Mycobacterium tuberculosis Transmission and Disease Progression

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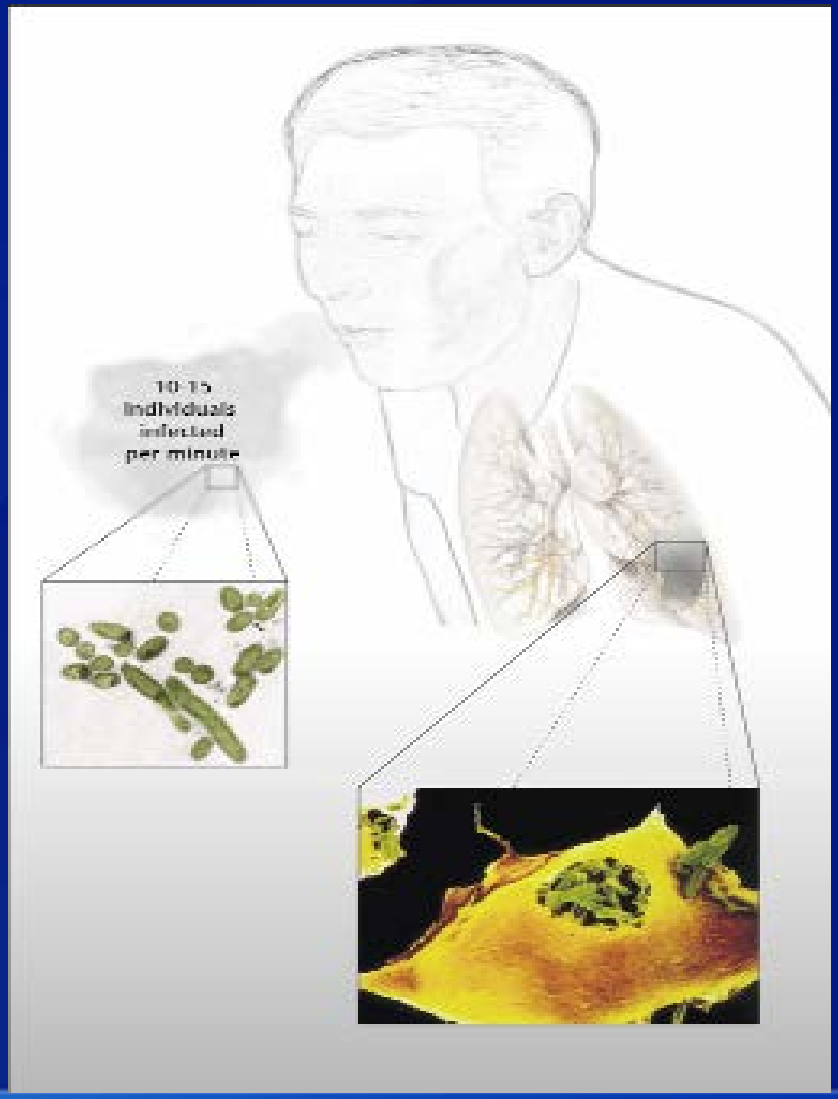
Centers for Disease Control and Prevention

TB Intensive Workshop
Newark, NJ
April 12, 2011

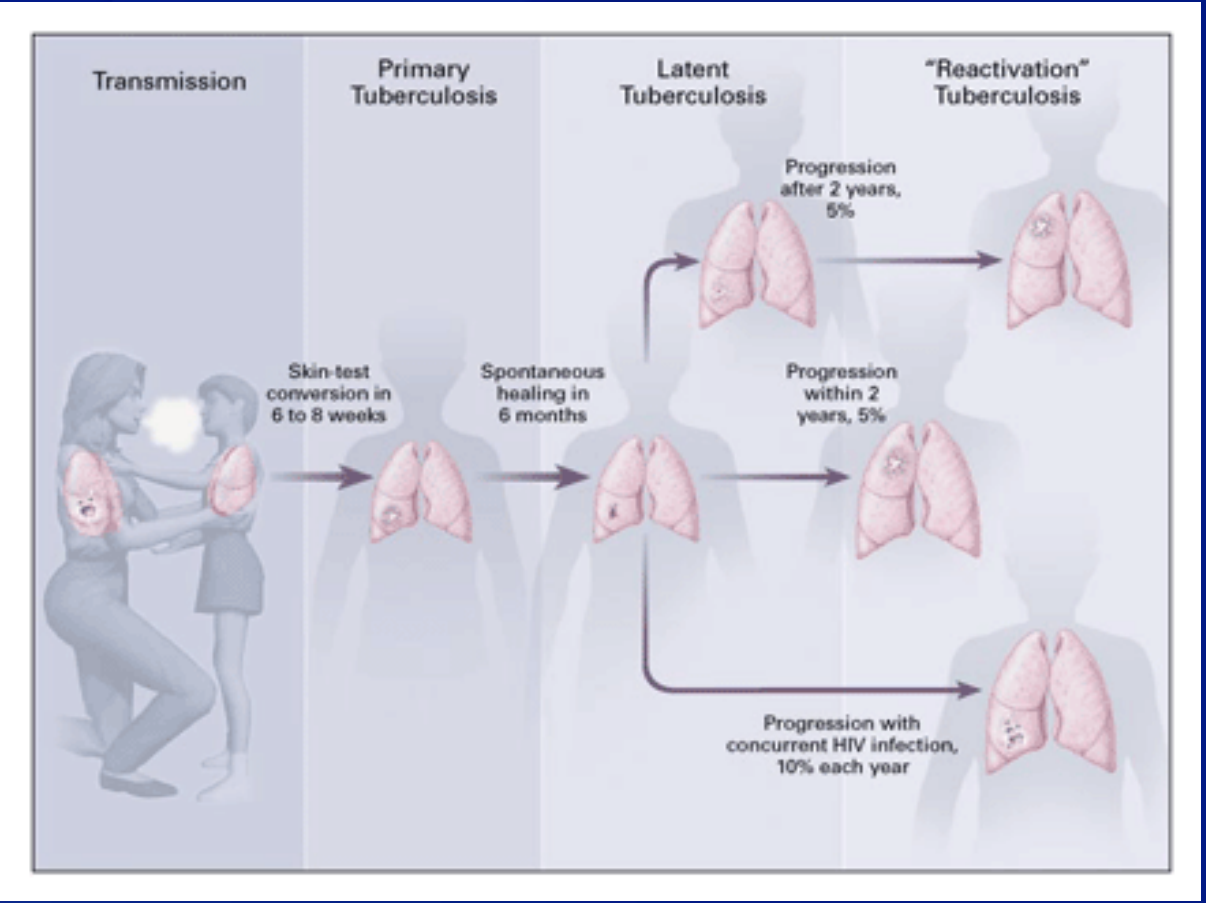
Objectives

- Understand transmission dynamics
- Review TB immunology and pathogenesis
- Demonstrate public health implications
  - Vaccination and therapeutics
  - Diagnostics

Route of Transmission



Transmission of Tuberculosis



N Engl J Med 345:189-200, 2001

Probability of Transmission

- Host
  - Inoculum (smear, culture, cavitation)
- Organism
  - Virulence factors
- Environment
  - Space/ventilation
  - Time

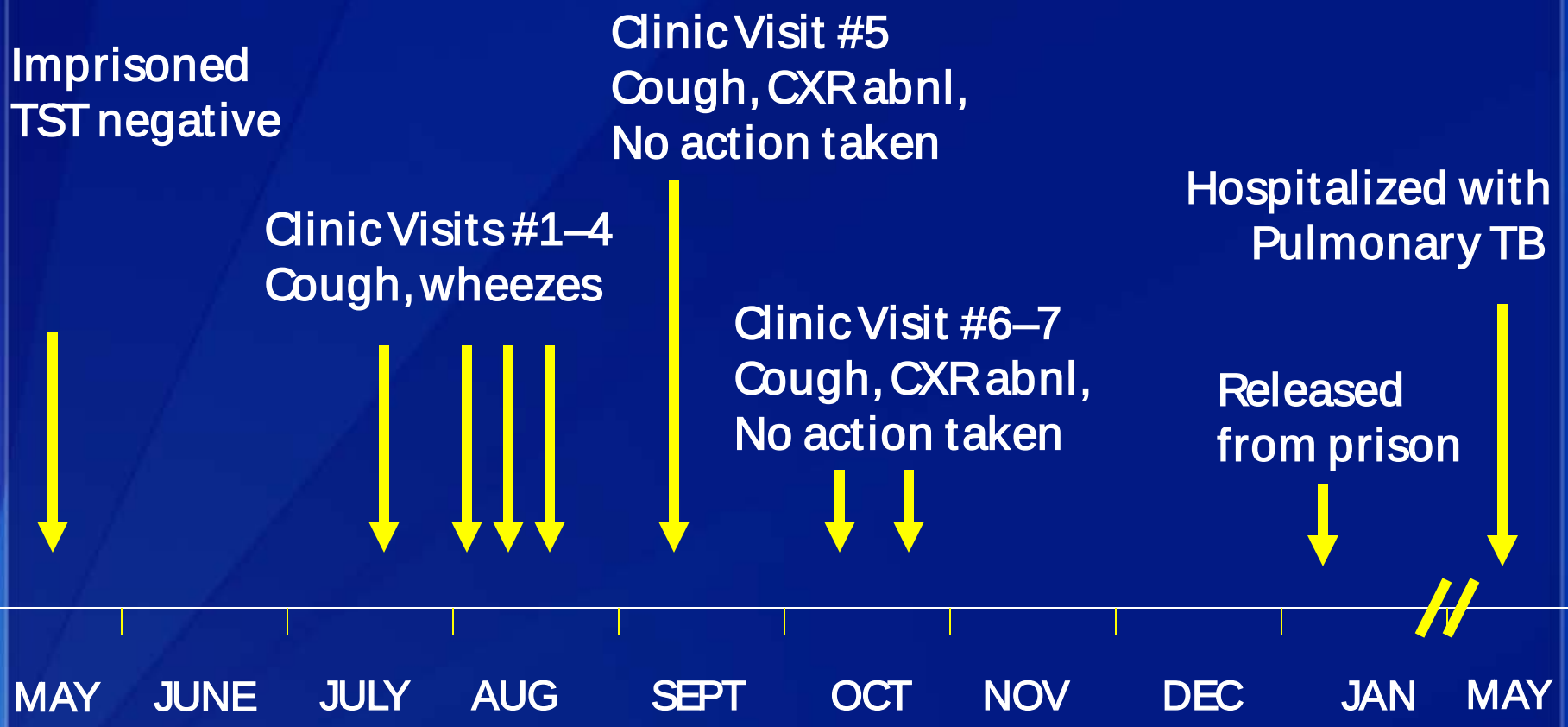
Variations in Inoculum

- Estimates of *M. tuberculosis* aerosol production (quanta per hour)
  - Patient on early treatment ~1
  - Untreated cavitary TB 13
  - Laryngeal TB 60
  - Bronchoscopy 250

Fennelly KP. Int J Tuberc Lung Dis 1998; 2: S103

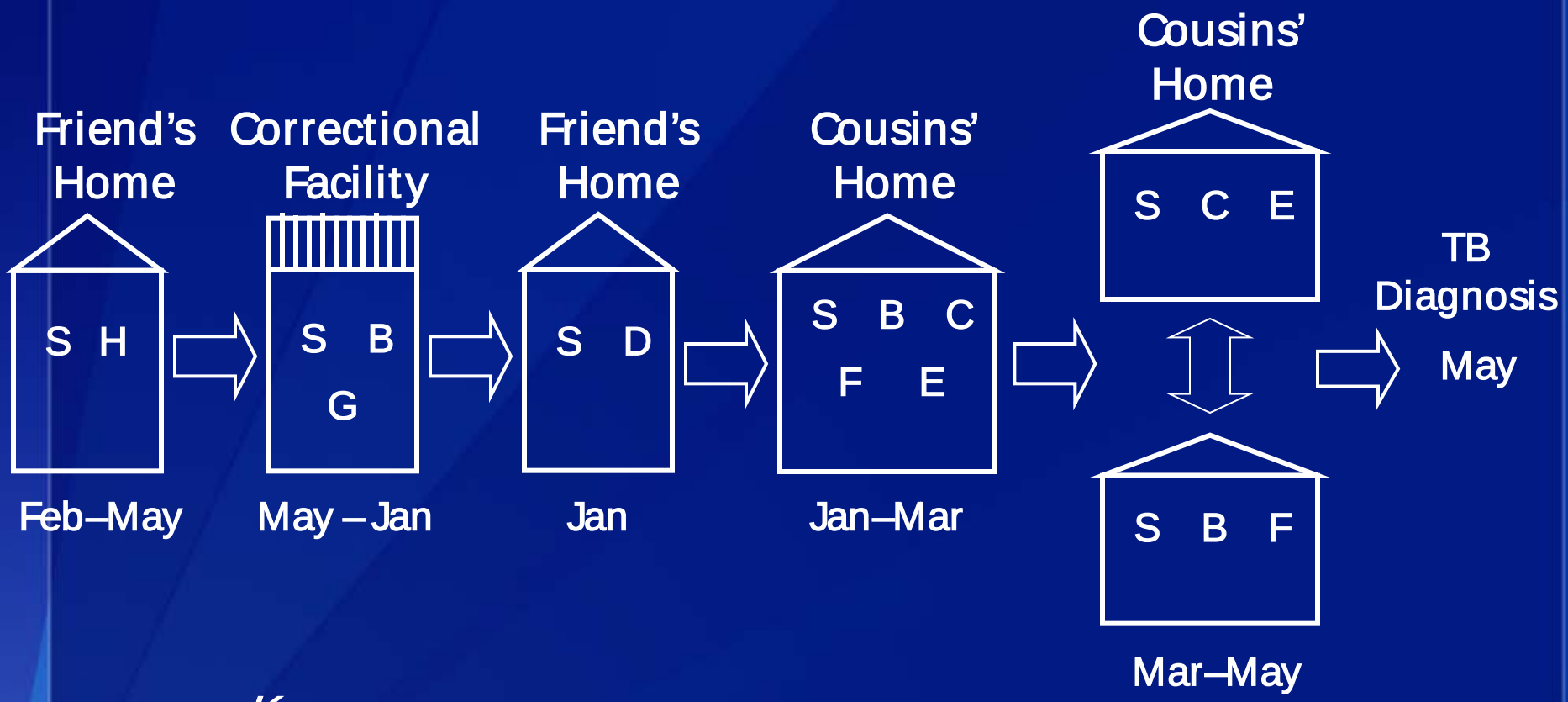
Environment

TB Outbreaks Move Through Time



Sosa L. *Inter J TB Lung Dis* 2008;12:689

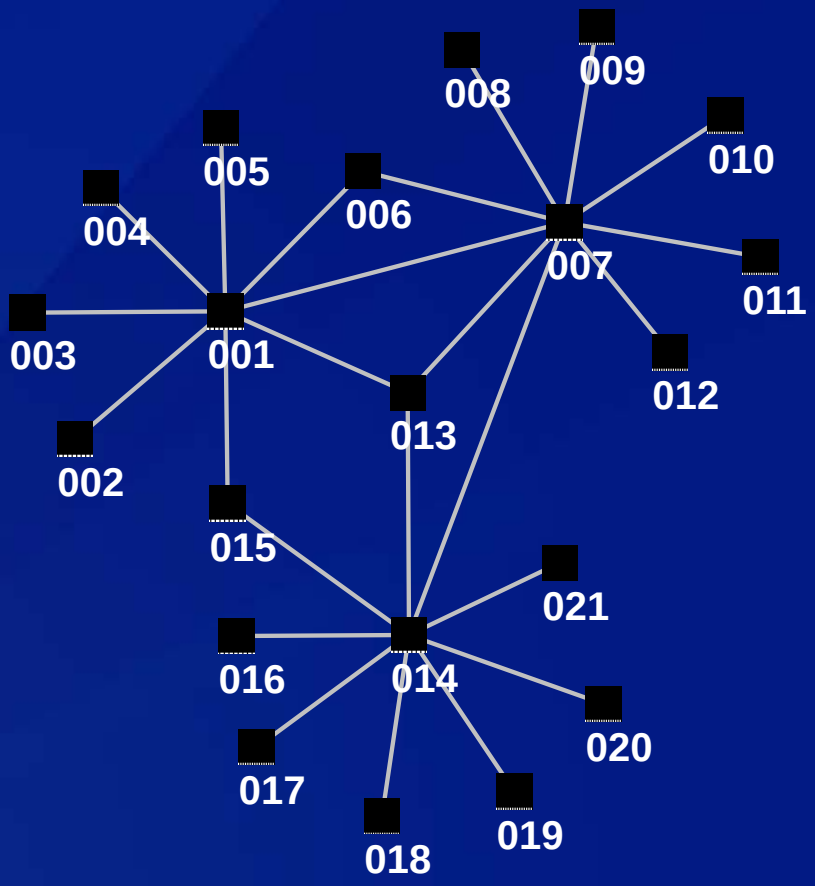
TB Moves Through Place



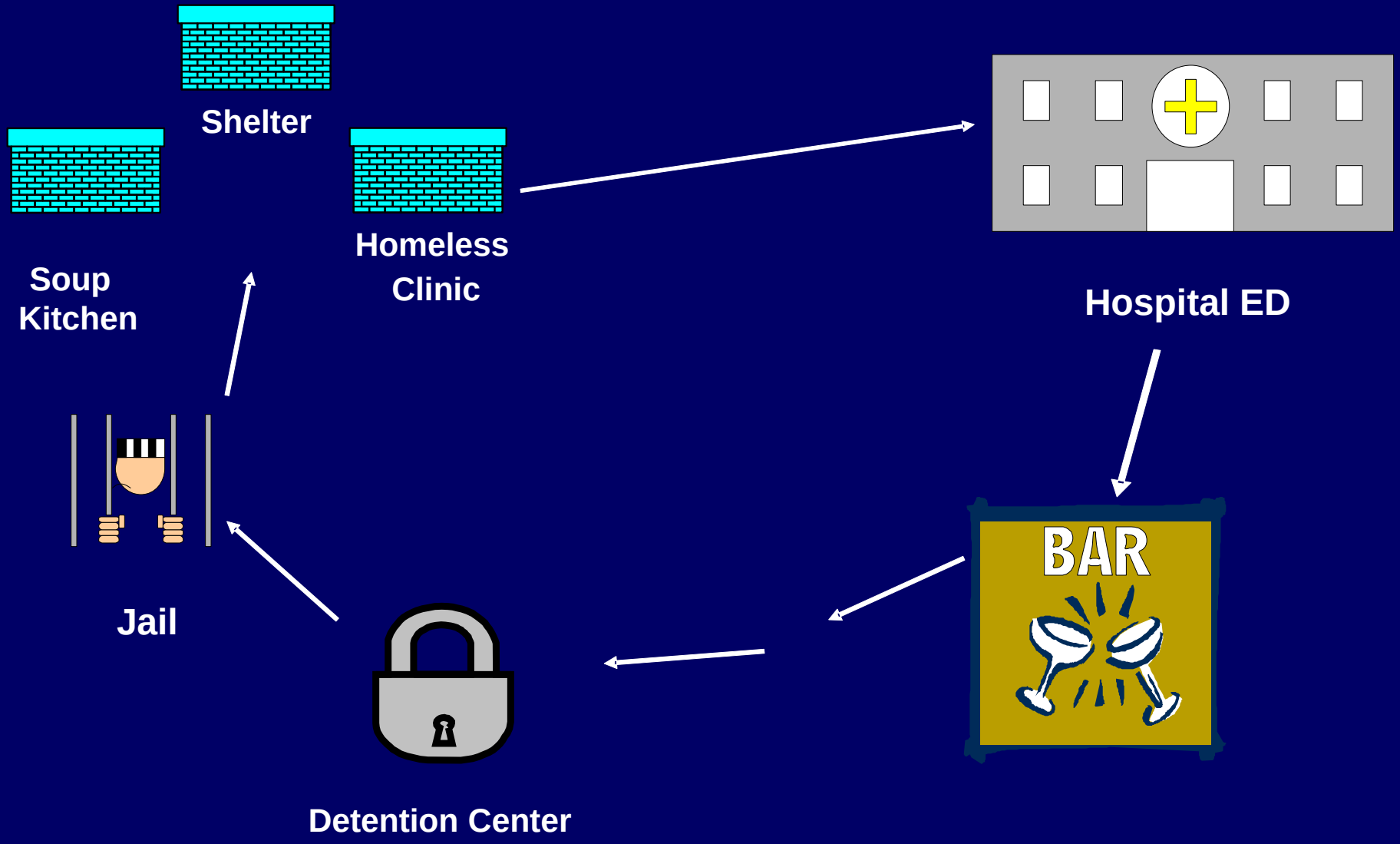
Key

- Location
- (S) Source patient
- ( ) Secondary patients

TB Can Appear as Outbreaks

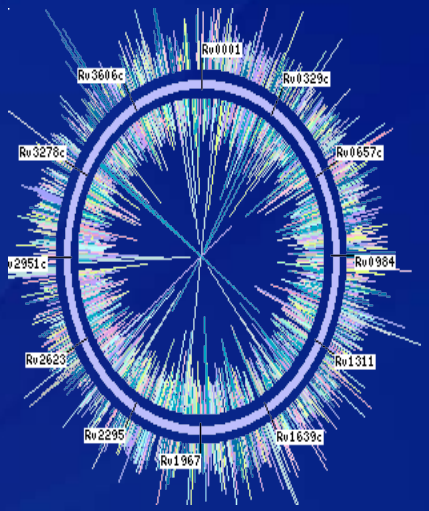


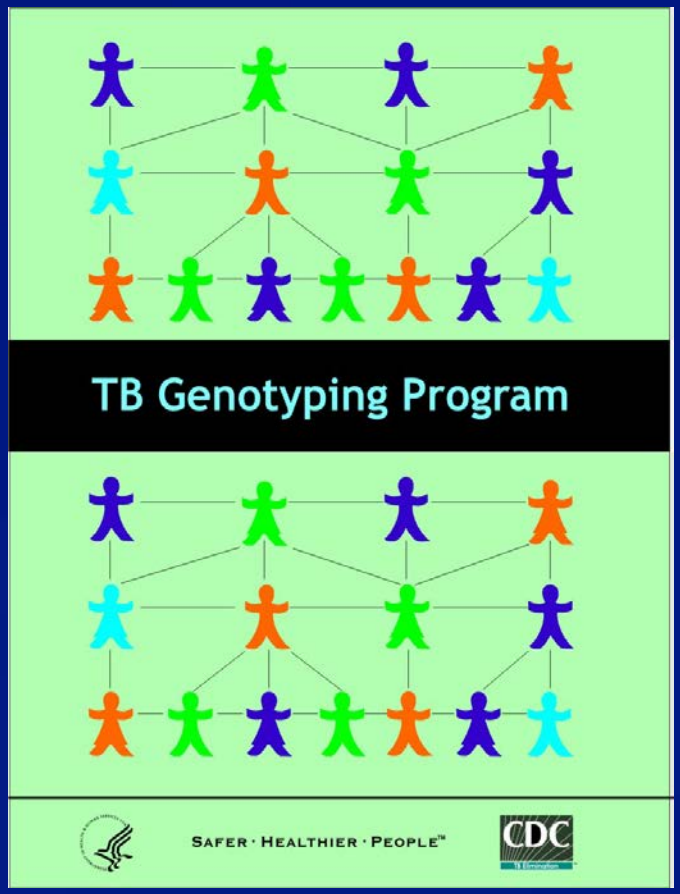
Amplifiers of TB Transmission



TB Genotyping Program

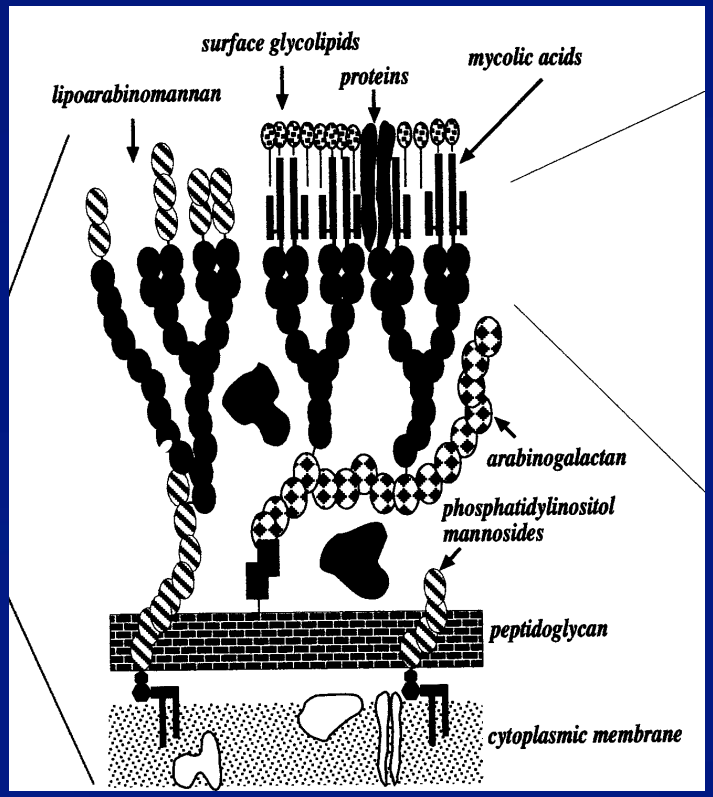
- Spoligotyping
- Mycobacterial interspersed repetitive units (MIRU)





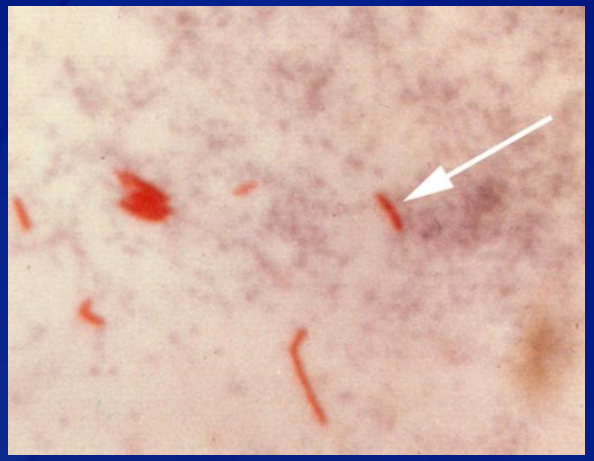
Mycobacterium tuberculosis

- Obligate aerobes
- Slow-growing
- Intracellular pathogens
- Hydrophobic: lipid content in the cell wall
- *LAM* (lipoglycan lipoarabinomannan)
- "Acid-fast bacilli"

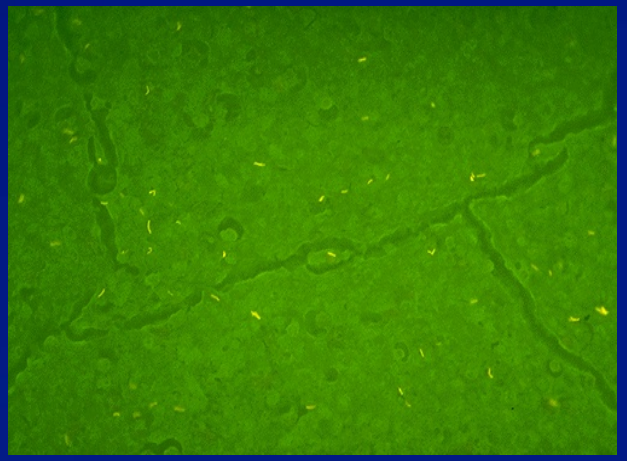


Remer L et al. Molecular Genetics of Mycobacteria, Ed. Hatfull G and Jacobs W. ASM Press, 2000

Acid Fast Bacilli



carbolfuchin stain



fluorochrome stain

Pathogenesis

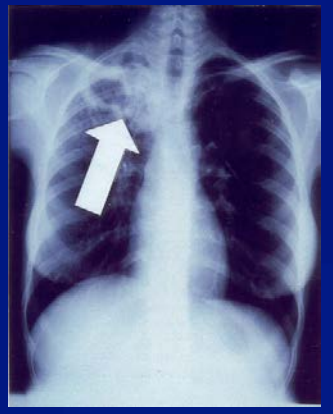
- Outcome from infection depends on immune responses
- Certain medical conditions increase risk for progression to TB disease

Photo: David Rochkind

Conditions Increasing Likelihood of Progression from Infection to Disease

- Very young age
- T-cell deficiency (e.g., HIV)
- Treatment with TNF-alpha antagonists
- Solid organ transplantation
- High-dose corticosteroids
- Diabetes mellitus
- End-stage renal disease
- Malnutrition
- Silicosis
- Hypercholesterolemia?

Natural History of TB Infection

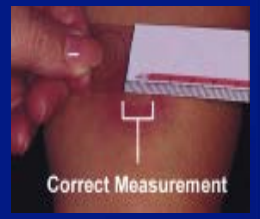


1 progressive disease (<5%)

Reactivation disease (5%)

Persistent infection (90%)

Bacterial load



Innate (TST-)

Adaptive (TST+)

Acute

Chronic

Adapted from: Dr. Henry Boom, Case Western Reserve University

Antimycobacterial Immunity

Innate Immunity

- Cell populations (Toll-like receptors)
- Bactericidal molecules
  - Enzymes (lysozyme, etc.)
  - Reactive nitrogen and oxygen intermediaries

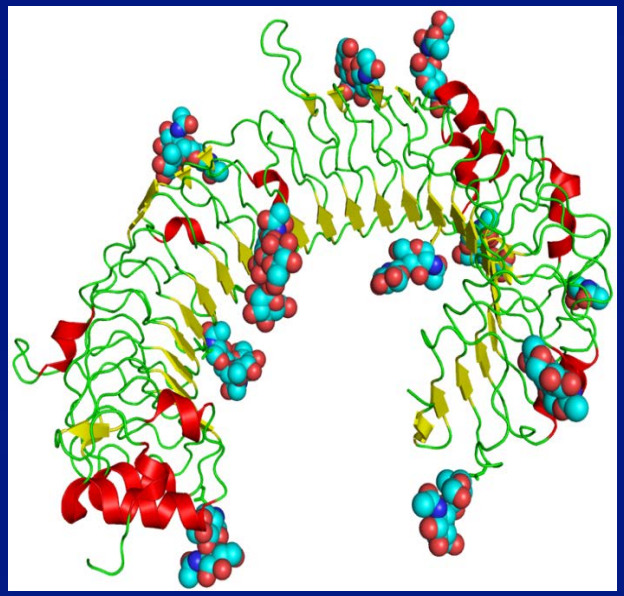
Humoral Immunity

Adaptive Immunity

- Cell-mediated Immunity
- Phagocytes (Antigen presenting cells)
  - Macrophage
  - Dendritic
  - Monocytes
- Effector cells
  - CD4+, CD8+ T cells
  - CD1 (NKT)
  - γδ T cells
- Cytokines (IFN-g, TNF-α, IL-12, IL-4)

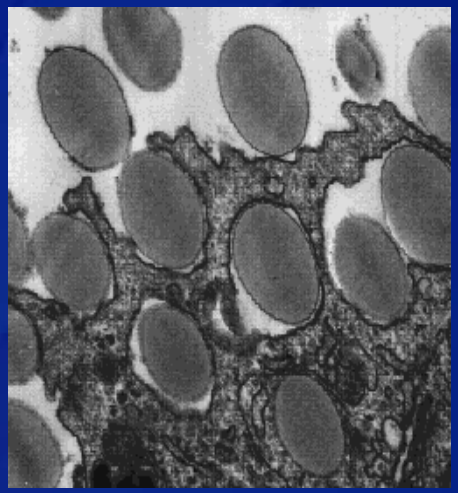
Toll-like Receptors (TLRs)

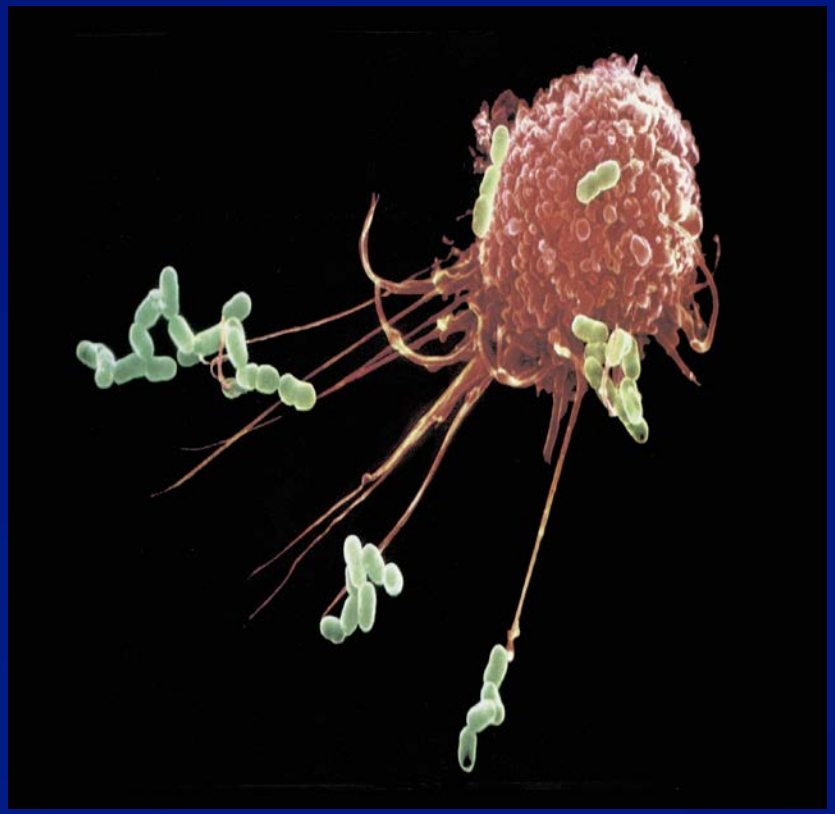
- TLRs initiate first immune response
- TLR-8 on the X chromosome
- Males have 1 copy- may be more susceptible



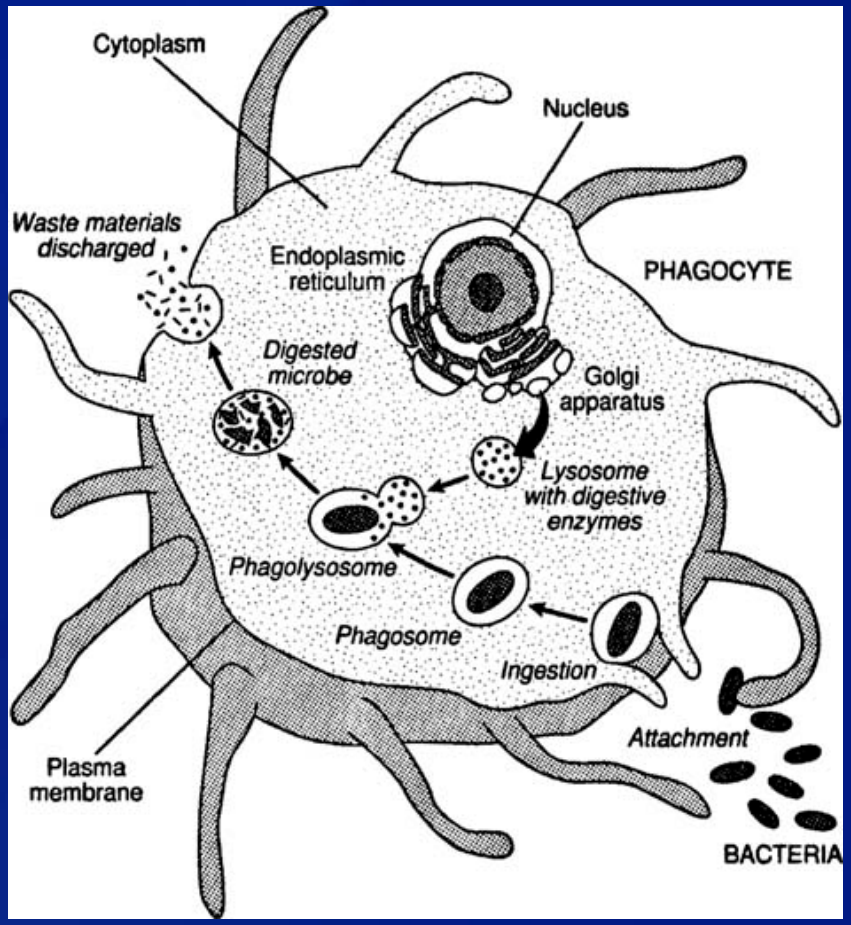
First line of defense

- Dendritic cells
- Macrophages
- Stimulated T cells

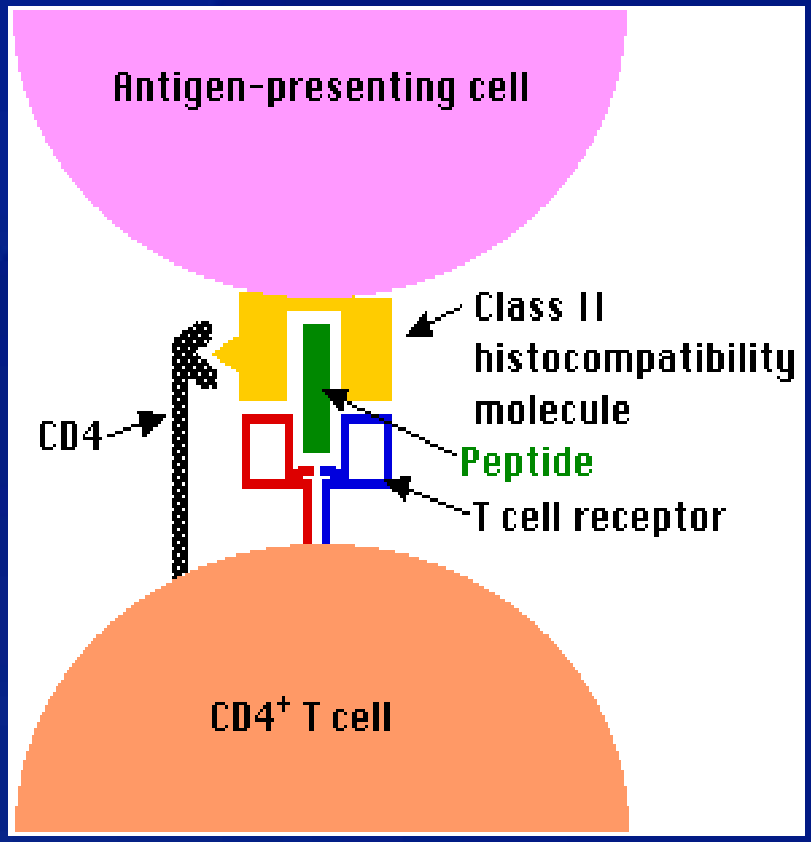




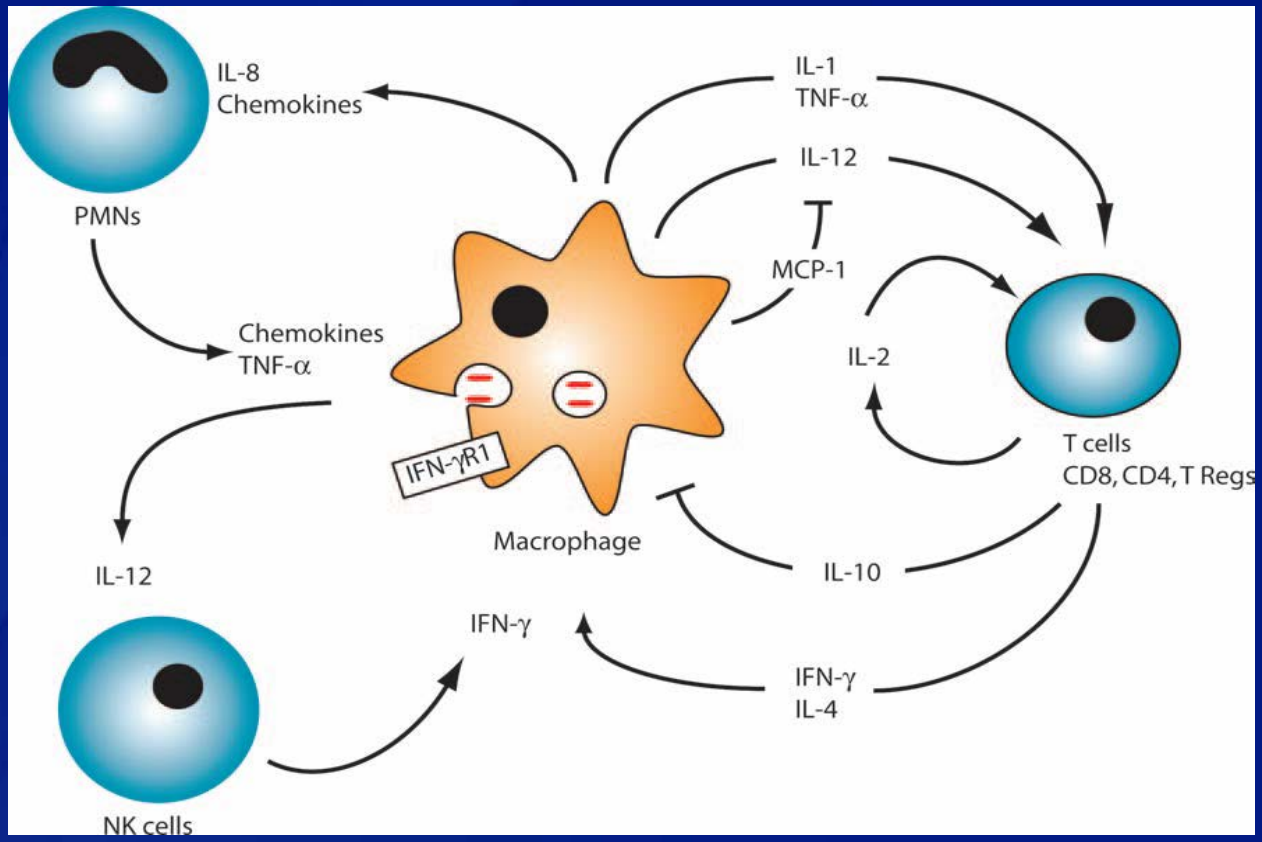
Microscopic Level



CD4+ / Human Leukocyte Antigen Interaction



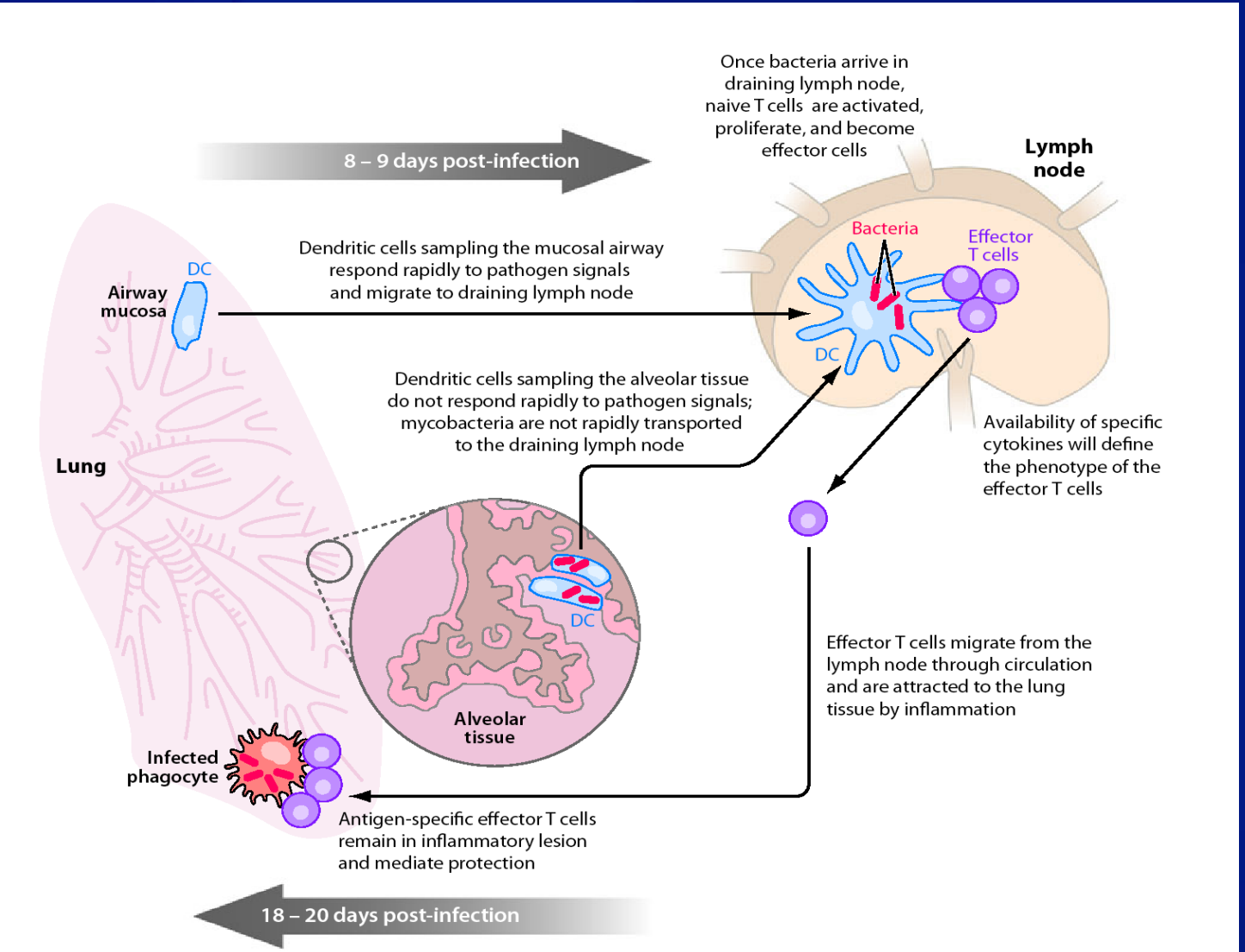
Cellular Immune Response



Cytokine Storm

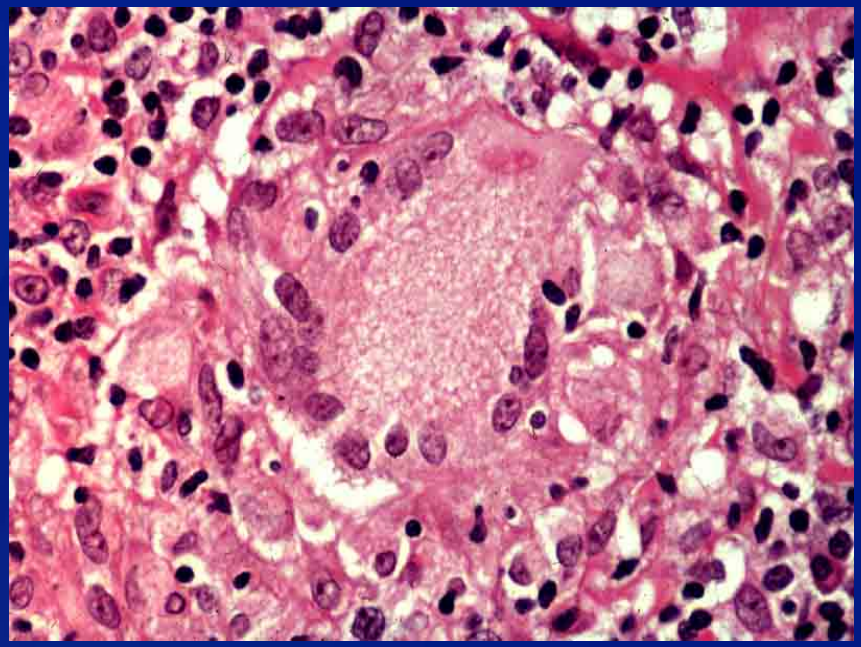
http://www.medclip.com/index.php?page=videos&section=view&vid_id=101067

Host Responses



Cooper AM. Annu Rev Immunol 2009 27:393

Granuloma

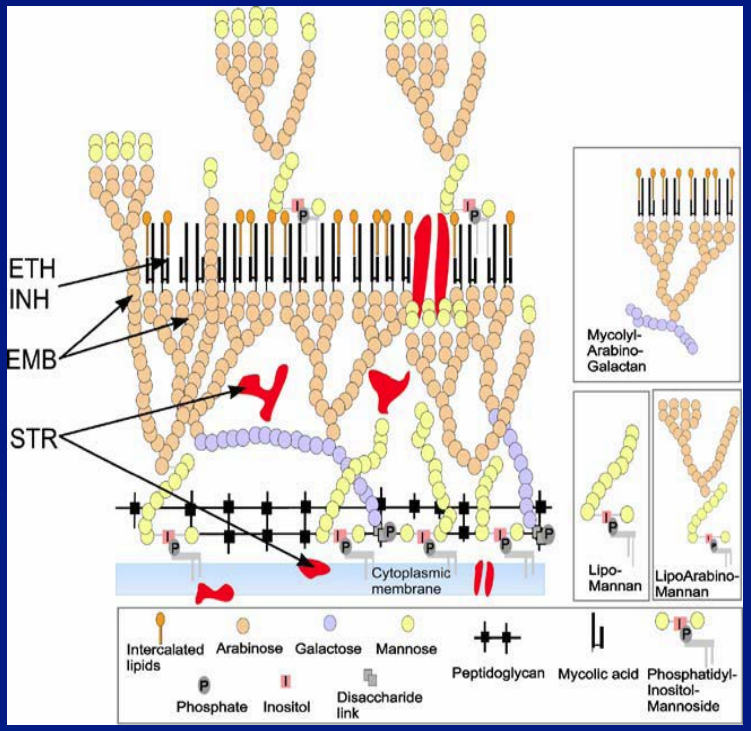


When Host Immunity Fails

- Mycobacteria are spread by migrating cells to local lymph nodes
- From the lymph nodes, they disseminate via the blood stream to different body sites
- They may continue to grow and cause early disease at any site
- They may be contained, then "reactivate", especially in the lung apices, but anywhere is possible

M. tb Strategies to Evade Host Immunity

- Cell membrane
  - Fatty acids
  - NO arginase inhibition
  - Efflux pumps
  - Mannose coating
- Resistance to phagosome pH
- CD4 cells remain compartmentalized unable to be mobilized to lymph nodes

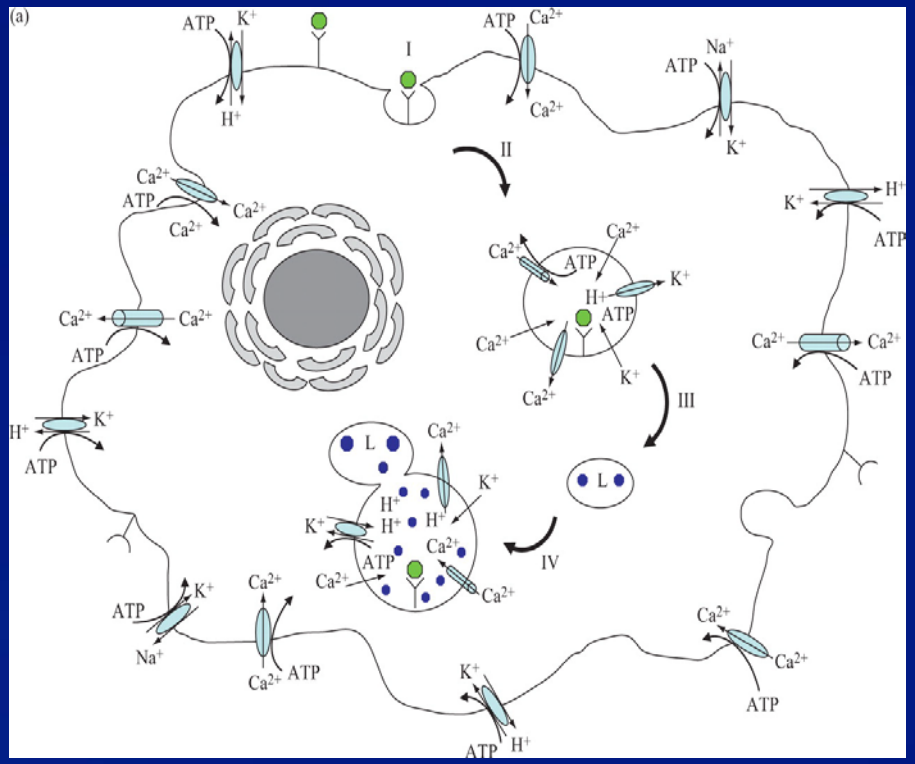


Alsteens D. Eur J Physiol 2008;456:117–125

Evasion of Acidic Conditions

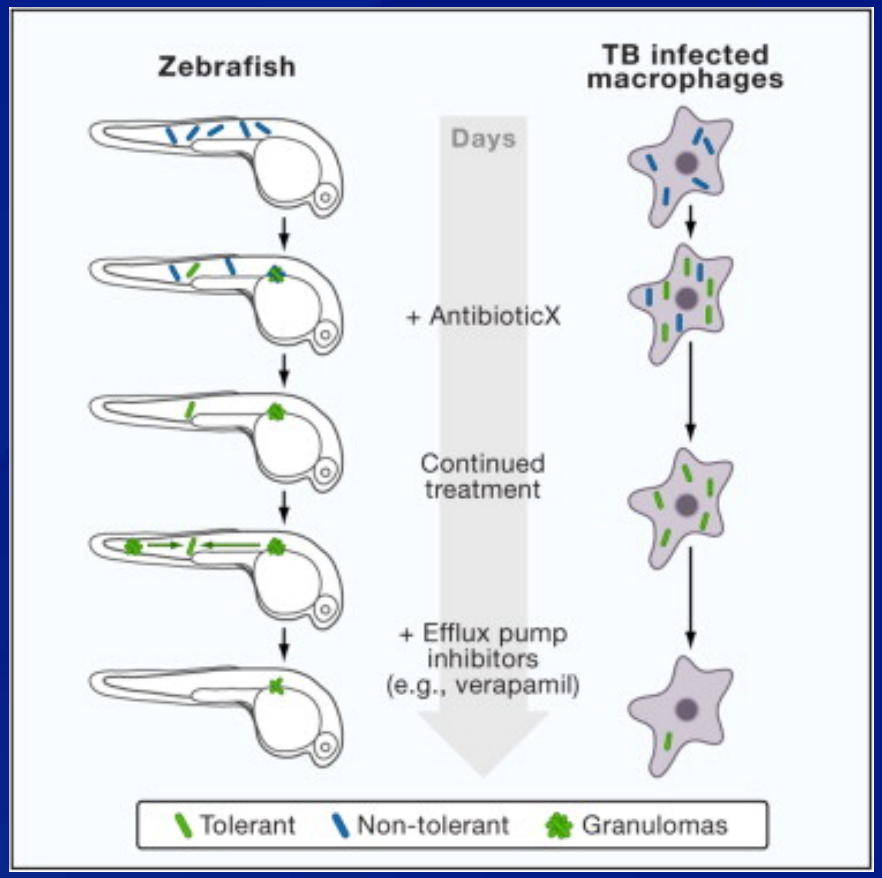
Inhibition of

- Phagosome-lysosome fusion
- Lysosome acidification
- Activation of hydrolytic enzymes



Amaral L. Journal of Antimicrobial Chemotherapy 2007;59:1237

Role of Efflux Pumps



Adams KN, et al. Cell doi:10,1016/jcell.2011.02.002

Public health implications

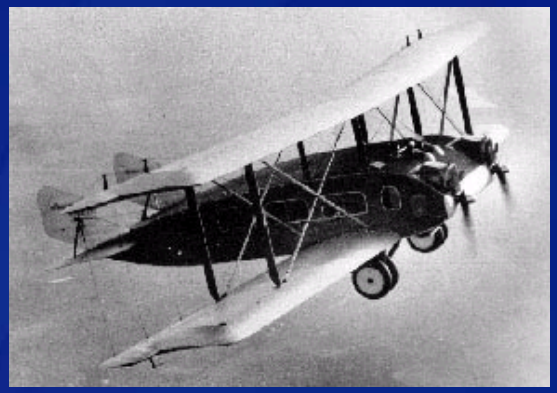
LAM Assay for MTB Screening

The usefulness of urine-LAM (lipoglycan lipoarabinomannan) is limited because of low sensitivity. Sputum-LAM has better sensitivity but poor specificity.

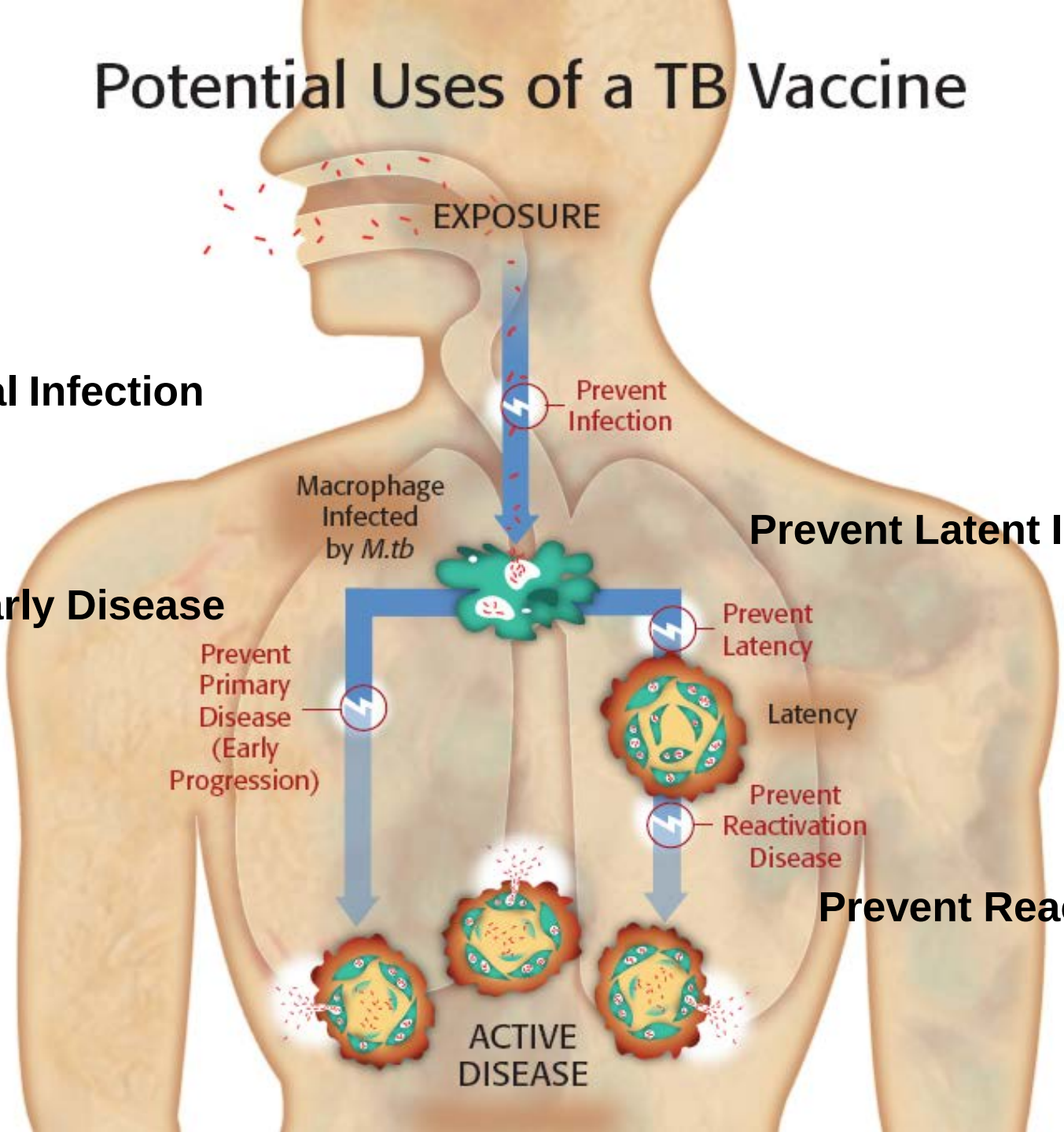
Dheda K, et al. Clinical utility of commercial LAM-ELISA assay for TB diagnosis in HIV-infected patients using urine and sputum samples. PLoS ONE 2010;5: e9848

Priming the Immune System: Bacille Calmette-Guérin (BCG) Vaccine

- Calmette & Guérin 1908-1921
- No new TB vaccine in 90 years



Potential Uses of a TB Vaccine



Block Initial Infection

Prevent Latent Infection

Prevent Early Disease

Prevent Reactivation

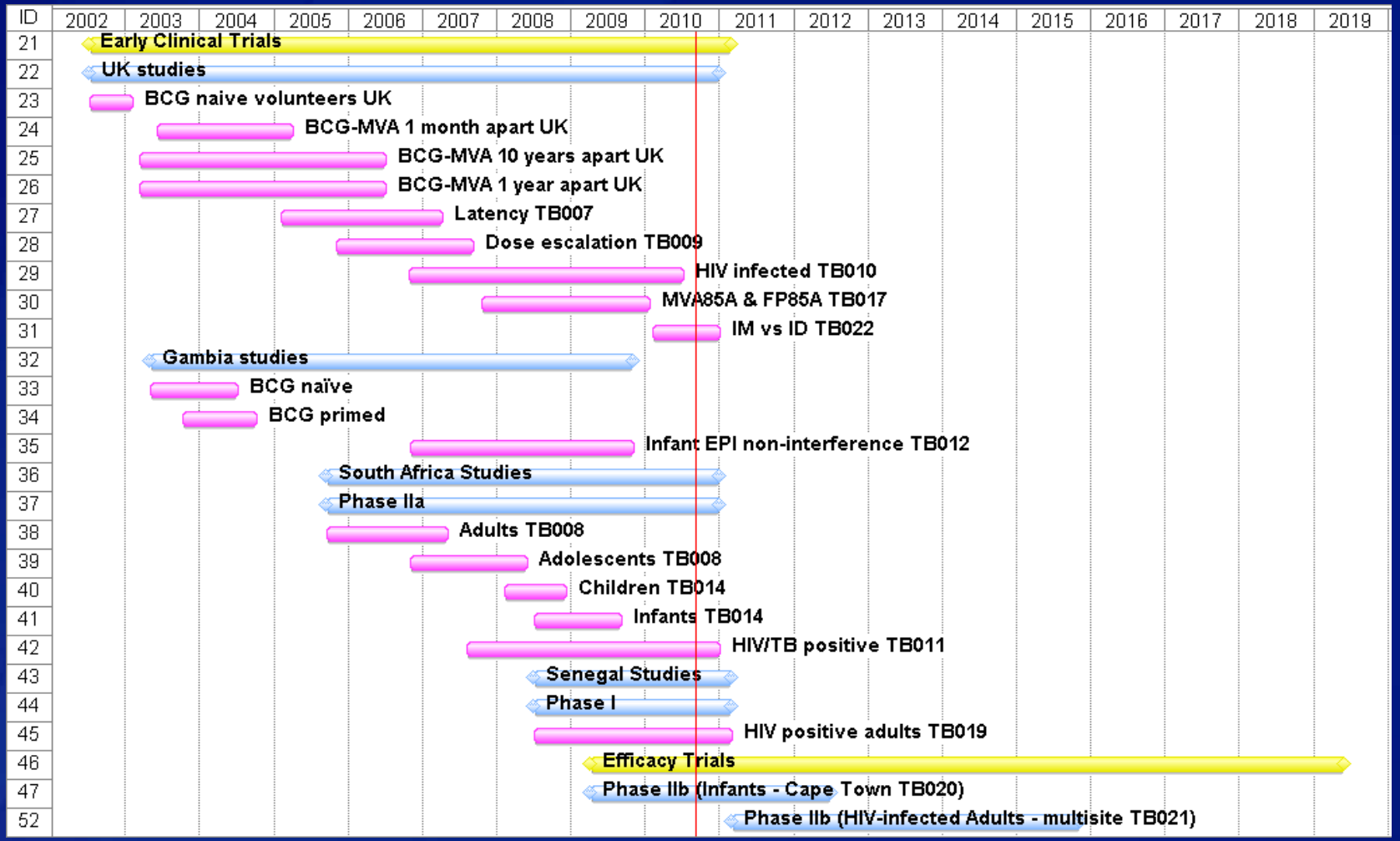
Vaccine Development

- *Live attenuated vaccines*
  - Genetically-modified BCG
  - Genetically engineered mutants
  - Live attenuated vectors (viruses or bacteria)
- *Subunit vaccines*
  - Protein, peptide, lipid, or carbohydrate antigens, with or without adjuvants
- *DNA vaccines*
  - DNA encoding whole proteins or peptide epitopes of *M. tuberculosis*

TB Vaccine Pipeline

Vaccine Candidate	Pre-Clinical	Phase I	Phase II	Phase IIb	Phase III
AERAS402/Crucell Ad35 *Crucell N.V./Aeras*					
MVA85A/AERAS-485 *OETC/Aeras*					
GSK M72 *GSK Biologicals/Aeras*					
Hybrid 1 SSI IC-31 *SSI, TBVI, Intercell*					
HyVac4/AERAS-404 *sanofi pasteur/SSI/Intercell/Aeras*					
VPM 1002 *Max Planck/Vakzine Projekt Management GmbH/TBVI*					
AdAg85A *McMaster University*					
RUTI *Archivel Farma, S.I.*					
Hybrid 1 SSI CAF01 *SSI*					
AERAS-rBCG *Aeras*					
AERAS-Capsid *Aeras*					
Other rBCG rMtb *Albert Einstein S. of Med., Institute Pasteur, Univ. of Zaragoza, TBVI*					
AERAS-other virus *Aeras*					
Protein/Polysaccharides *Inst. Pasteur de Lille/Inserm, Albert Einstein S. of Med., Aeras, Karolinska Instit.*					

Clinical trials with MVA85A



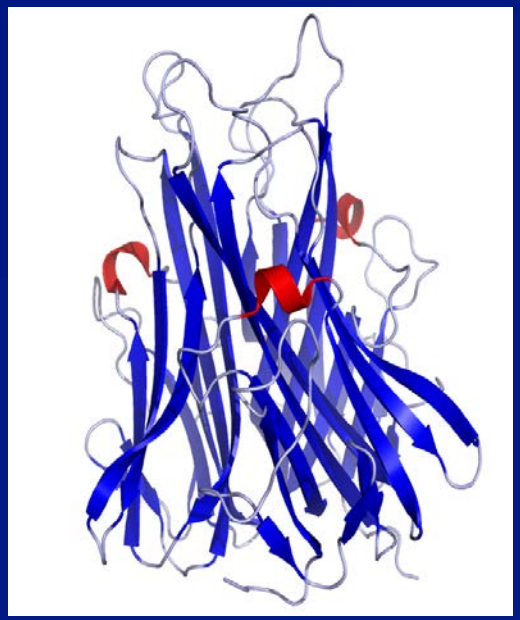
Helen McShane. Jenner Institute, University of Oxford. 2010.

Implications for Therapy

- Immune modulation
  - Use of IFN-α as an immune modulator
  - *Ex vivo* pulsing of dendritic cells to prime T cells
- Target specific sites
  - Receptors
  - Efflux pump
  - Genes

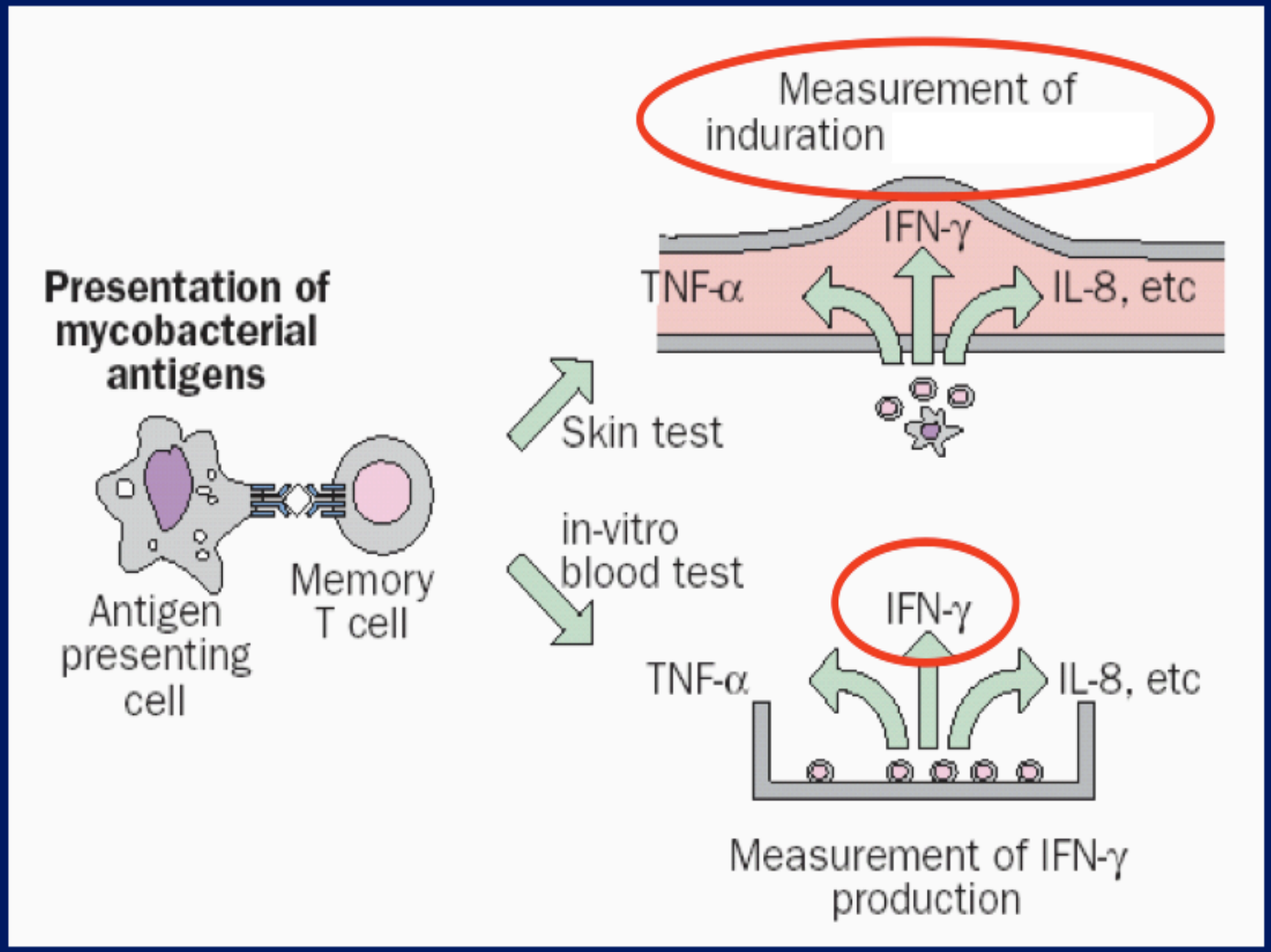
Clinical Correlate

- Tumor necrosis factor (TNF)-α
  - Maintain granuloma compartmentalization
  - Factor in pathogenesis of RA
- TNF blockers reactivate LTBI



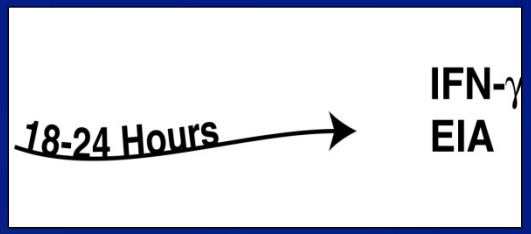
MMWR 2004; 53(30): 683-686

TST Versus In-vitro Assays

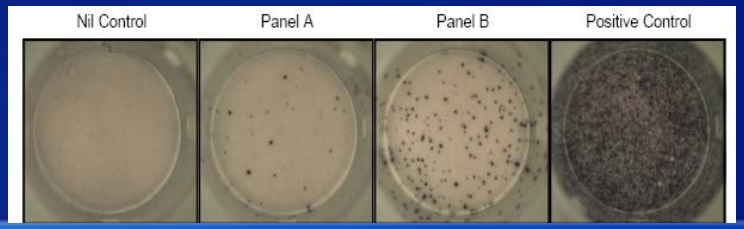


T cell-Based Diagnostics
IFN-gamma Release Assays (IGRA's)

- IFN-g is a pro-inflammatory cytokine released by T cells and NK cells
- Two commercially available tests:
  - QuantiFERON®-TB Gold IT

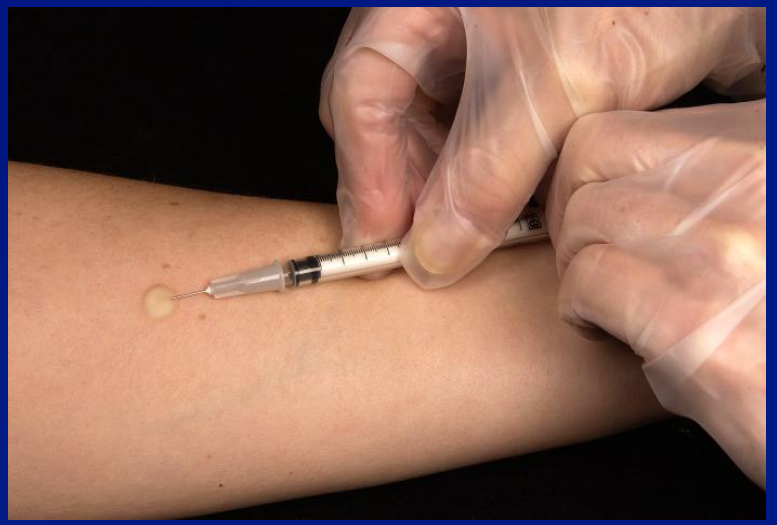


  - T-Spot®.*TB*



Tuberculin skin test

1900



2011

Special Circumstances

Reaction	Causes	At risk	Action
False-positive	NTM BCG	MOTT Vaccinated	Evaluate Assess
False-negative	Anergy Recent Infants	HIV infected < 10 weeks Age <6 mos	No panel Retest Retest

Summary

- *M. tb* is an intracellular organism with several virulence and defense mechanisms
- Host response is mediated especially by the T helper
- Knowing host/organism interactions is useful for developing diagnostic tests and treatment modalities including vaccines

Thank you!


New England TB
Consortium
Connecticut • Maine • Massachusetts • New Hampshire • Rhode Island • Vermont