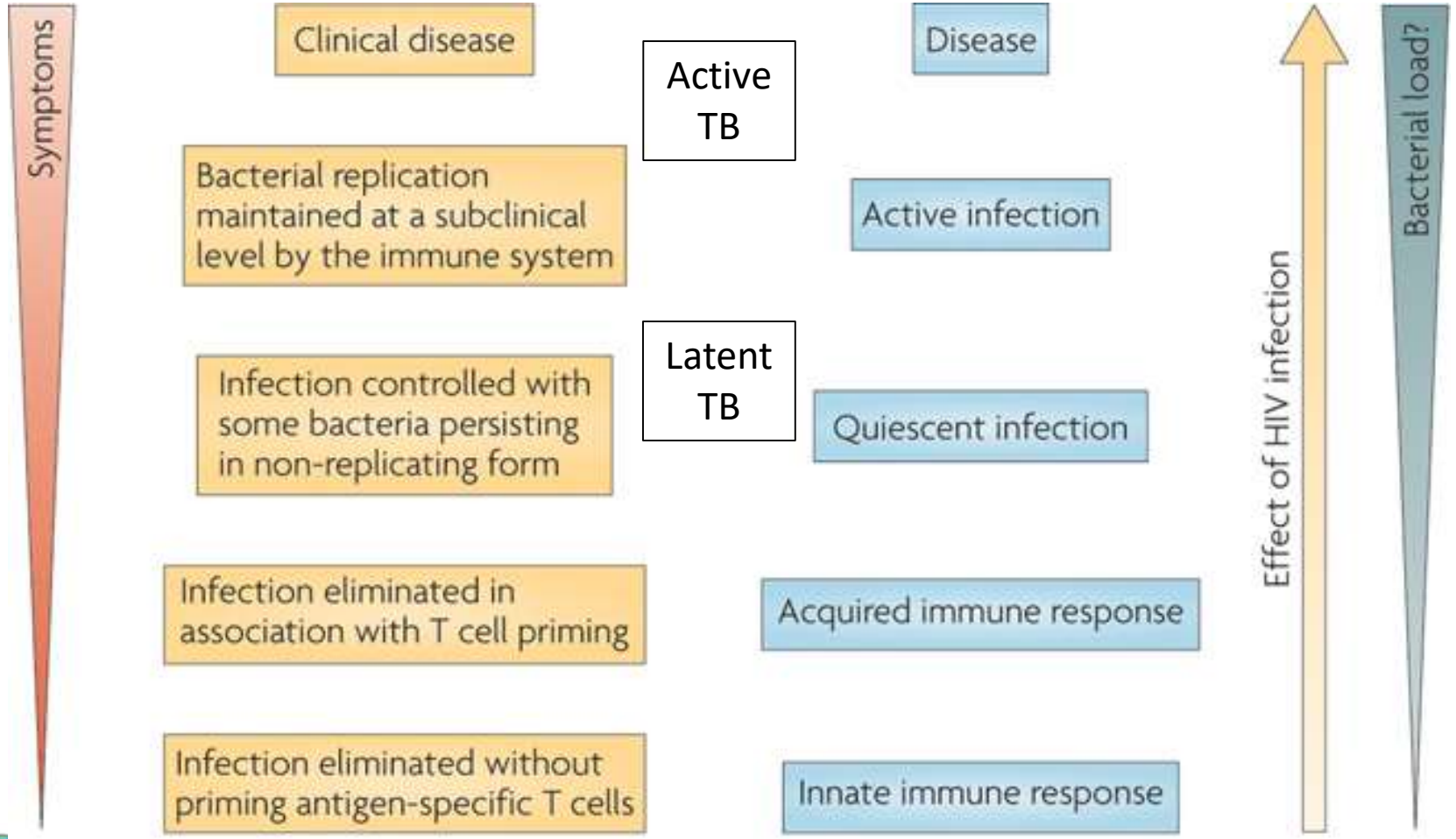
Koul et al. *Nature*, 2011.

The Spectrum of Tuberculosis



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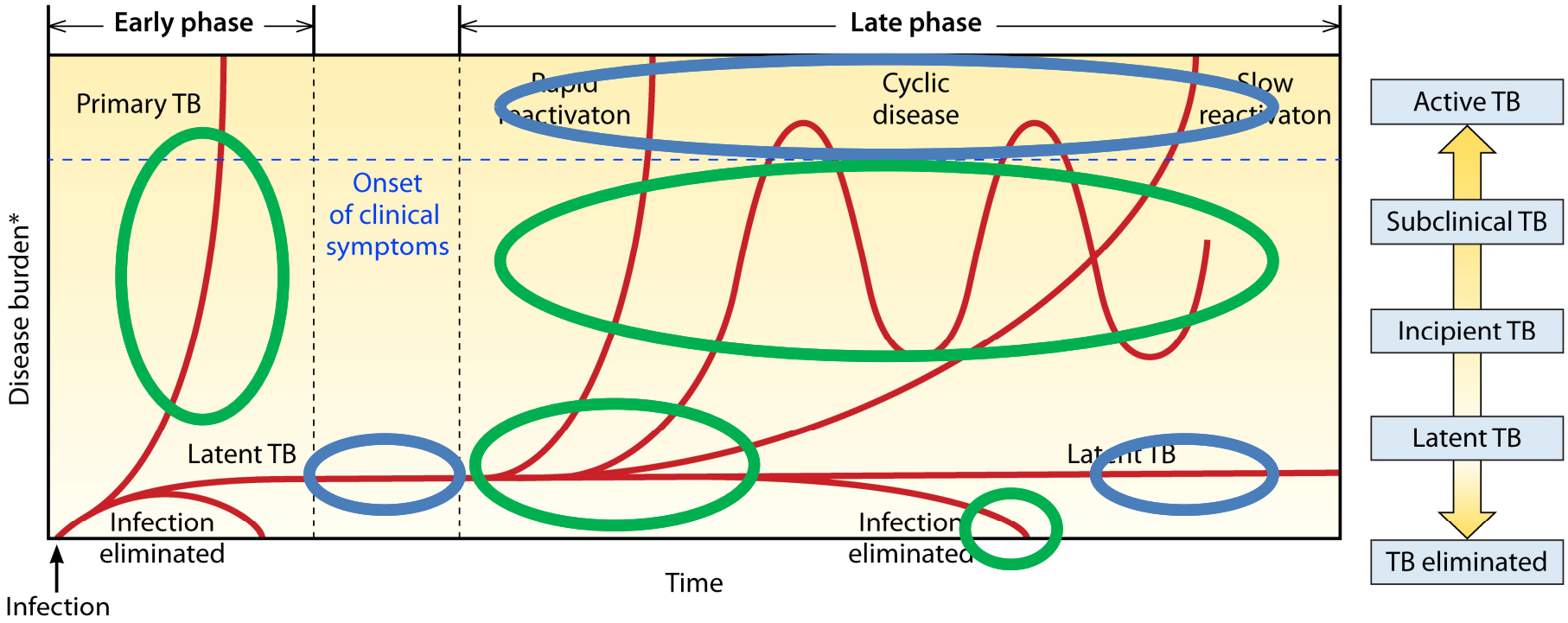
Barry CE et al. Nature Reviews Micro 2009

Pathophysiologic Perspective



*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

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Drain PK. Clinical Micro Reviews, 2018.

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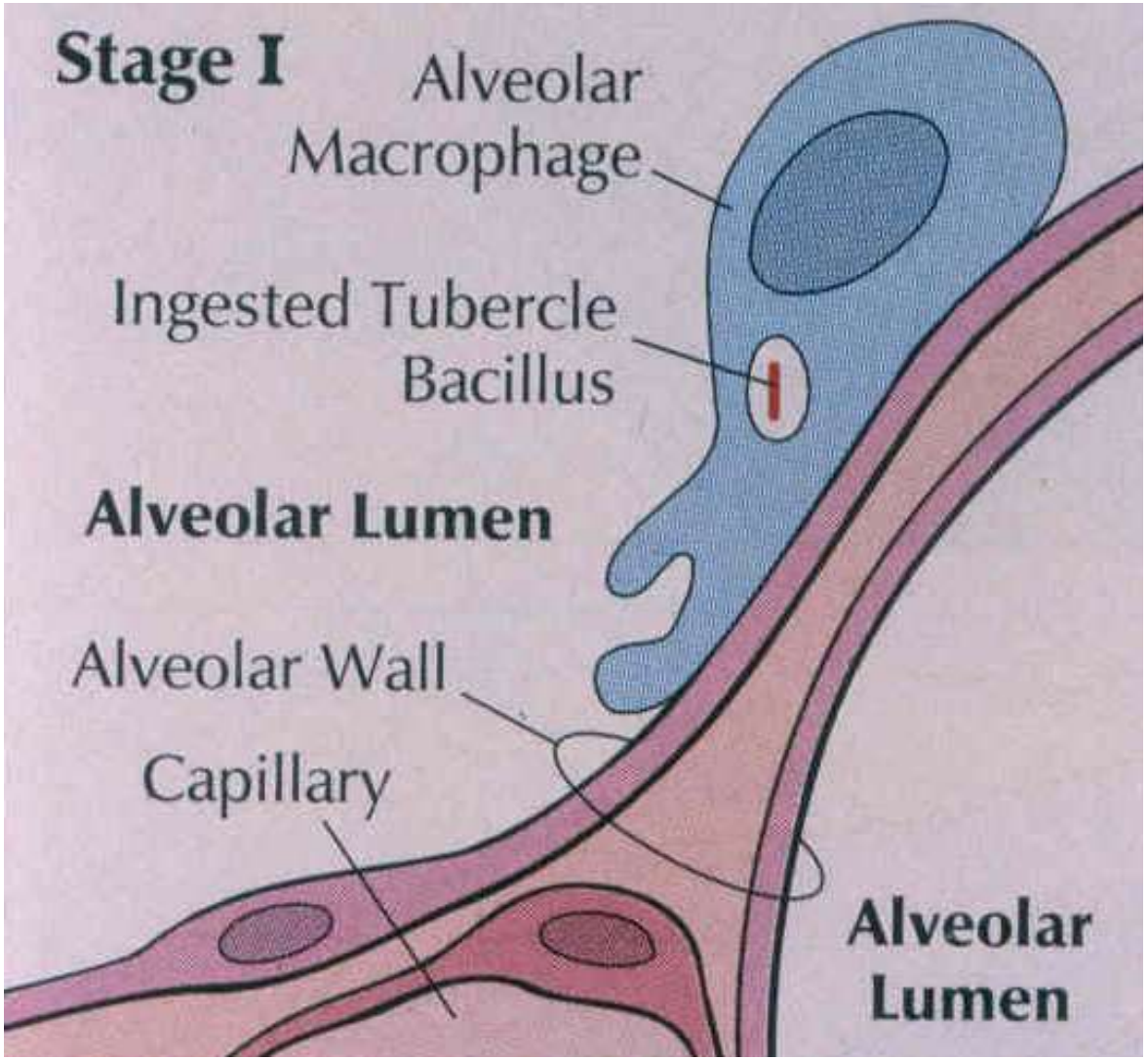
Stage 1 – TB Pathogenesis



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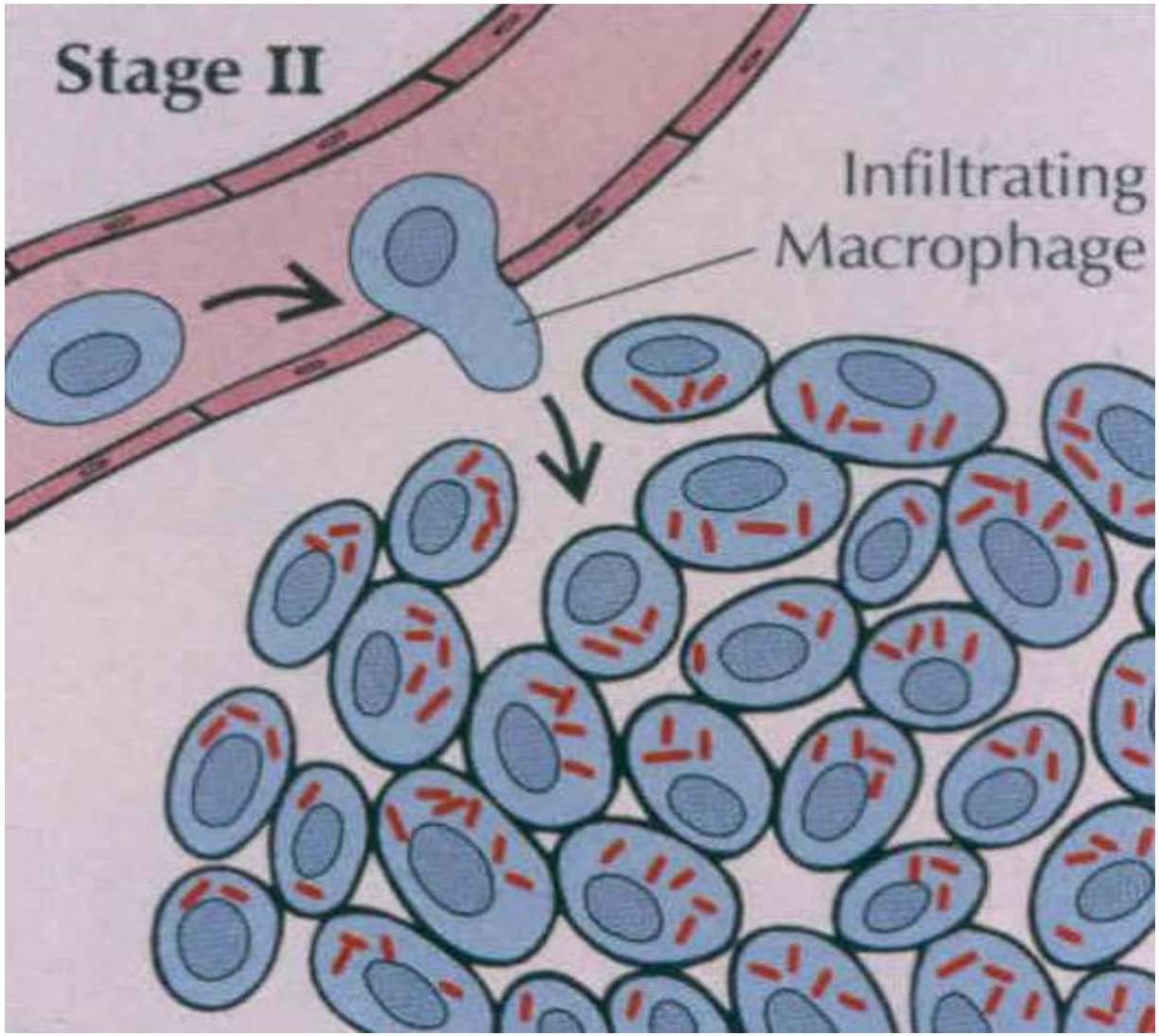
Stage 2 – TB Pathogenesis



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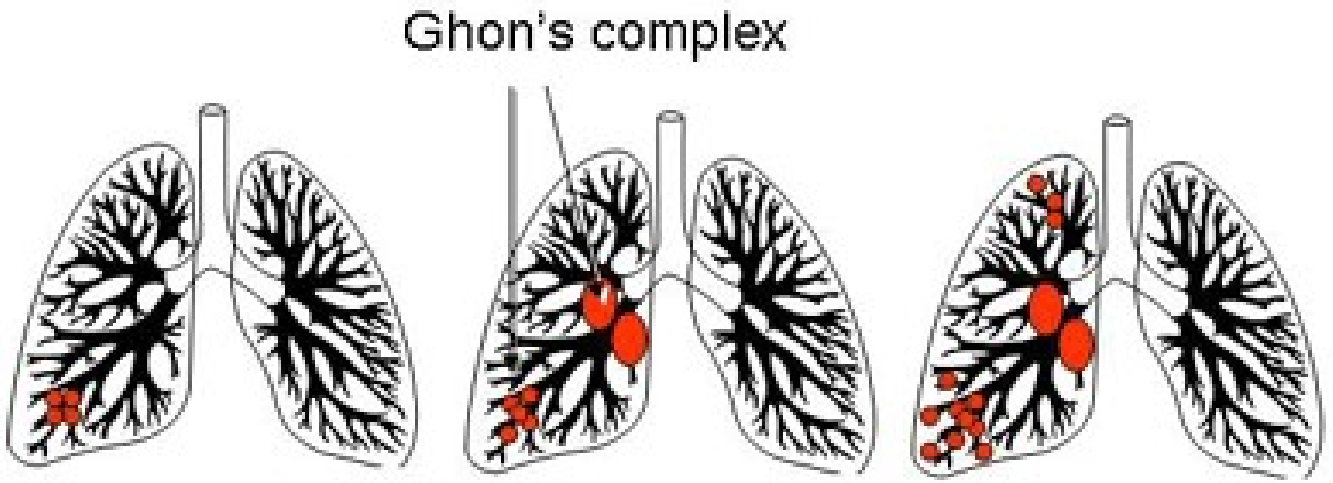
Stage 2 – TB Pathogenesis



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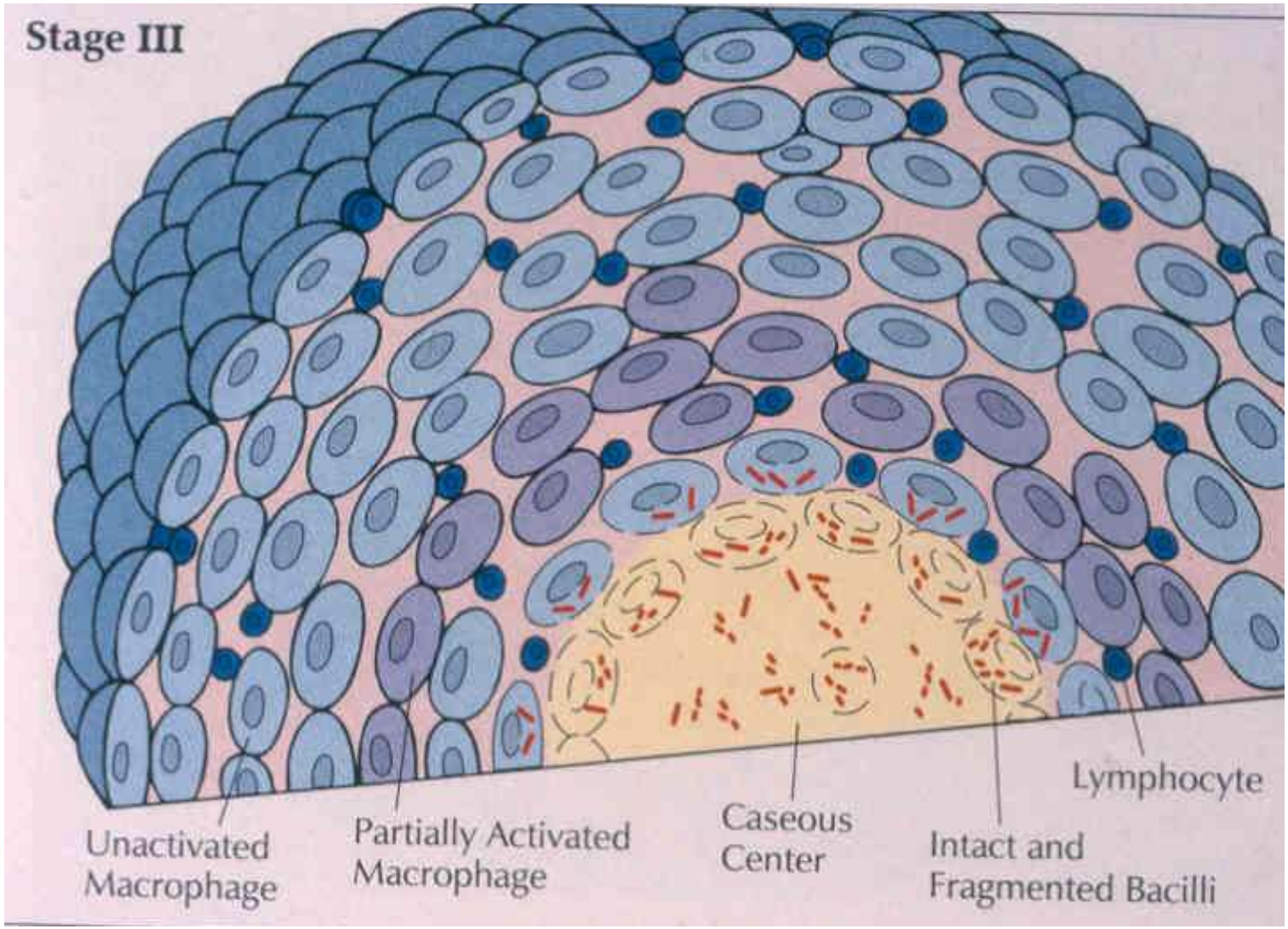
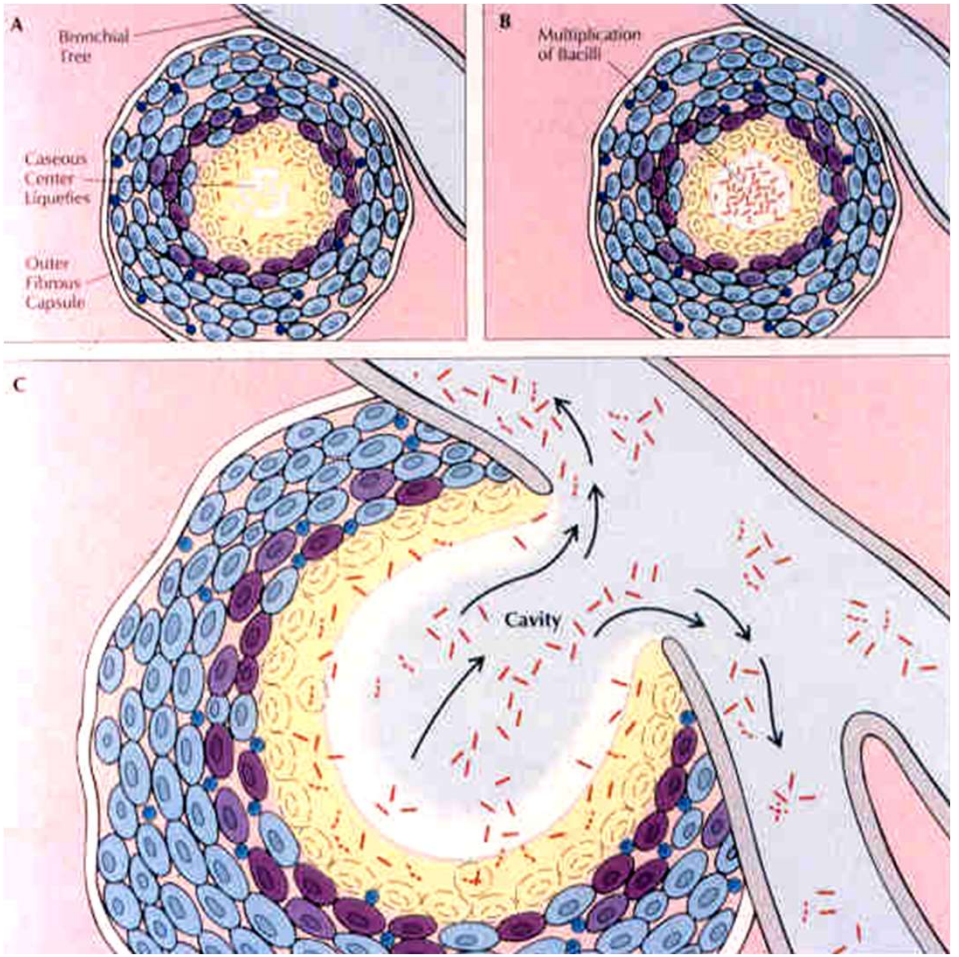
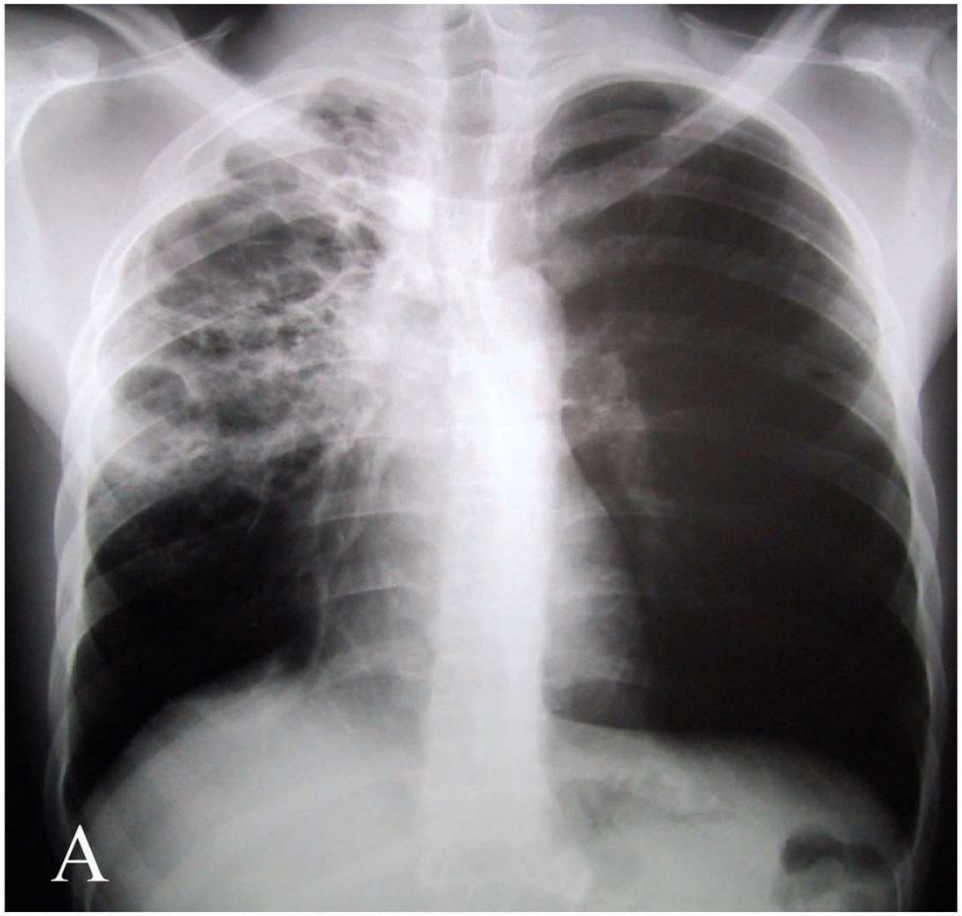
Stage 3 – TB Pathogenesis

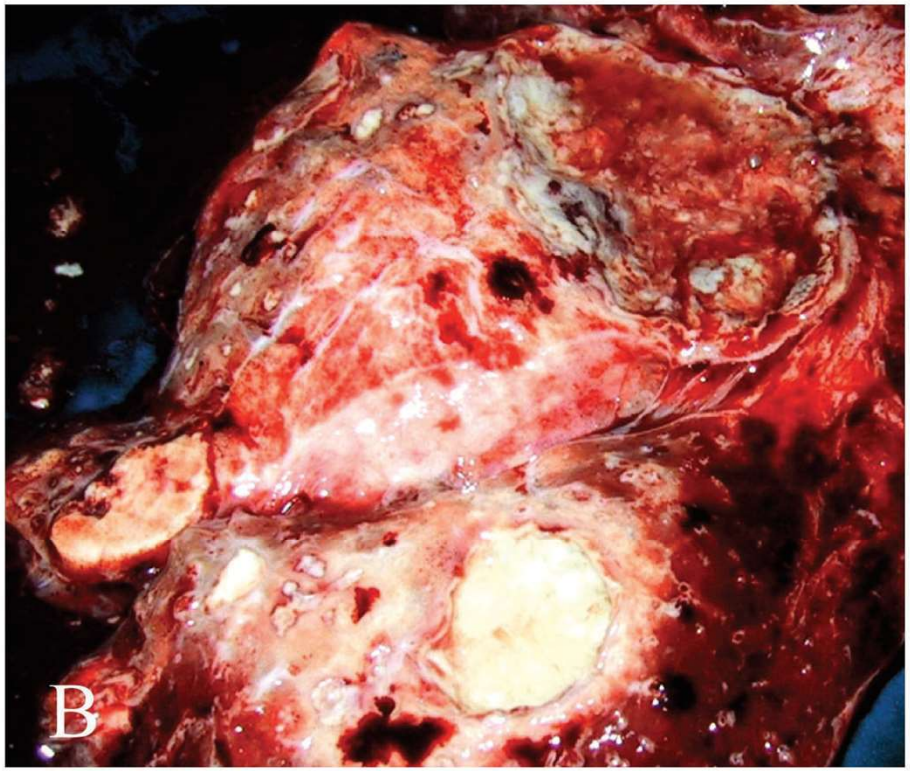


Stage 4 – TB Pathogenesis

- After *M. tb* has grown to high numbers, a 'high moi' death rate forms central caseation and liquefies
- This coincides with high TNF expression, inflammation, and tissue necrosis, and greater multiplication of TB
- *M. tb* subverts the host immune system (using the inflammatory response) to complete its life cycle, by passage into airways to induce cough







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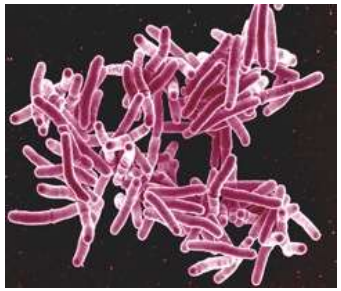

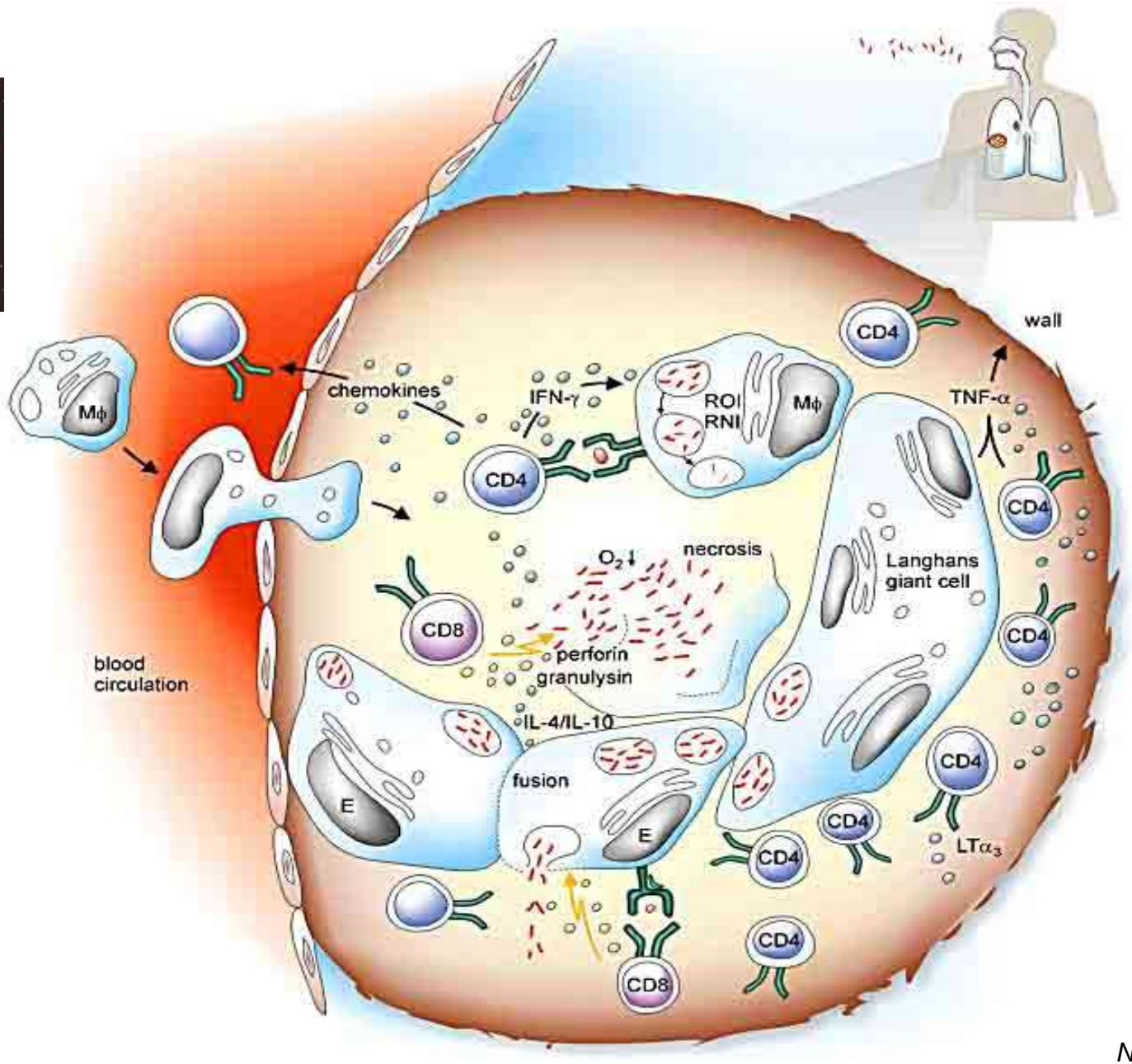

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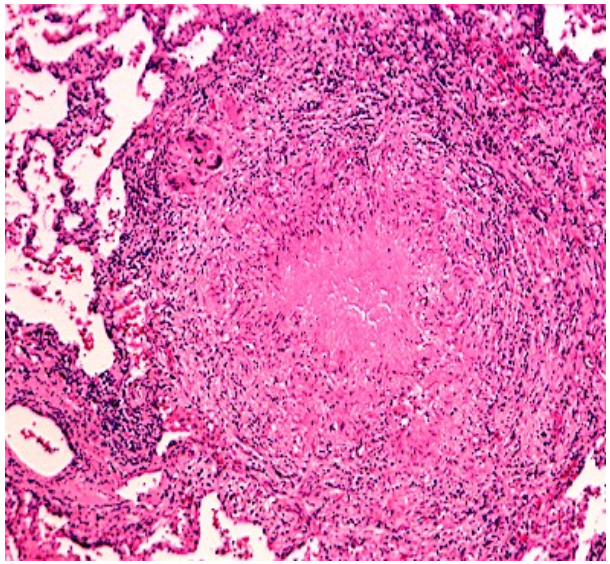
NIAID, 2012.
Ulrichs & Kaumann. *Front Biosci.* 2002.

Granuloma – TB Pathogenesis

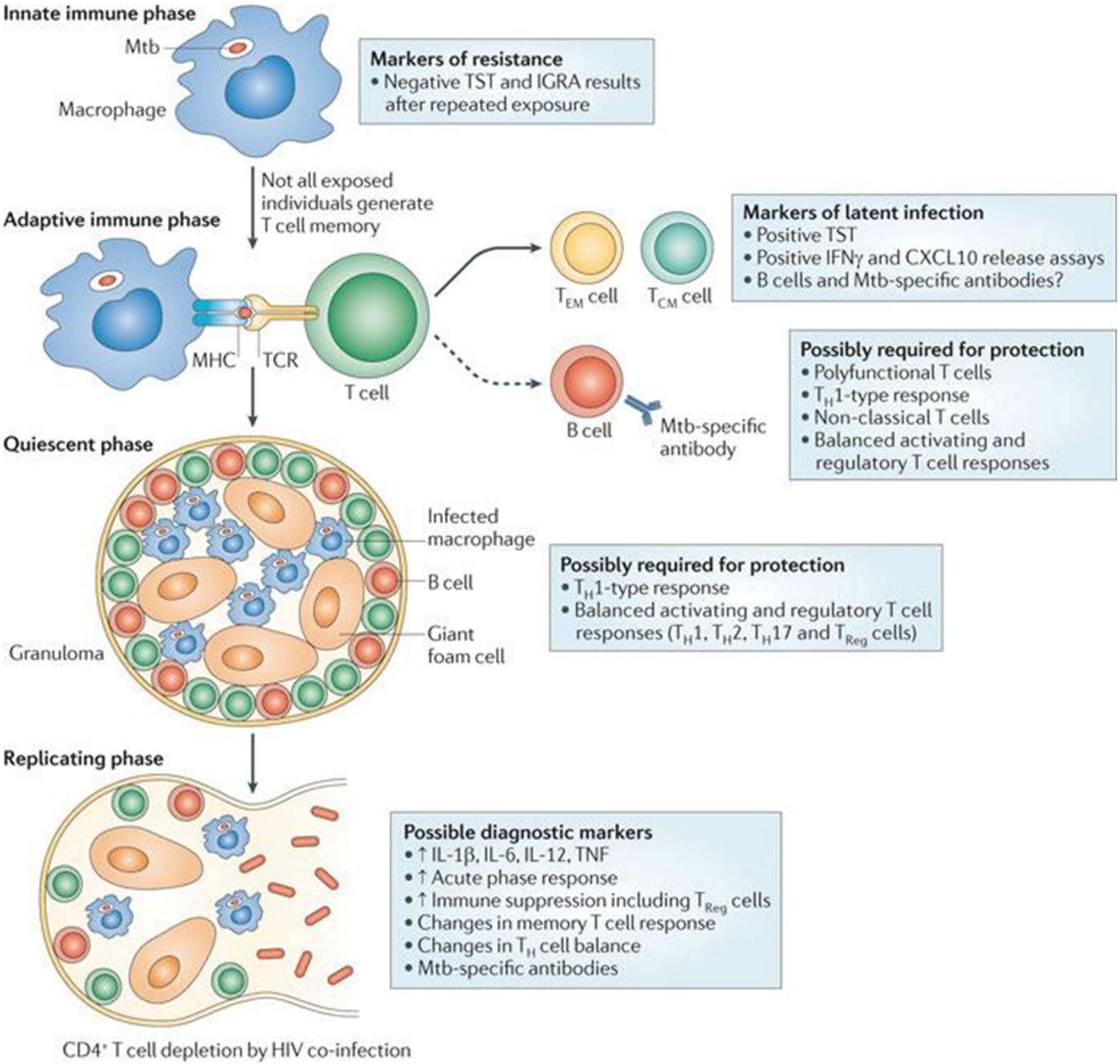
Bacterial vs. Host Stalemate

- *TB*
  - Uses granuloma formation to hide from host for survival/proliferation
  - Interferes with early TNF-mediated apoptosis
  - Prevents incorporation of ATP/proton pumps into the phagosome (no acidification of phagosome)
- Host
  - Alveolar macrophages induce phagocytosis of TB
  - Try to kill *TB* through CD4/CD8-mediated apoptosis



Increased Risk of TB Activation

- HIV-related impairment of CD4 lymphocyte functions (especially IFNγ)
- Anti-TNFα therapies prescribed for rheumatologic, inflammatory bowel disease, and other conditions
- Genetic susceptibilities:
  - Animal models – variation in susceptibility/ resistance to TB
  - Twin studies – TB risk is higher among mono vs. dizygotic twins
  - Allelic variations in the *NRAMP1* gene assoc. with TB susceptibility
  - Association of HLA-DR2 with vulnerability to TB
  - Familial clusters of disseminated TB infections – IFNγ receptor gene



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How is TB transmitted between humans?

1. Fecal-oral contamination
2. Skin-to-skin contact
3. Aerosolized droplet nuclei
4. Blood-borne exposure

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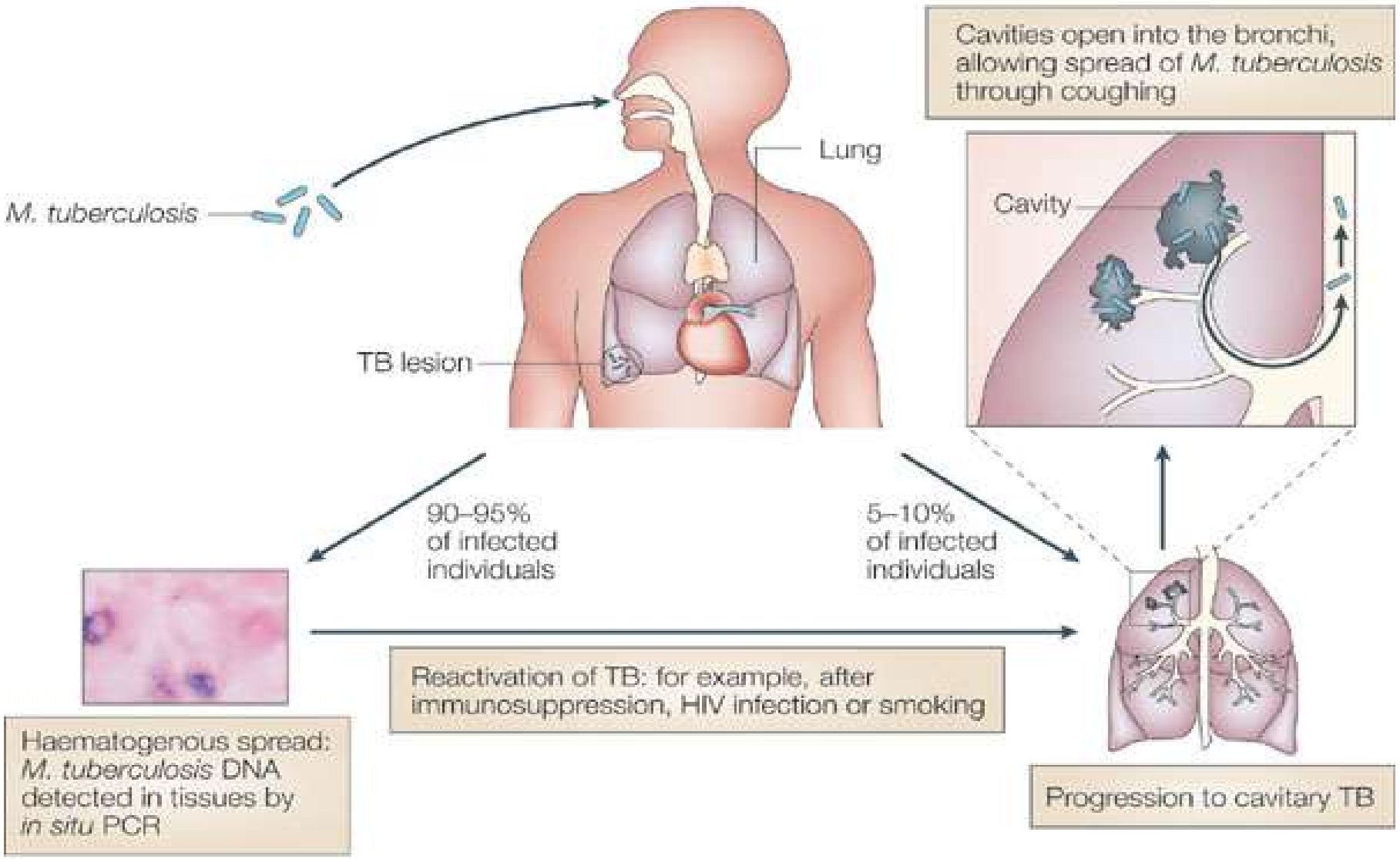

Nature Reviews | Immunology

TB Transmission

- Patient with active, symptomatic TB disease has millions of TB bacilli
- The most important factor is droplet size
  - Intermediate-size droplets desiccate to form "droplet nuclei" (1-5 μm) to reach alveoli
  - Droplet nuclei can remain airborne indefinitely
  - *M. tuberculosis* is stable in droplet nuclei
- Coughing and sneezing projects TB
  - Cough releases 3,000 droplet nuclei
  - Sneeze release >10,000 droplet nuclei
- Average TB patient generates 75,000 infectious droplets/day before therapy
  - Decrease to 25 infectious droplets/day within 2 weeks of starting effective therapy

“Droplet Nuclei” Theory

Small droplets likely contain no TB

Intermediate droplets fall slowly, but evaporate into inhalable “droplet nuclei”

Large droplets fall to the ground quickly, before evaporating

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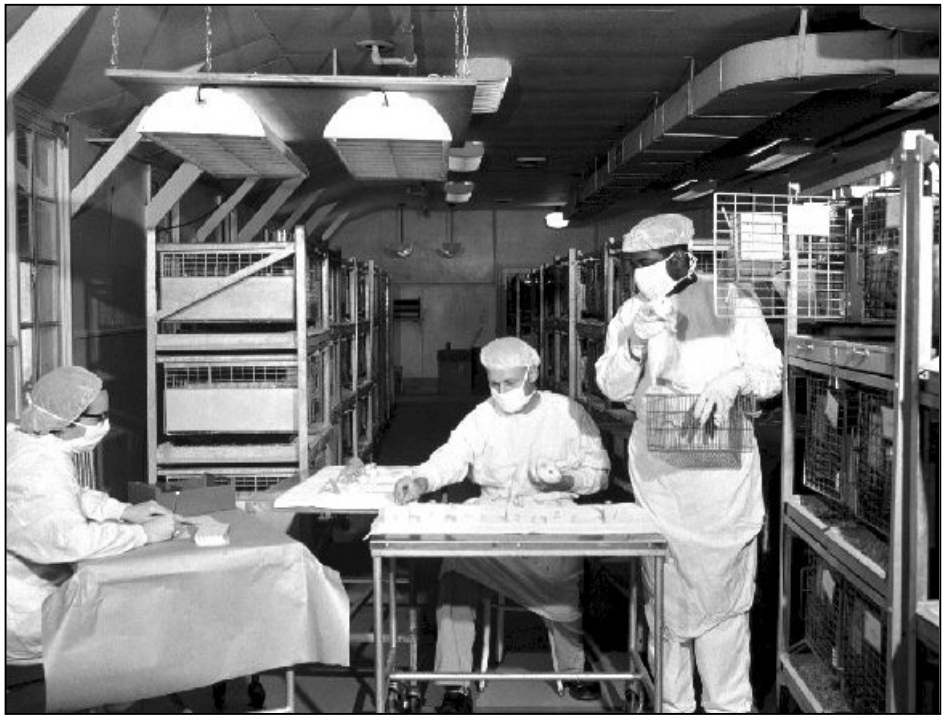
TB Transmission

- The Baltimore VA Pilot Ward
- Effluent air passed through guinea pig cages
- Guinea pigs monitored by TST, sacrificed (and replaced) if TST+
- Time to infect one guinea pig was ~10d
- Infected animals usually had only a single lung “tubercle”



“most droplets atomized into air evaporate almost instantly, leaving disease germs drifting like cigarette smoke in the droplet nuclei”

- Wells 1948

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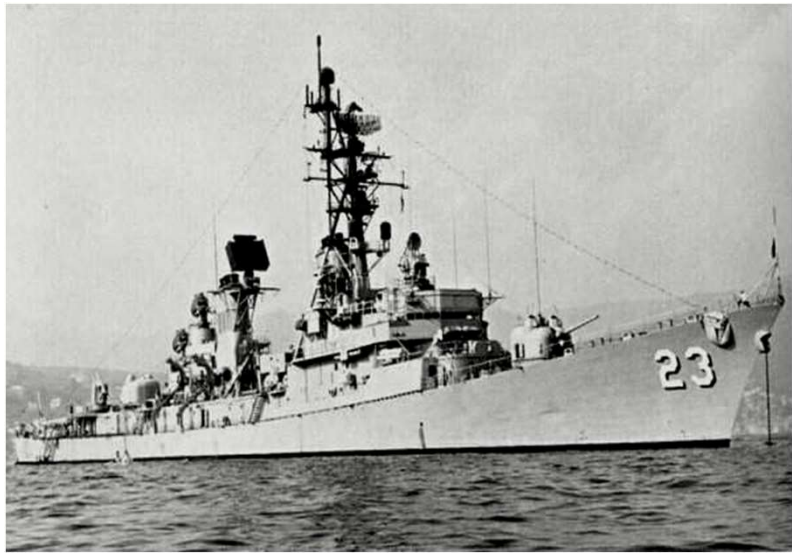
TB Transmission

- *U.S.S. Richard E. Byrd* - 437 ft. destroyer, commissioned at Puget Sound Naval Shipyard in 1964
- Index patient: coughing with cavitary AFB smear-positive pulmonary TB
- Extensive characterization of all sailors, incl. work/sleep locations, ventilation patterns, etc.
- Overall, 139 of 308 (45%) enlisted crew converted TST; and 7 had active disease at the initial screening
- TST conversion rate was 80% in shared compartment, 53% in adjacent compartment with partially shared ventilation, and far lower elsewhere on ship



Houk et al. 1968

TB Transmission - Droplets

Activity	Particles ≤ 100 mm
Breathing	?
Speaking	0 – 210
Speaking for 5 min	0 – 3,000
Coughing	0 – 3,500
Sneezing	4,500 – 1,000,000

Size	Time in Air
1-3 uM (“droplet nuclei”)	indefinite
10 uM	17 minutes
20 uM	4 minutes
100 uM	10 seconds

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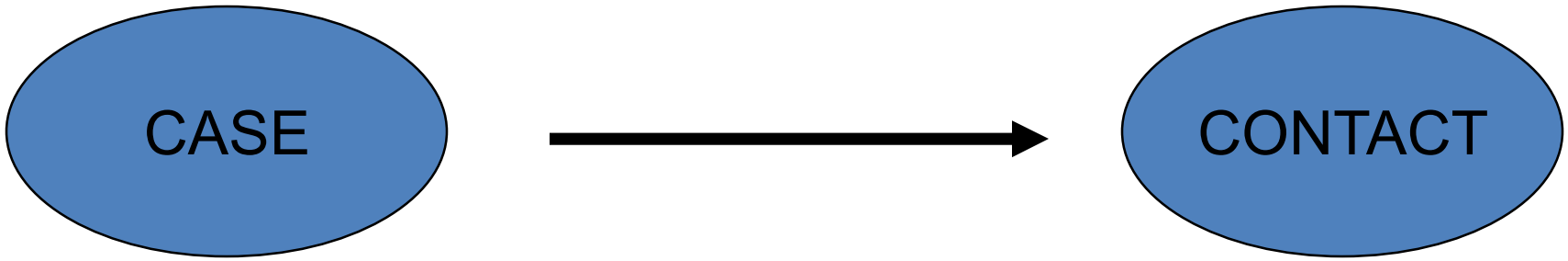
Duguid 1946; Knight, NY Academy Sci, 1980

TB Transmission – Risk Factors



- Site of TB
- Cough
- Bacillary load
  - smear+
  - cavity
- Treatment

- Filtration
- Ventilation
- U.V. light
- Procedures
  - sputum induction
  - bronchoscopy
  - wound irrigation
  - autopsy

- Exposure/duration of contact
- Prior TB infection
- HIV
- Immunosuppressed
- Diabetes
- Smoking

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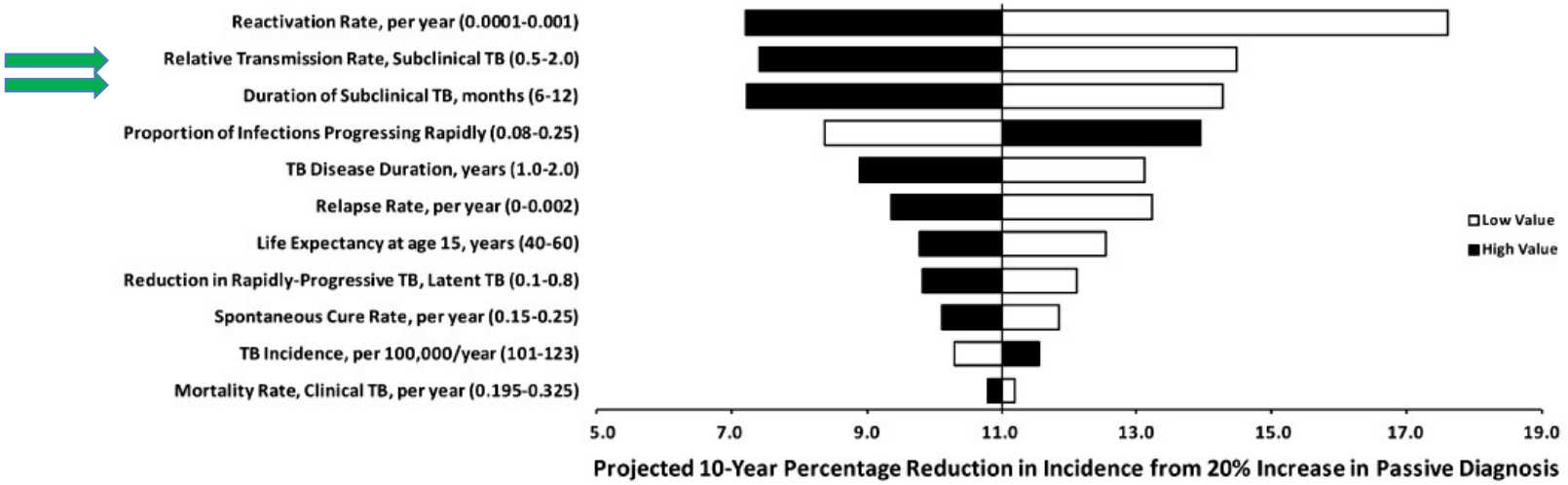
US Groups at Highest Risk for TB

- Close contact of TB case
- Foreign-born persons from high prevalence area
- Residents of long-term care facilities
- Homeless
- Injection drug users
- Elderly persons
- Persons with occupational TB exposures

Transmission of Subclinical TB

- Dowdy et al assumed 25% transmission for Subclinical TB, as compared to active TB transmission



Dowdy DW, et al. AJRCCM. 2012

No clinical studies have measured viable Mtb bacilli in cough aerosols for Subclinical TB, or determined the role of Subclinical TB to Mtb transmission

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TB Transmission - Summary

- TB is spread person-to person via aerosolized “droplet nuclei”
  - Spread by persons with active TB symptoms (cough)
  - Especially cavitary, smear positive cases
  - Droplet nuclei are inhaled by the target host
- Transmission is aided by crowding, absence of UV light, and poor ventilation
- Risk depends on concentration of droplet nuclei
  - Source case factors: Rate of cough production, TB diseases
  - Environmental factors: Filtration, Ventilation, UV light
  - Contact person factors: Duration of exposure, Host resistance

TB Transmission - Airline Travel

- Limited evidence for airline transmission
- Most airlines use air filters at 3μM, which are small enough to remove droplet nuclei
- Most airplanes have 15 air-exchanges/hour
- Est. prevalence of active TB cases:
  - 0.05/100,000 (range 0 - 0.36/100,000), assuming flights to/from Africa or India

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Byrne, Travel Med Infect Dis, 2007; Abubakar, Lancet ID, 2010

Which respiratory secretions are most responsible for TB transmission?

1. Secretions on hands from sneezing (fomites)
2. Large, mucous droplets with many organisms
3. Small droplet nuclei with few organisms
4. Normal air from speaking

A Word about *M. bovis*

- Primarily transmitted to humans in unpasteurized dairy products
- Cause of TB in cattle
- A significant cause of human TB in California
- More likely to cause extrapulmonary and multisite disease
- Resistant to PZA

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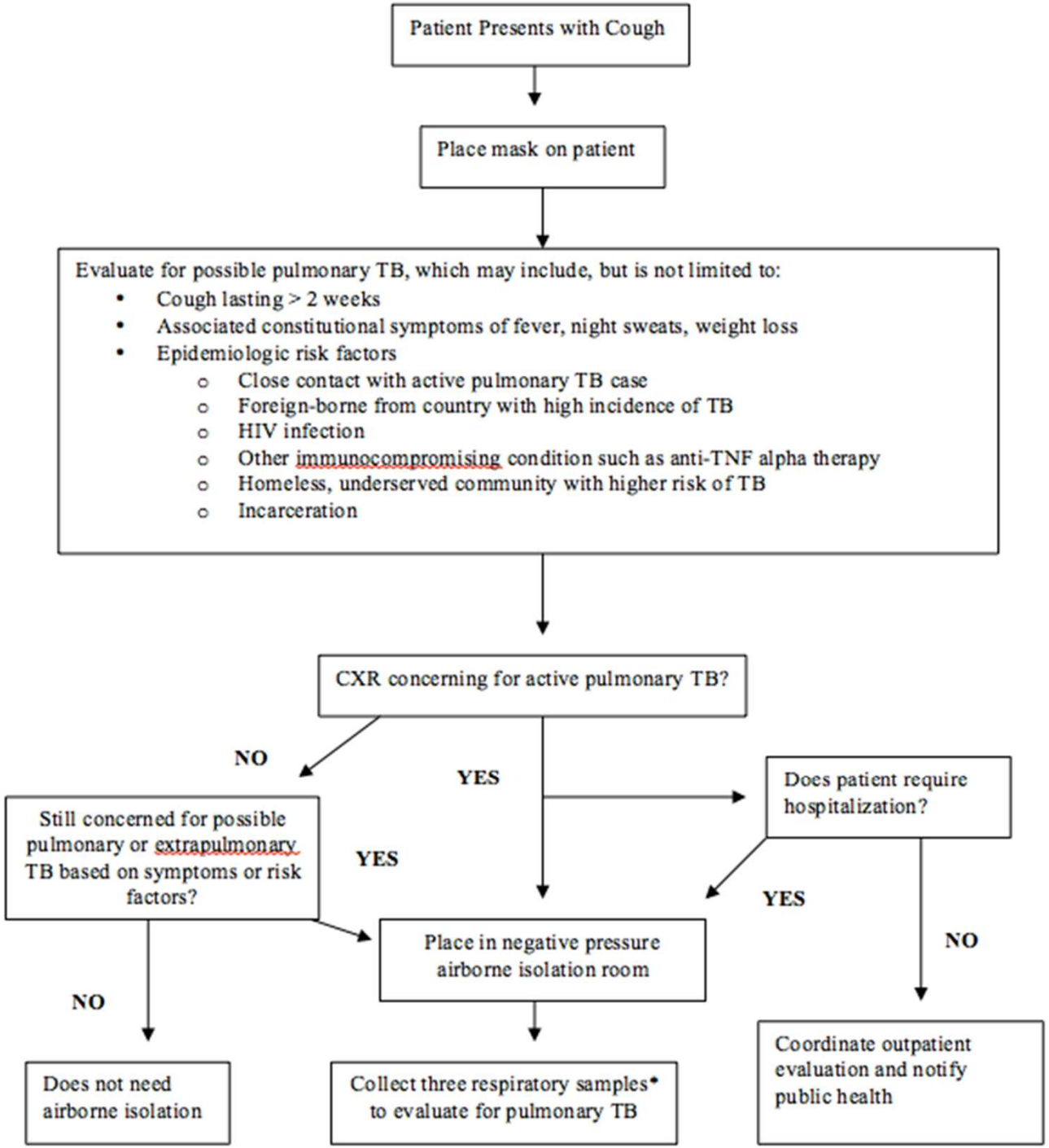
- TB Transmission
- **Clinical Summary**



HMC algorithm for TB isolation

Clinical steps for TB suspect

- Place patient in negative pressure isolation
- Collect 3 sputum samples for AFB microscopy and culture to rule out infectious active TB
  - Spontaneous sputum expectoration (morning preferred, can do Q8H)
  - If non-productive - sputum induction with hypertonic saline
  - If still unable to get sputum - bronchoscopy with BAL
- Consider consult to Infectious Disease team
- If positive, notify TB Dept. at King County

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Advanced TB Research Training Course

September 18-22, 2023

7:30 AM - 11:00 AM PACIFIC TIME

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Thank You!

Remember, World TB Day is March 24!

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