



# TB transmission and pathogenesis

In the context of TB infection control



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# Objectives for this session

- Explain basic immunological concepts on TB transmission and pathogenesis
- Explain how TB is transmitted
- Explain the difference between TB infection and TB disease
- Describe how TB infection can progress to TB disease
- Discuss the risk factors that can influence the natural history of TB



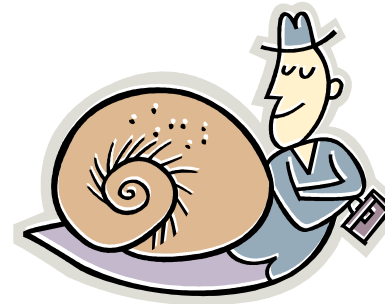
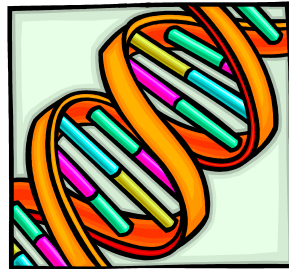
# The TB bacillus

- Mycobacterium tuberculosis
- Thick, waxy walls (needs special stains and drugs)
- Various populations in a lesion:



**Active,  
growing**

**intermediately  
active  
(intracellular)**



**slow-growing  
semi-dormant**



**dormant**

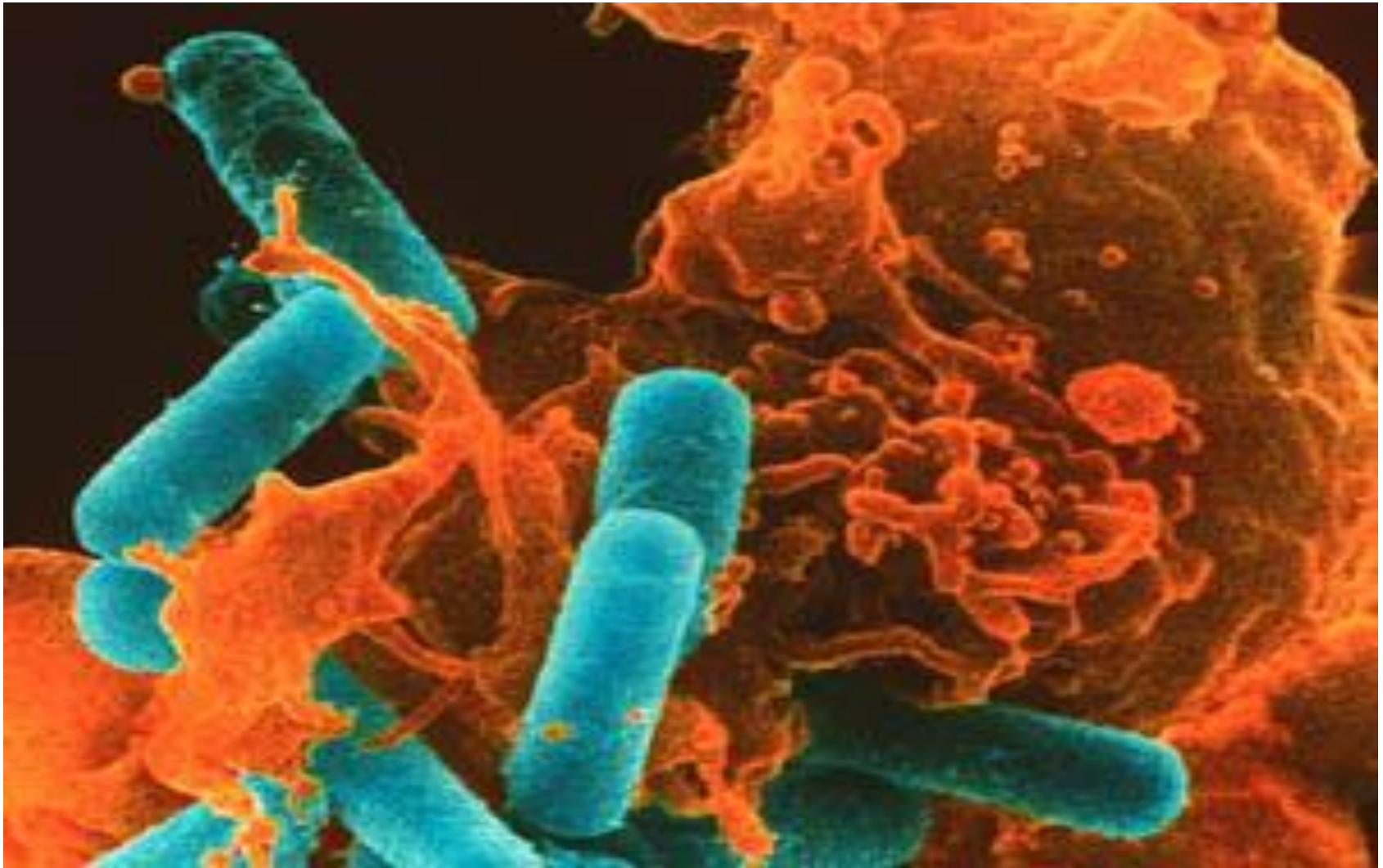
- Susceptible to direct sunlight



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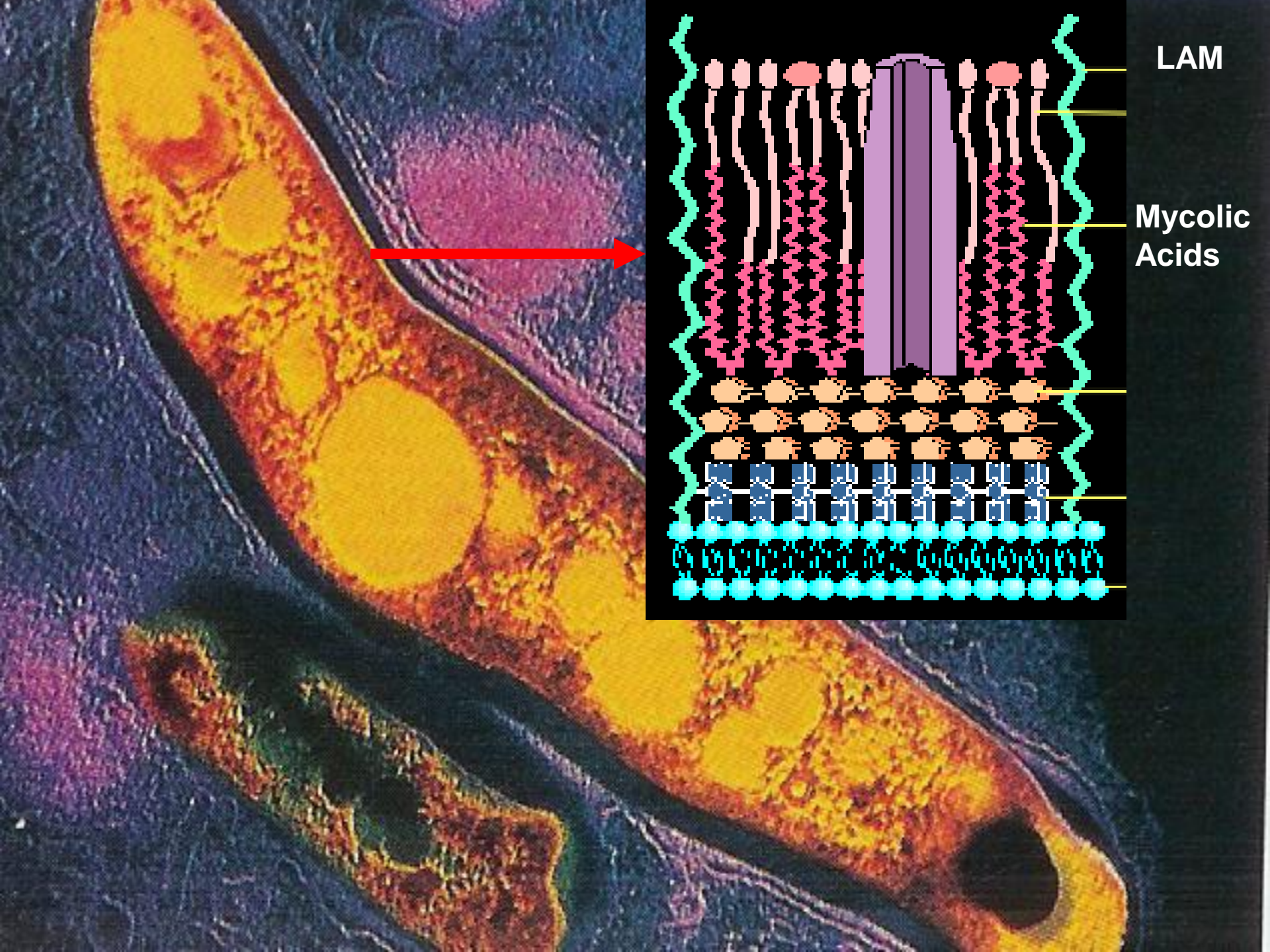
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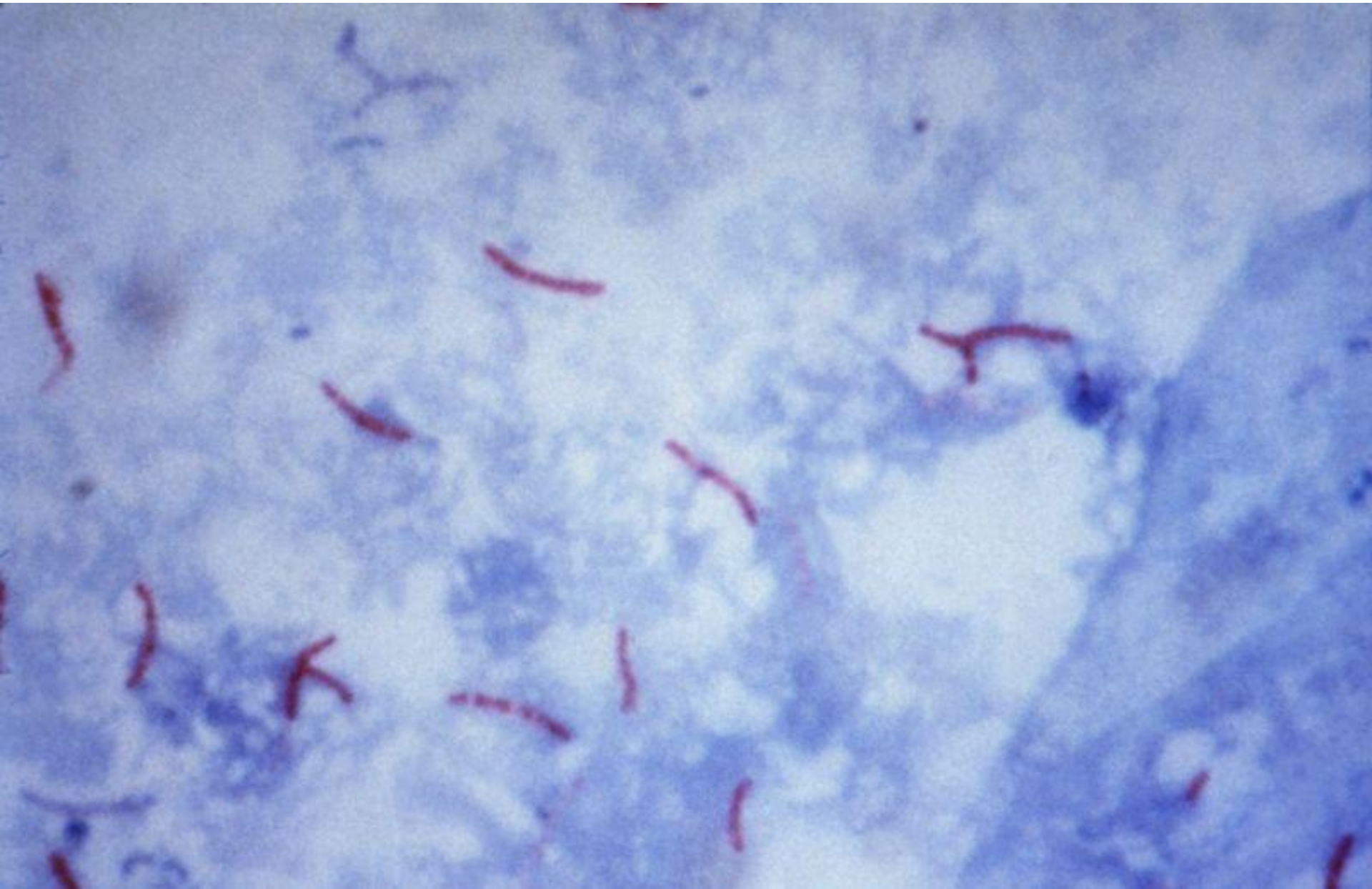


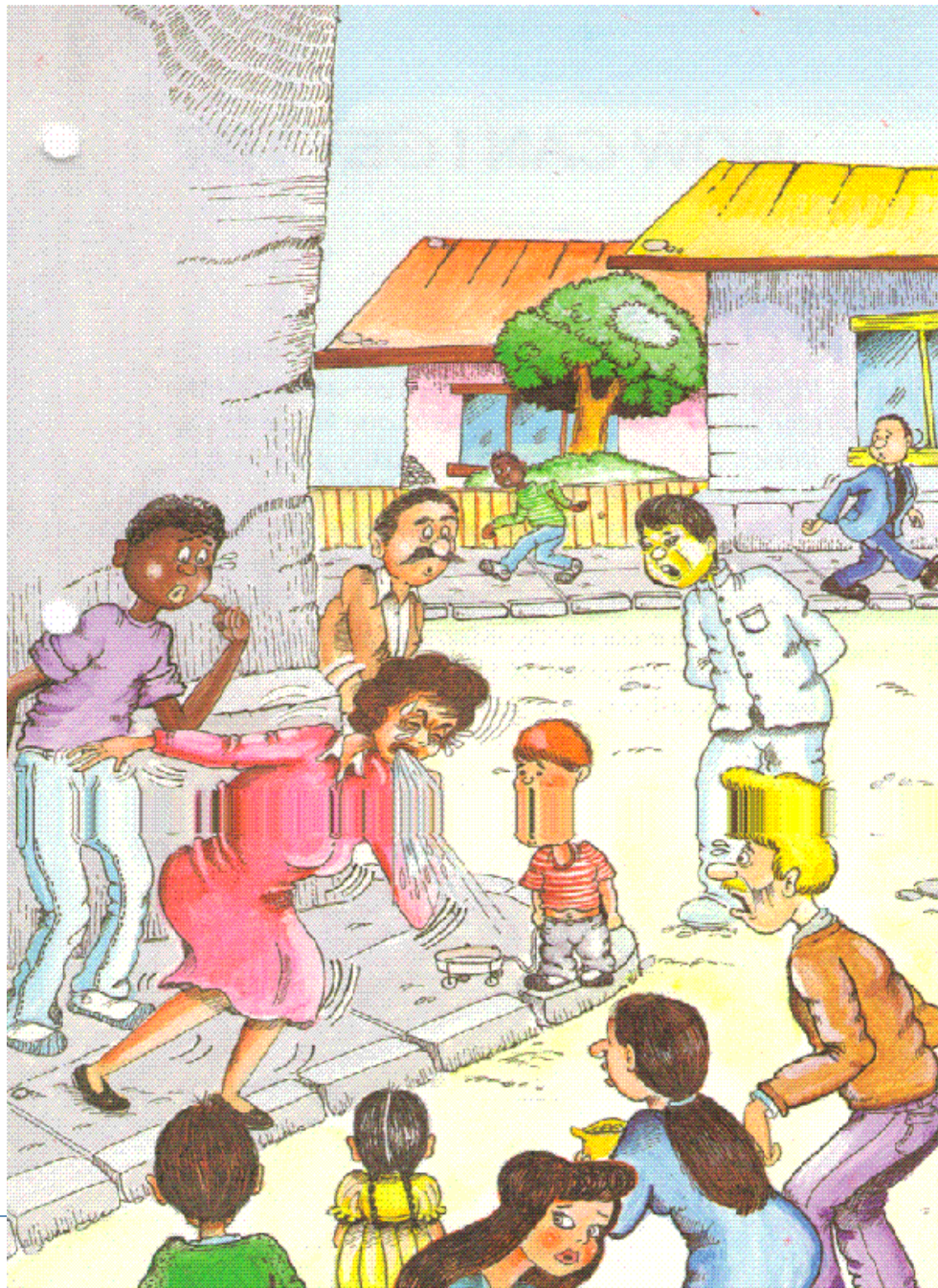
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# TB – immunology

- TB does not produces any toxins
- TB itself is not toxic to the host
  
- **The damaging effects of TB are mediated by the host's own defensive responses to bacilli!!!**



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# TB – immunology

## **Phase 1 Transmission**

Aerosol transmission by droplet nuclei, deposition in alveoli.  
Bacilli are phagocytosed by alveolar macrophages.

## **Phase II Initiation of infection, proliferation and dissemination**

Bacilli kill alveolar macrophages causing chemokines to attract T lymphocytes, NK cells.  
Bacilli continue to proliferate, killing host cells and spreading locally and systemically.

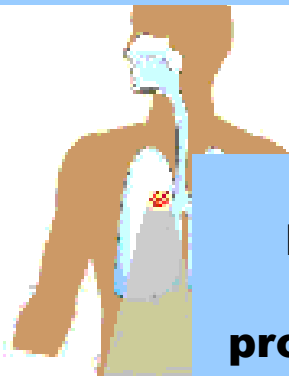
## **Phase III Evolution of host immune response**

Antigen presentation to macrophages causes T cell release of cytokines; protective cellular and tissue damaging immune responses.  
Primary lung lesion, remote extra-pulmonary foci involute  
**OR** Host fails to mount effective response with progressive primary disease at initial lung infection and/or extra-pulmonary disease

## **Phase IV Liquefaction and accelerated bacillary proliferation**

Pulmonary focus reactivates - liquefaction with cavity formation. Extracellular bacilli multiply exponentially  
Patient coughs bacilli in secretions, cycle is repeated.

# Phase 1 Transmission



## Phase II Initiation of infection, proliferation and dissemination

Spontaneous Healing (?)

Acute Disease (Immunocompromised)

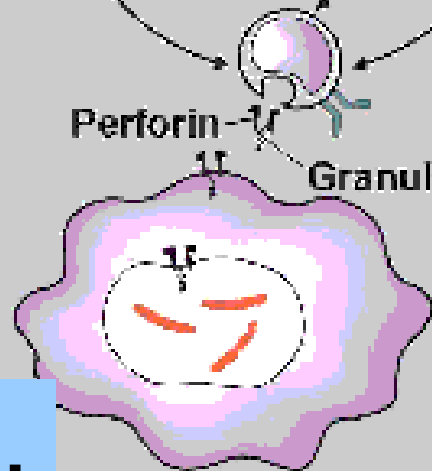
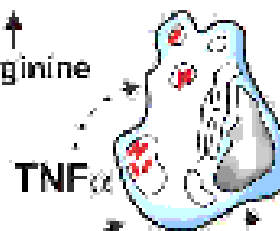
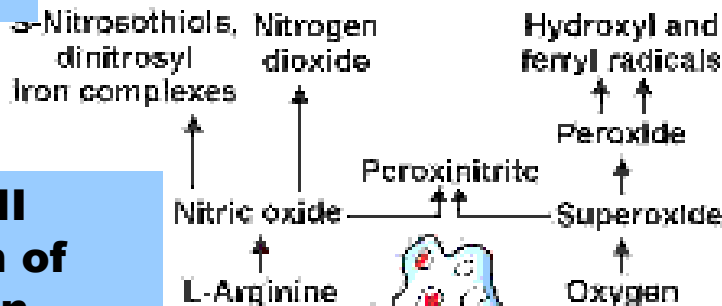
Containment (>90%)

Reactivation (<10%)

Dissemination  
Transmission

## Phase IV Liquefaction and accelerated bacillary proliferation

Phagolysosome fusion | Acidification | Iron restriction | ROI



## Phase III Evolution of host immune response

# Transmission of Tuberculosis - Principles

- Spread predominantly by droplet nuclei
- Infectivity related to the number of organisms in sputum
- Factors which enhance sputum aerosolization increase infectivity (**sputum induction!**)
- Risk of infection increased
  - in an enclosed environment
  - with increased time spent with source case
  - with increased proximity to source case
- Most effective way to decrease infectivity is to initiate chemotherapy



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# Infectious Particles for TB: Droplet Nuclei

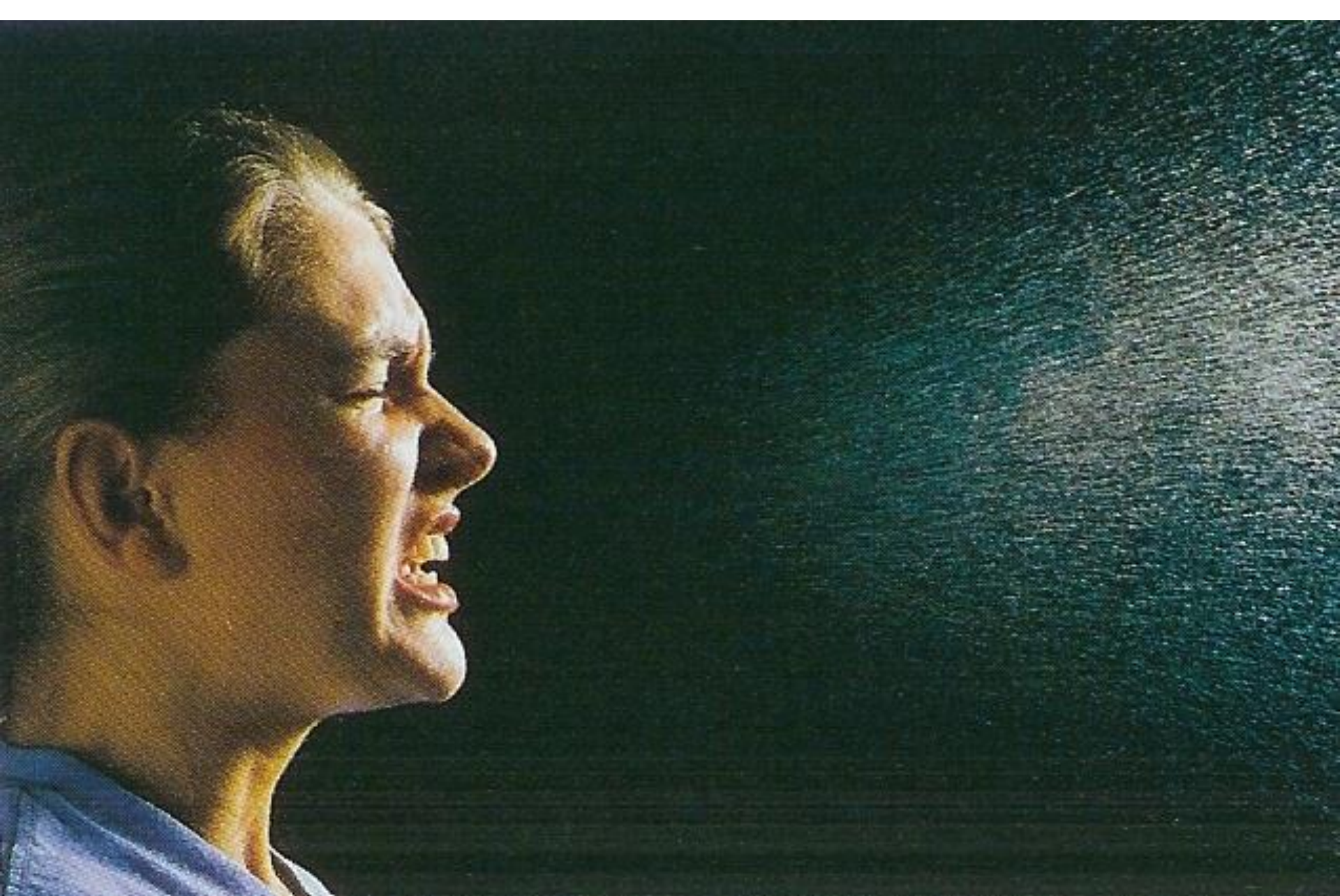
- Microscopic droplets generated by coughing, sneezing, speech, singing
- Larger droplets settle quickly
- Smaller particles evaporate to droplet nuclei (1-3 microns)
  - Depending on the relative humidity of the air in the space
- Droplet nuclei remain suspended in the air
  - 1.0  $\mu\text{m}$  **Droplet Nucleus** will settle at a rate of 0.0035 cm/s or 3 m in 24 hours!
- Small size permits droplets to lung alveoli
- Disperse with the flow of air



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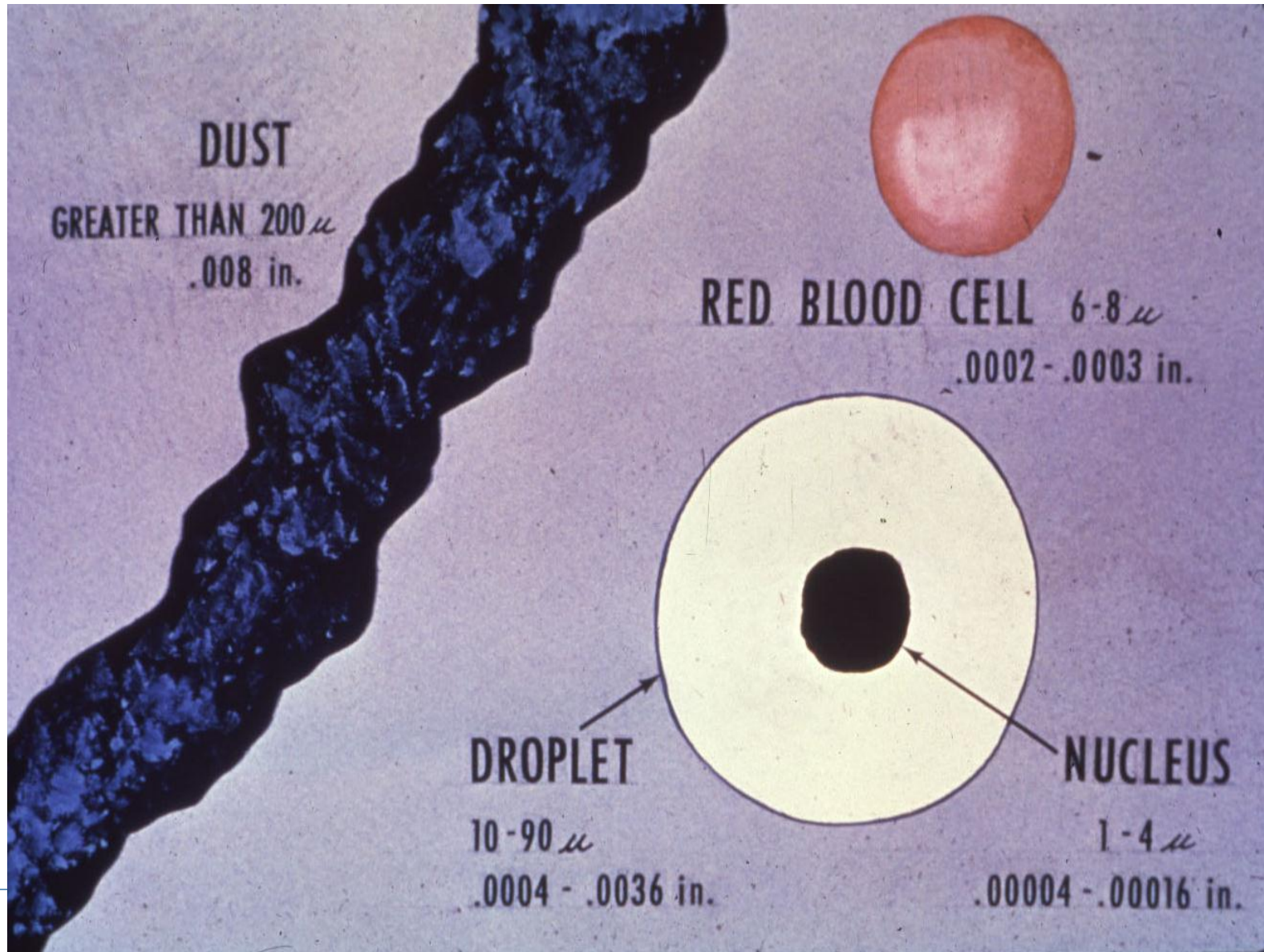
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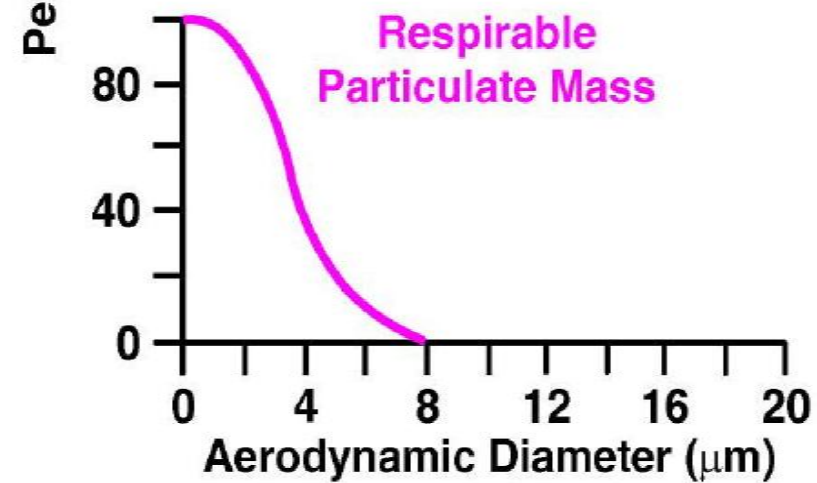
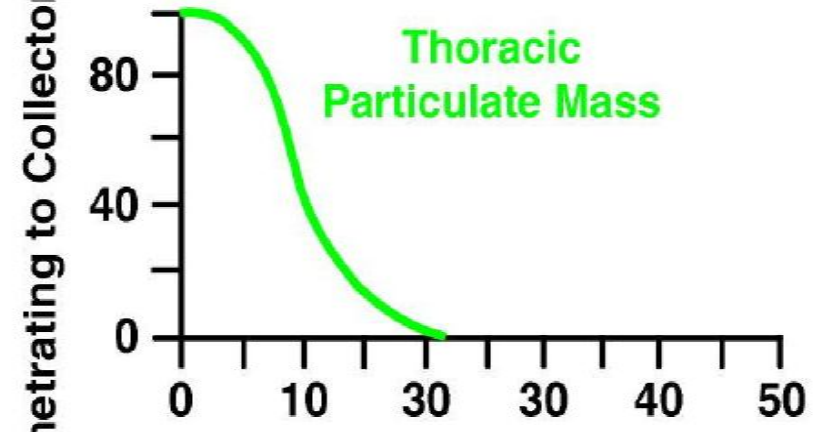
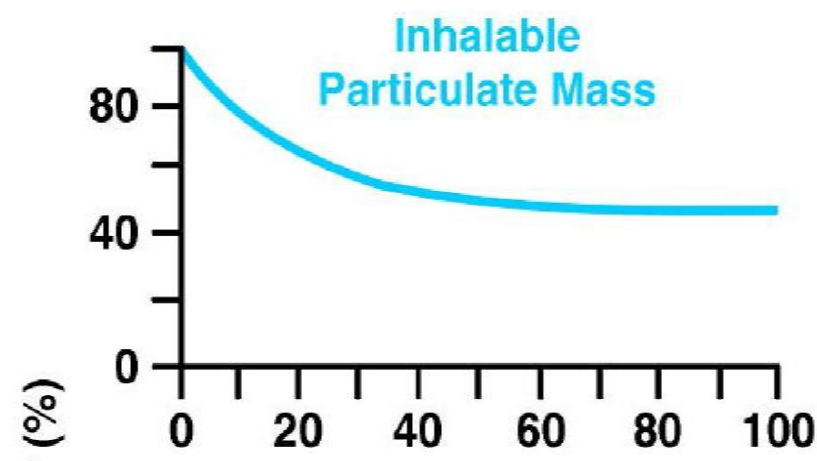
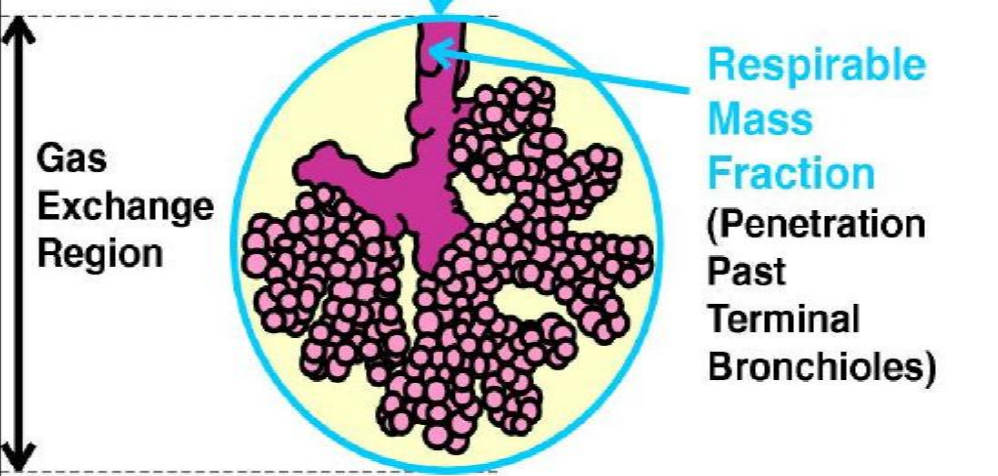
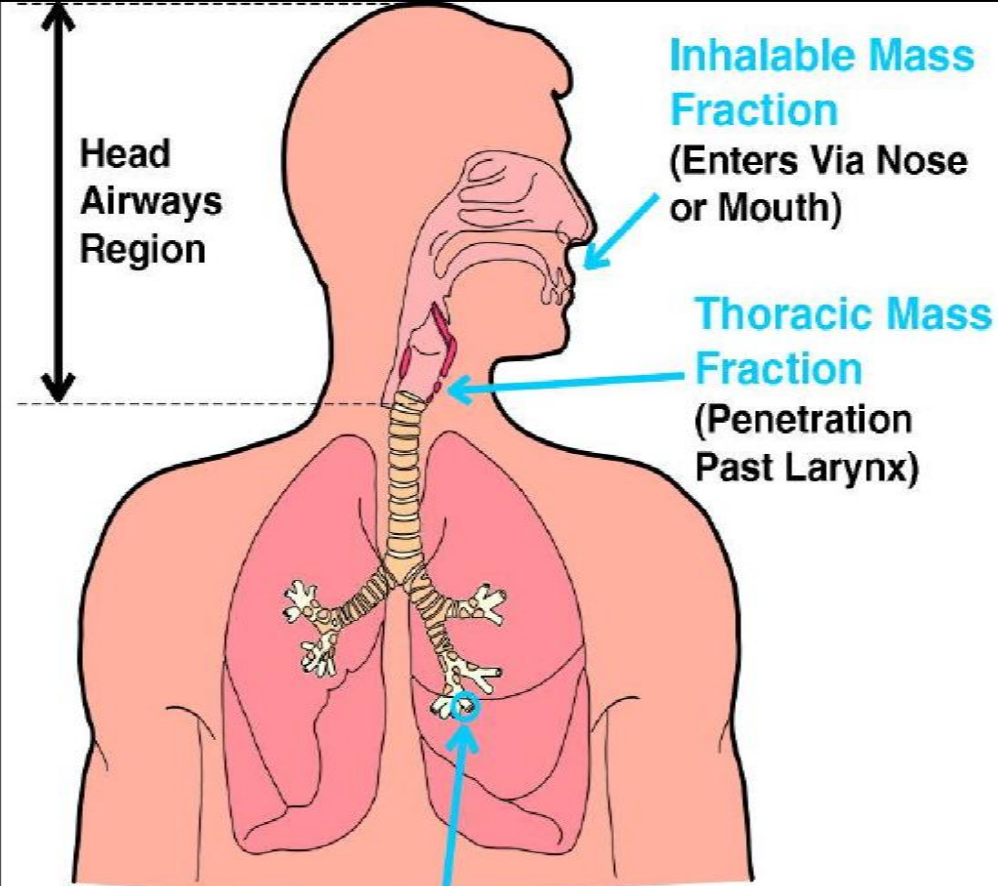
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A close-up profile of a person's face as they sneeze. A large, bright, yellowish-white spray of particles is being emitted from their nose, filling the right side of the frame. The background is dark blue with many small, white, star-like specks, suggesting a microscopic or scientific context.

**Violent sneeze:  
4500-1,000,000  
organisms liberated**

# Droplet Nuclei





# Determinants of infection

## Risk of Infection Given Exposure: Largely Exogenous Factors

$$\frac{\text{Particles}}{\text{Volume}} \times \text{Exposure time}$$

Particles:

Production of infectious droplet nuclei

Volume:

Volume of air and ventilation

Exposure time:

Time of inhaling air with droplet nuclei

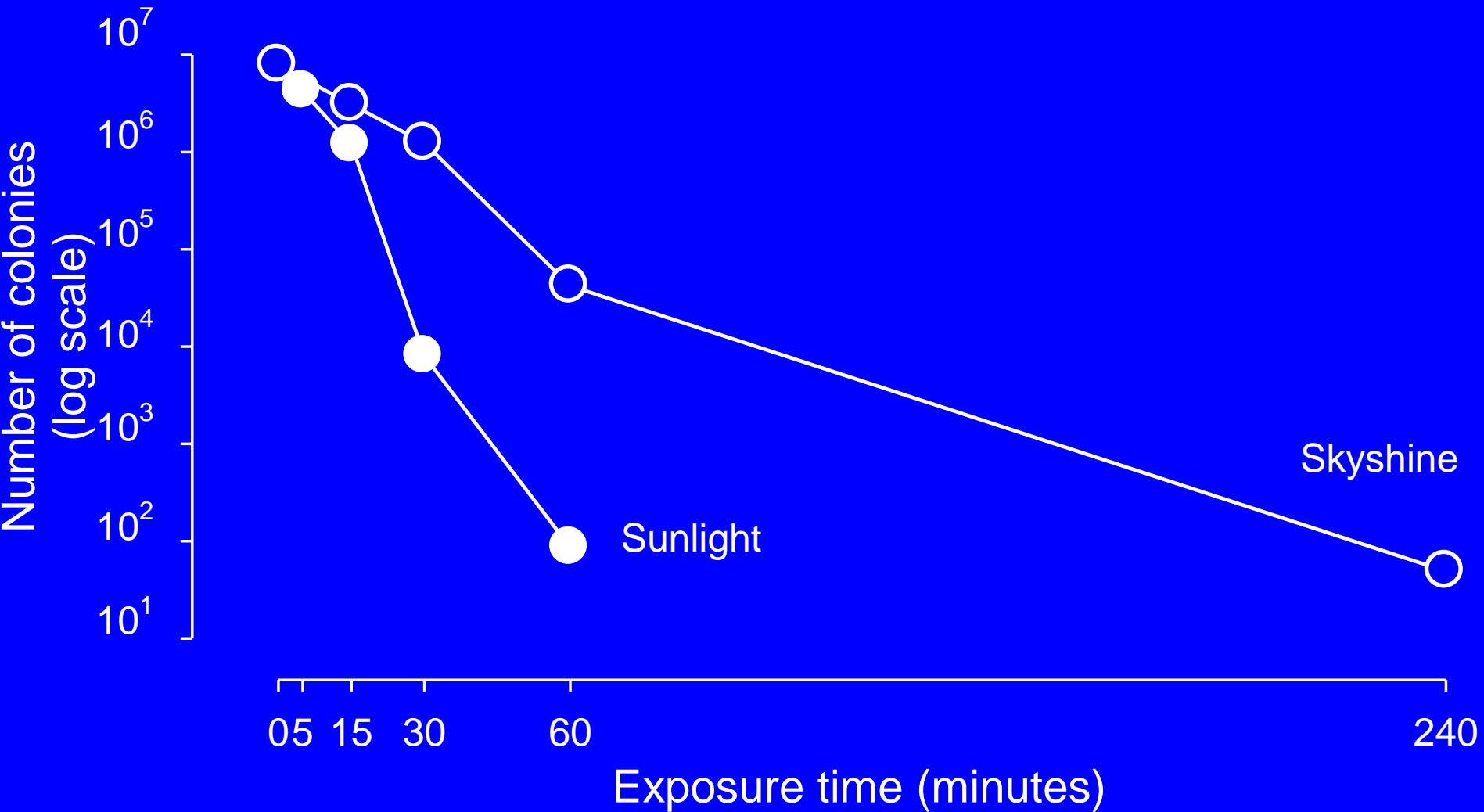


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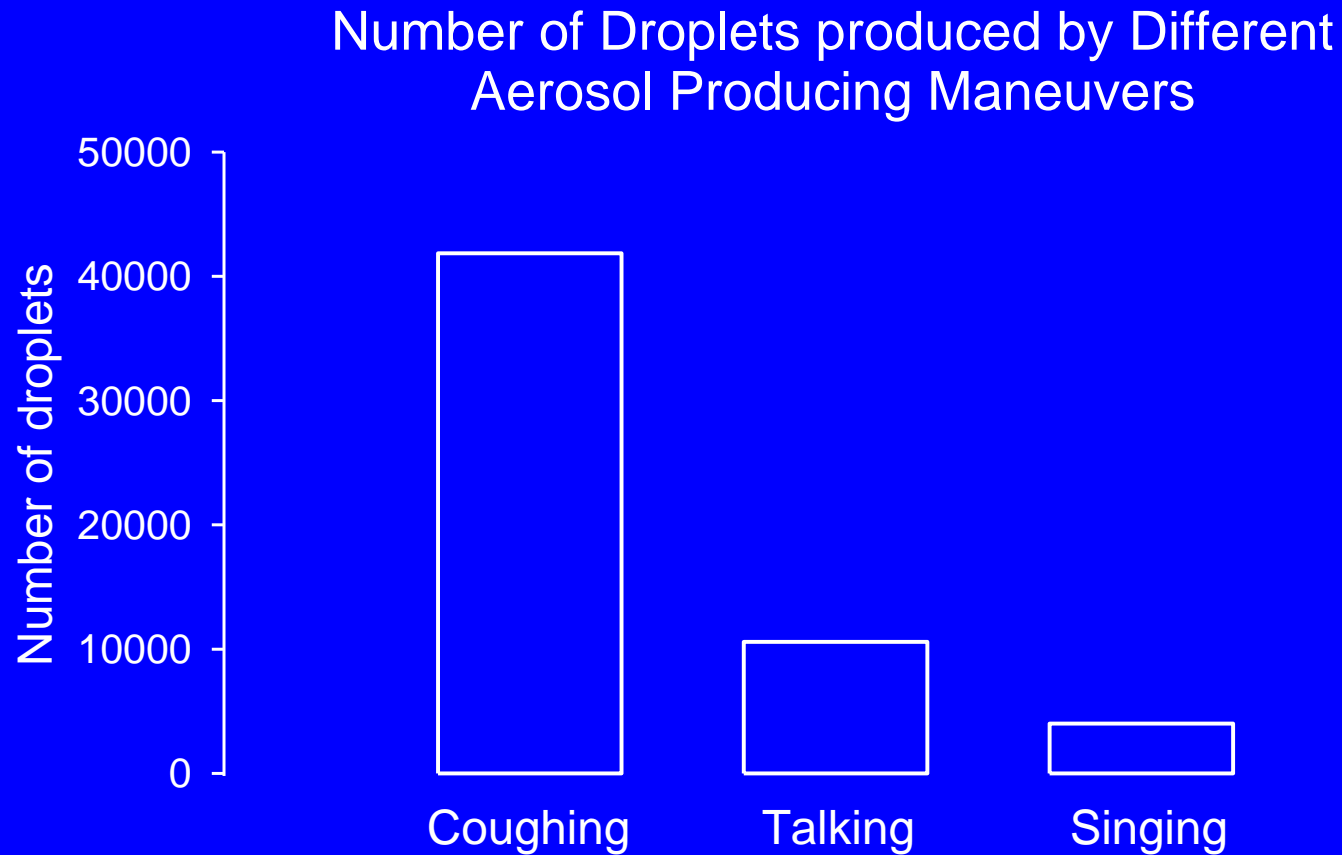
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# Killing of BCG by Sunlight and in Open Sky Without Direct Exposure to Direct Rays of the Sun



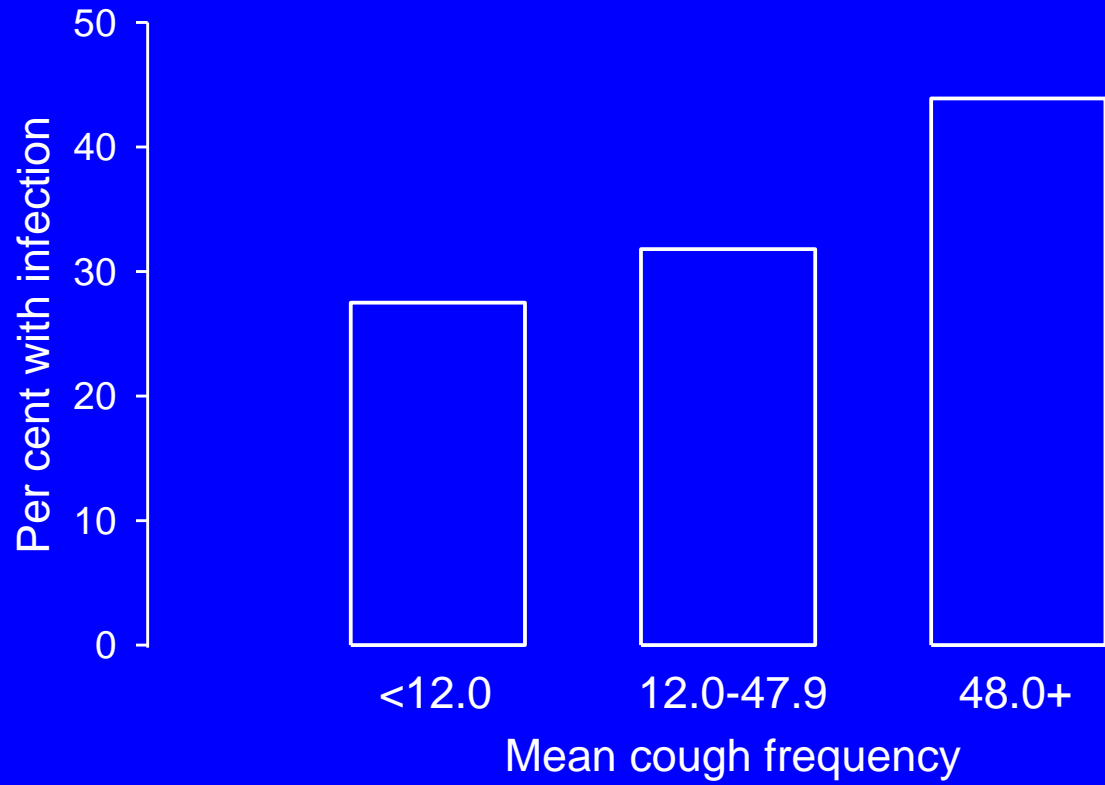
# Determinants of infection: Factors affecting particle concentration



*Loudon RG, et al. Am Rev Respir Dis 1968;98:297-300*

# Determinants of infection: Factors affecting particle concentration

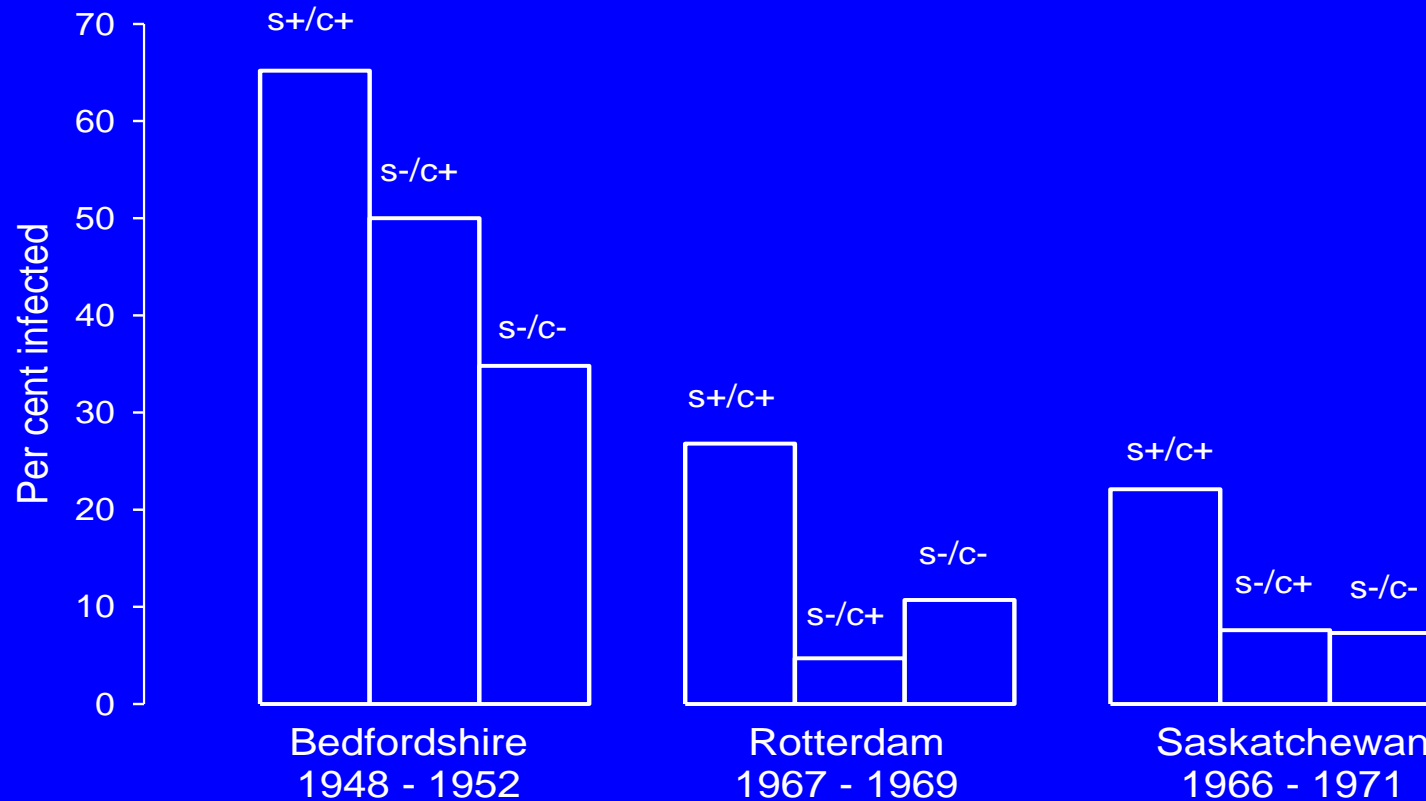
Proportion of Contacts <15 Years with Tuberculous Infection, in Relation to Cough Frequency of Source



Loudon RG, et al. *Am Rev Respir Dis* 1969;109-111

# Determinants of infection

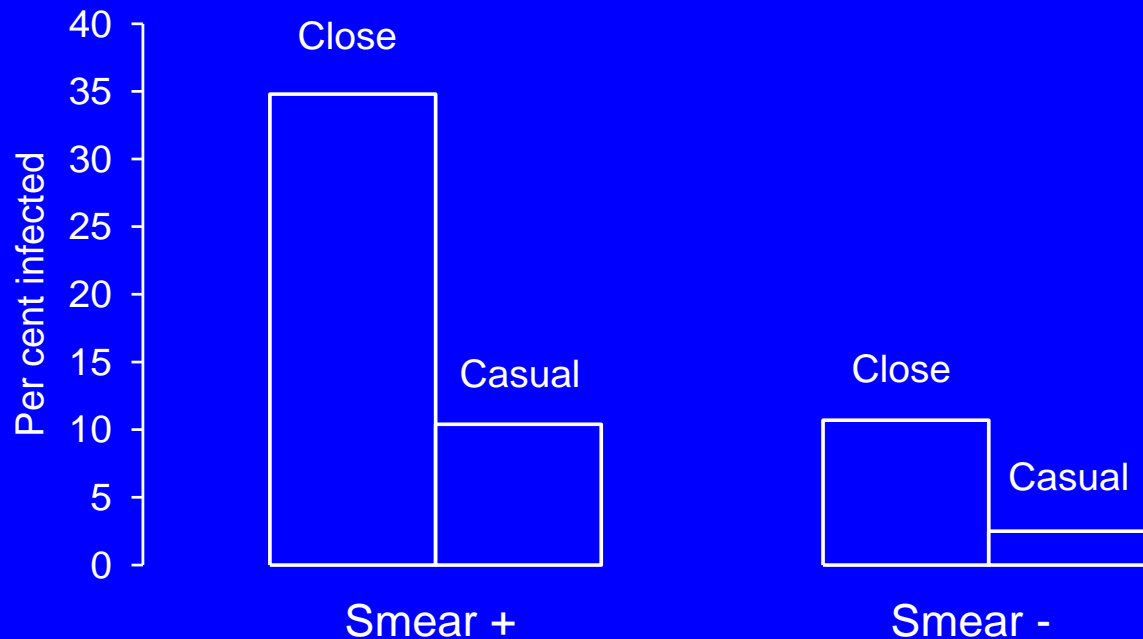
Tuberculous Infection Among Close Contacts (Children <15 yr)  
by Bacteriologic Status of Index Case



Shaw JB, et al. *Am Rev Respir Dis* 1954;69:724-32  
van Geuns HA, et al. *Bull Int Union Tuberc* 1975;50:107-21  
Grzybowski S, et al. *Bull Int Union Tuberc* 1975;50:90-106

# Determinants of infection

Tuberculous Infection Among Children by Type of Contact and Bacteriologic Status of Index Case, British Columbia and Saskatchewan, 1966 - 1971



Grzybowski S, et al. *Bull Int Union Tuberc* 1975;50:90-106

# Determinants of infection

Take home message:

**Almost ALL spread of TB is  
caused by smear positive  
cases**



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# EXPOSURE

**Transmission:**

- airborne (infectious droplets)
- indoors

**Ventilation**  
**Direct sunlight**

**Number of droplets**  
**Time exposed**  
**Susceptibility**

**TB-treatment:**  
**less infectious,**  
**less cough**

# INFECTION

**Tuberculin test positive**

**HIV**  
**Age (very young/old)**  
**Other diseases**  
**Malnutrition**  
**Medication**  
**Stress**

**↑ Risk in 1<sup>st</sup> 2 yr**

**10% in a lifetime**  
**HIV+: 10% per year**

**Strain virulence**  
**Genetic-environmental**  
**Medical conditions**

# DISEASE

# TB Infection versus TB Disease

TB Infection	TB Disease (in the lungs)
<i>M. tuberculosis</i> in the body	
Tuberculin skin test reaction usually positive	
No symptoms	Symptoms such as cough, fever, weight loss
Chest x-ray usually normal	Chest x-ray usually abnormal
Sputum smears and cultures negative	Sputum smears and cultures usually positive*
Not infectious	Often infectious before treatment
Not a case of TB	A case of TB

\*Sputum smears more often negative in HIV-infected cases



# TB disease

**Primary TB:**  
Primary complex:  
granuloma lung +  
lymphadenopathy

Delayed  
hypersensitivity +  
cell-mediated  
immune response

Latent period

Endogenous reactivation  
Exogenous re-infection

No clinical  
disease  
(90%)

Hypersensitivity  
reactions

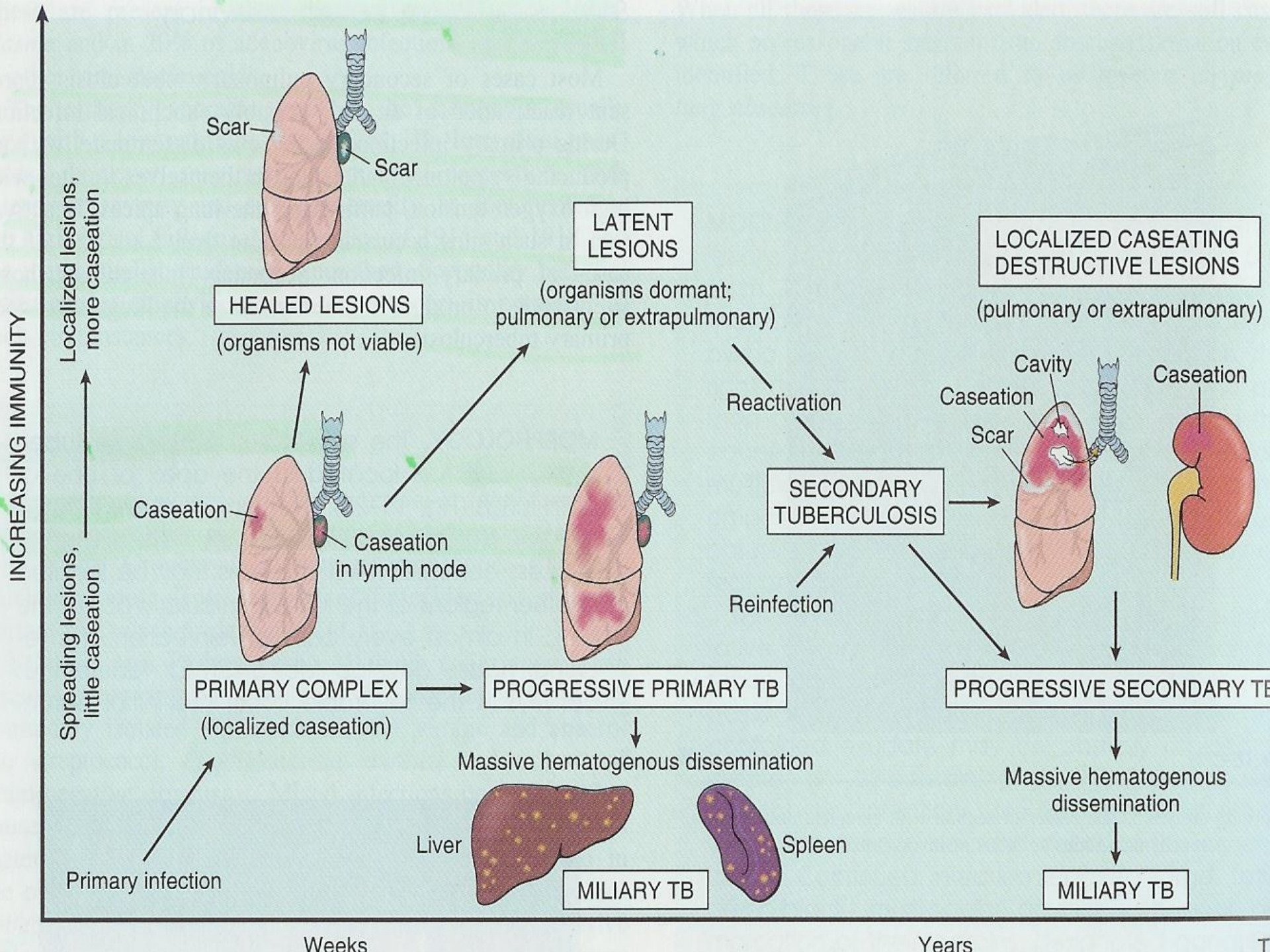
Disseminated  
disease

Pulmonary/  
pleural disease

(progressive  
primary disease)

**Post primary TB:**  
Pulmonary TB  
Extrapulmonary TB



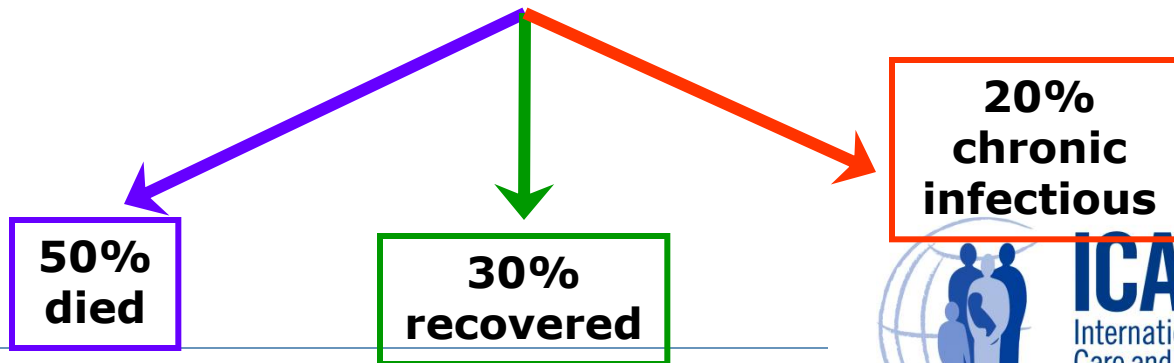


# Post primary (P)TB

## Extensive lung destruction:

- Cavitation
- Positive smears
- Upper lobe involvement
- No intrathoracic lymphadenopathy

Natural history of smear+ PTB  
(after 5 yrs without Rx):

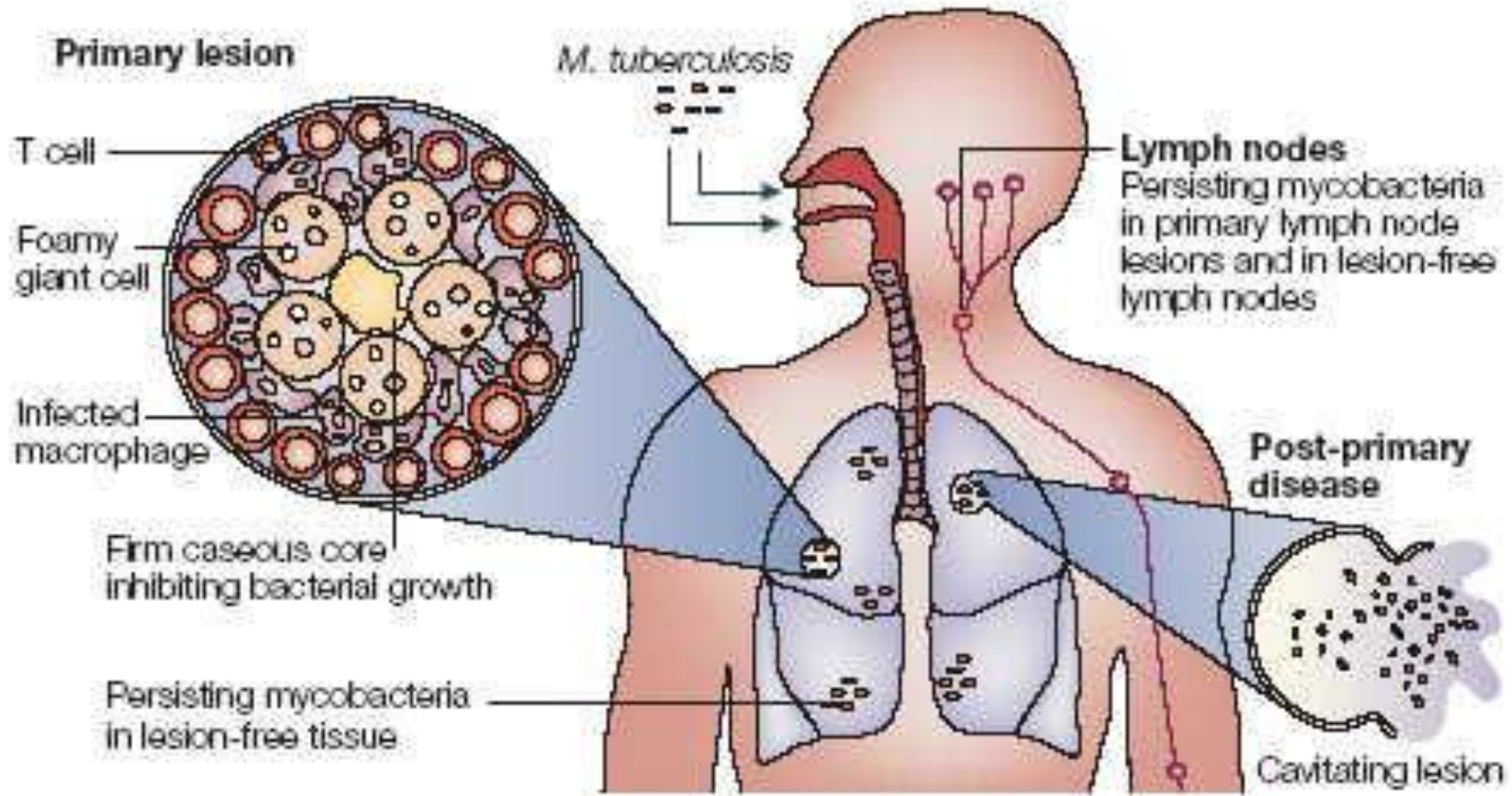


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# TB - histopathology

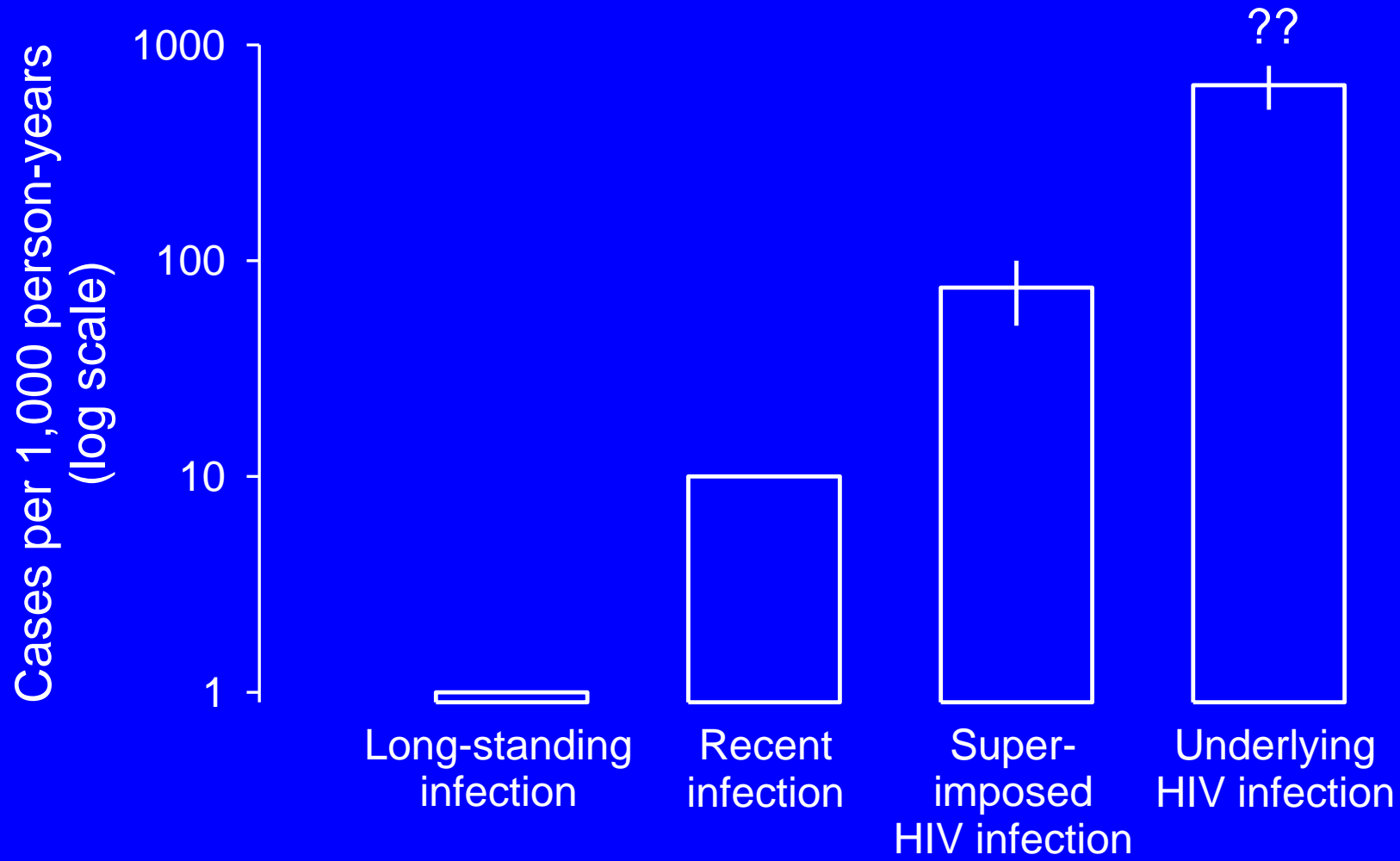


# Determinants of disease

- Post primary TB - within months of infection
- Reactivation TB
  - Risk decreases exponentially within first few years of infection, to a steady rate
  - Greatest risk within first 2 years
  - Risk factors include:
    - Age – greater risk in infancy and adolescence
    - Lower CD4+ count
    - Lower socioeconomic status
    - Occupation (e.g. mining)
- In populations with a high annual risk of developing TB:
  - High incidence of new TB cases
  - Age-related incidence peaks in **younger** age groups

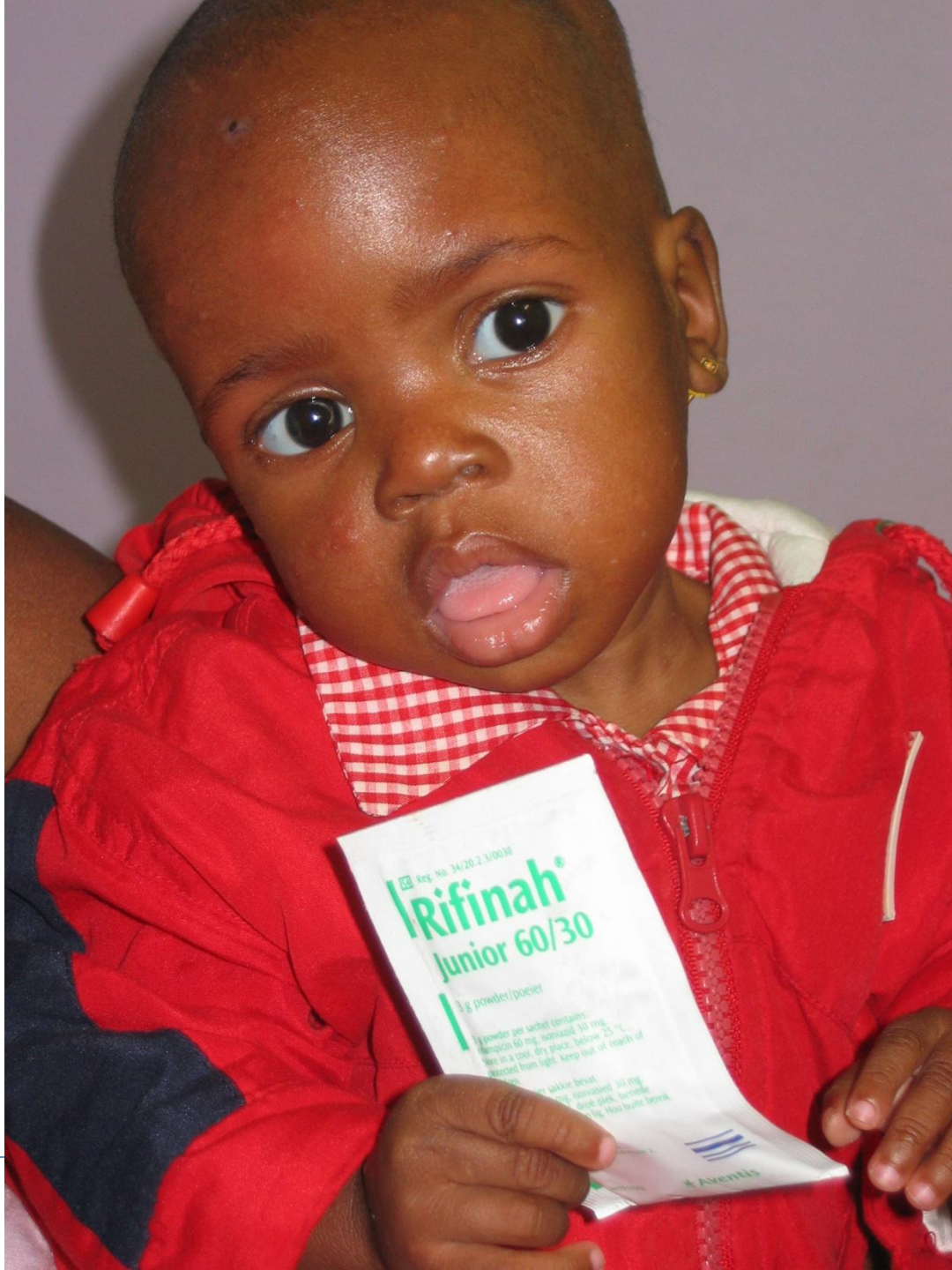


# Example of Risk Differences in Individuals Following Infection with *M. tuberculosis*



# What Causes Transmission and Outbreaks of TB Today?

- Patient delays in seeking care
- Provider delays in considering TB, pursuing a diagnosis
- Delays in starting and ensuring completion of treatment
- Inability to diagnose and treat drug-resistant TB
- Exposure of susceptible persons, especially HIV-infected populations
- Inadequate administrative and engineering precautions to prevent airborne transmission



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