



# HISTORY

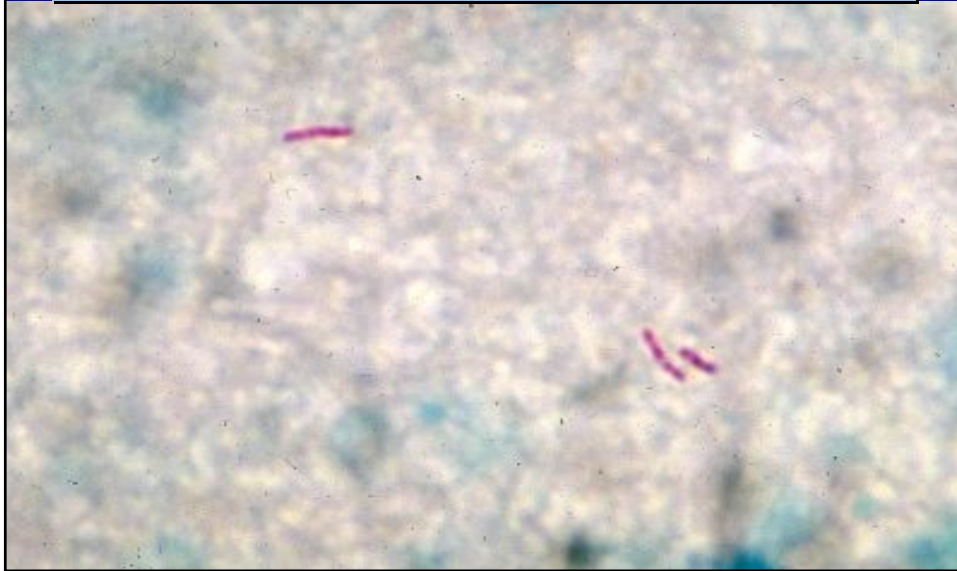
**EGYPTIAN MUMMIES: SPINAL TB**

**17<sup>th</sup>-18<sup>th</sup> CENTURIES- URBANIZATION**

**19<sup>th</sup> CENTURY INDUSTRIALIZATION**

**TB = 25% ADULT DEATHS**

**GERM THEORY OF DISEASE  
KOCH'S BACILLUS-1883**



**PRE-ANTIBIOTIC ERA**

**SANATORIUM REGIMENS & REST  
CAVITARY DISEASE & COLLAPSE  
THERAPY**

**FRESH AIR, SUNSHINE-ROOFTOPS  
SOLARIA**





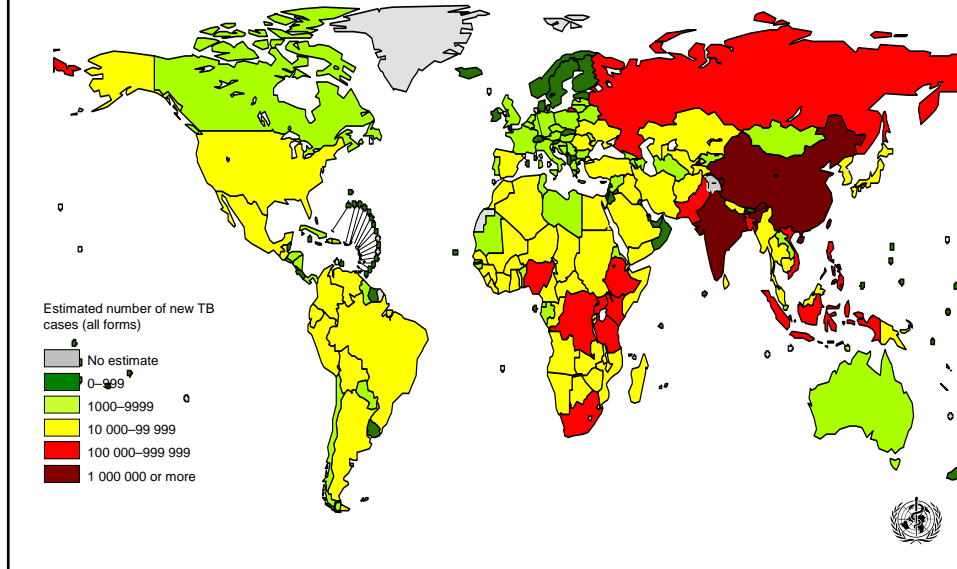
# ANTIBIOTICS

- 1946- STREPTOMYCIN
- RAPID DEVELOPMENT OF FAILURE WITH MONOTHERAPY
- INH =MAGIC BULLET- 1952
- RIFAMPIN & SHORT COURSE RX- 1970

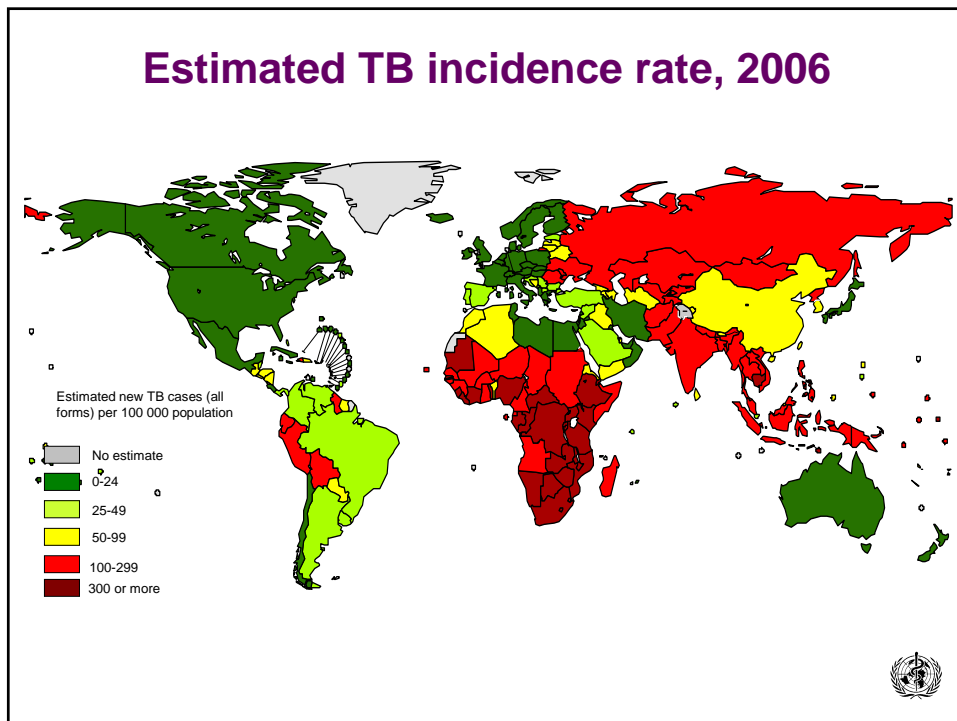
# EPIDEMIOLOGY

- M. TUBERCULOSIS INFECTS 1/3 WORLD'S POPULATION
- 9.2 MILLION NEW TB CASES 2006
- 1.7 MILLION DEATHS 2006
- 2<sup>ND</sup> TO HIV AS CAUSE OF DEATH FROM INFECTIOUS DISEASE
- 14.4 MILLION PREVALENT CASES

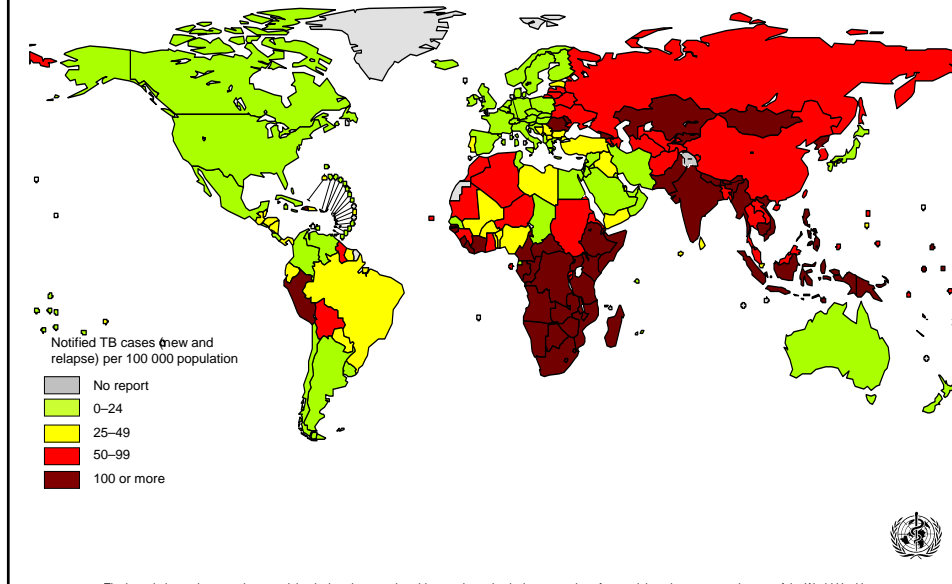
## Estimated numbers of new cases, 2006



## Estimated TB incidence rate, 2006



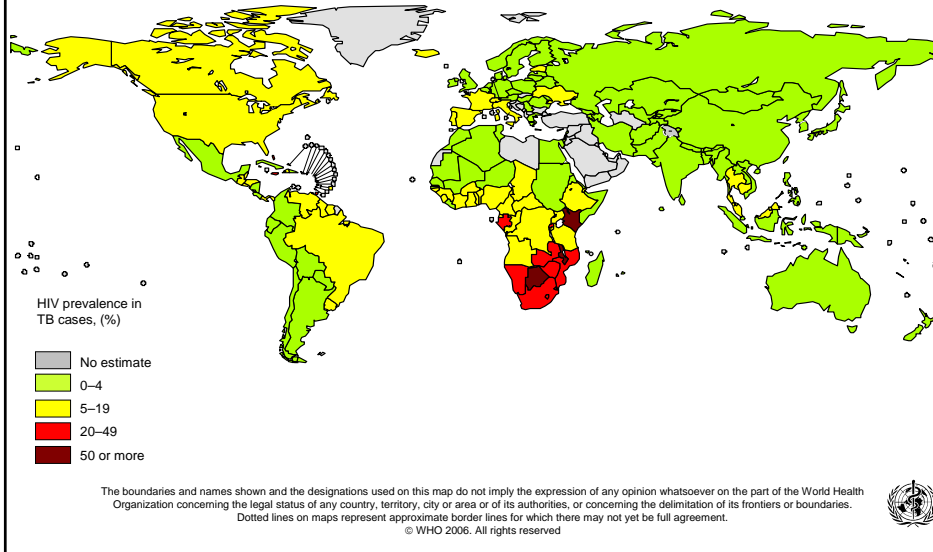
## Tuberculosis notification rates, 2006



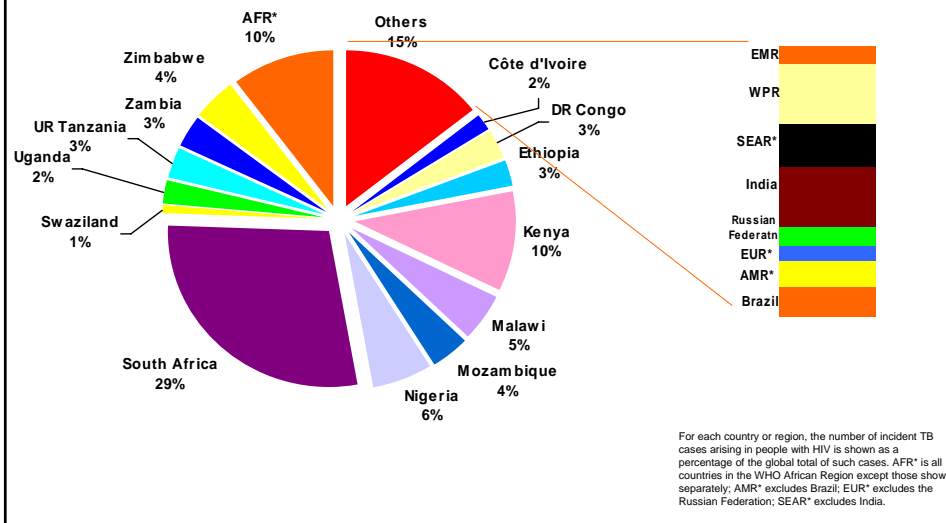
**TABLE 1.2**  
Estimated epidemiological burden of TB, 2006

	POPULATION 1000s	INCIDENCE <sup>a</sup>				PREVALENCE ALL FORMS		MORTALITY ALL FORMS		HIV PREV. IN INCIDENT TB CASES <sup>b</sup>
		ALL FORMS		SMEAR-POSITIVE		NUMBER 1000s	PER 100 000 POP PER YEAR	NUMBER 1000s	PER 100 000 POP PER YEAR	%
		NUMBER 1000s	PER 100 000 POP PER YEAR	NUMBER 1000s	PER 100 000 POP PER YEAR					
1 India	1 151 751	1 933	168	867	75	3 445	299	325	28	1.2
2 China	1 320 864	1 311	99	590	45	2 658	201	201	15	0.3
3 Indonesia	228 864	534	234	240	105	578	253	88	38	0.6
4 South Africa	48 282	454	940	184	382	482	998	105	218	44
5 Nigeria	144 720	450	311	198	137	890	615	117	81	9.6
6 Bangladesh	155 991	351	225	158	101	610	391	70	45	0.0
7 Ethiopia	81 021	306	378	136	168	520	641	68	83	6.3
8 Pakistan	160 943	292	181	131	82	423	263	55	34	0.3
9 Philippines	86 264	248	287	111	129	373	432	39	45	0.1
10 DR Congo	60 644	237	392	105	173	391	645	51	84	9.2
11 Russian Federation	143 221	153	107	68	48	179	125	24	17	3.8
12 Viet Nam	86 206	149	173	66	77	194	225	20	23	5.0
13 Kenya	36 553	141	384	56	153	122	334	26	72	52
14 UR Tanzania	39 459	123	312	53	135	181	459	26	66	18
15 Uganda	29 899	106	355	46	154	168	561	25	84	16
16 Brazil	189 323	94	50	59	31	104	55	7.6	4.0	12
17 Mozambique	20 971	93	443	39	186	131	624	24	117	30
18 Thailand	63 444	90	142	40	62	125	197	13	20	11
19 Myanmar	48 379	83	171	37	76	82	169	6.1	13	2.6
20 Zimbabwe	13 228	74	557	30	227	79	597	17	131	43
21 Cambodia	14 197	71	500	31	220	94	665	13	92	9.6
22 Afghanistan	26 088	42	161	19	73	60	231	8.3	32	0.0
<b>High-burden countries</b>	<b>4 150 313</b>	<b>7 334</b>	<b>177</b>	<b>3 265</b>	<b>79</b>	<b>11 889</b>	<b>286</b>	<b>1 330</b>	<b>32</b>	<b>11</b>

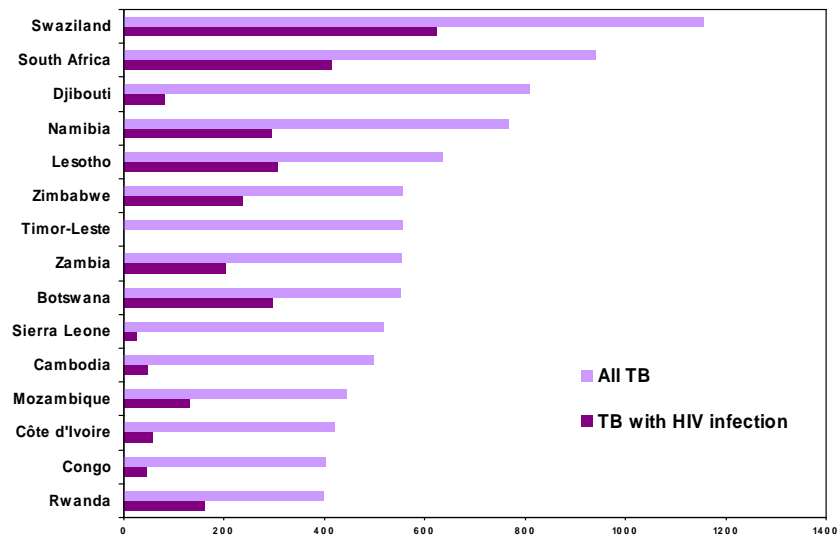
## Estimated HIV prevalence in new TB cases, 2006



## Geographical distribution of HIV-positive TB cases, 2006



**Fifteen countries with the highest estimated TB incidence rates per capita and corresponding incidence rates of HIV-positive TB cases, 2006**



**RIISING INCIDENCE  
WORLDWIDE**

**FAILURE OF PUBLIC HEALTH**

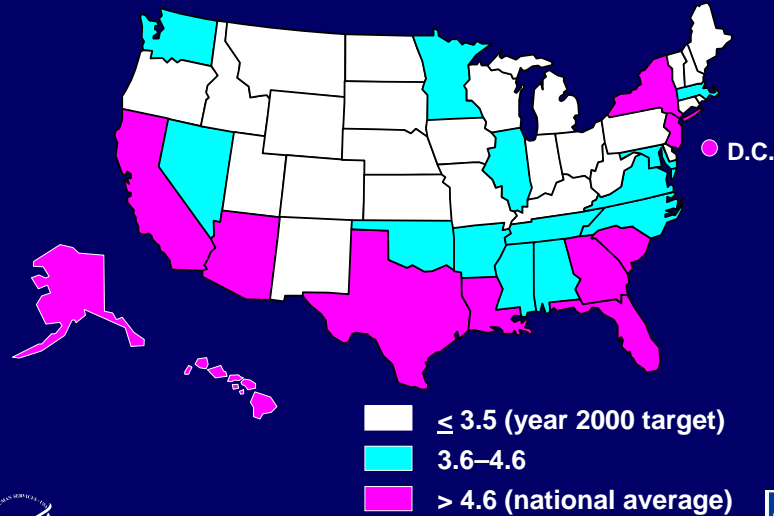
**FAILURE OF POLITICAL WILL**

**RX TO CURE COSTS \$12/PT**

**>95% TB IS IN RESOURCE  
POOR CONTRIES**

**MONEY & INFRASTRUCTURE**

## TB Case Rates,\* United States, 2006



\*Cases per 100,000.



## DEVELOPED WORLD TB

DOWNWARD TREND BEFORE  
ANTIBIOTICS: WHY?

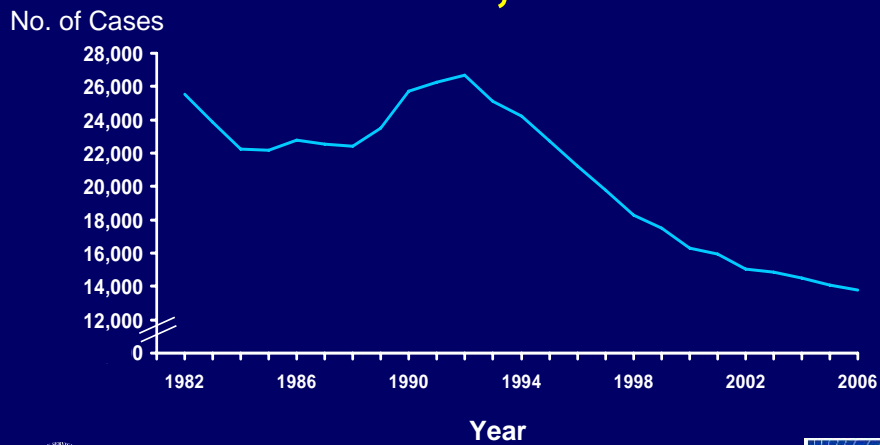
1900-WW2: ANNUAL DECREASE 4-  
6% IN DEVELOPING COUNTRIES

Higher natural resistance

Better living conditions-less crowding

Effect of sanatoriums

# Reported TB Cases\* United States, 1982–2006



\*Updated as of April 6, 2007.



**NEW YORK STRIKE TO CUT CRACK**  
**BIG IMPACT**  
**Highest Trial Measure Power**

By JAMES...  
special...

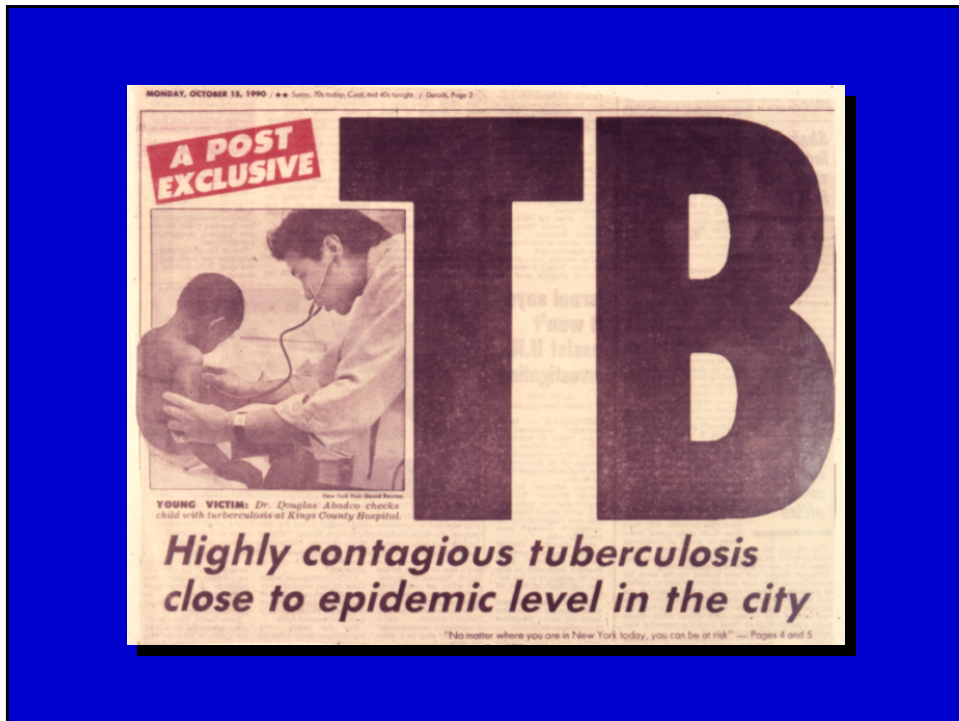
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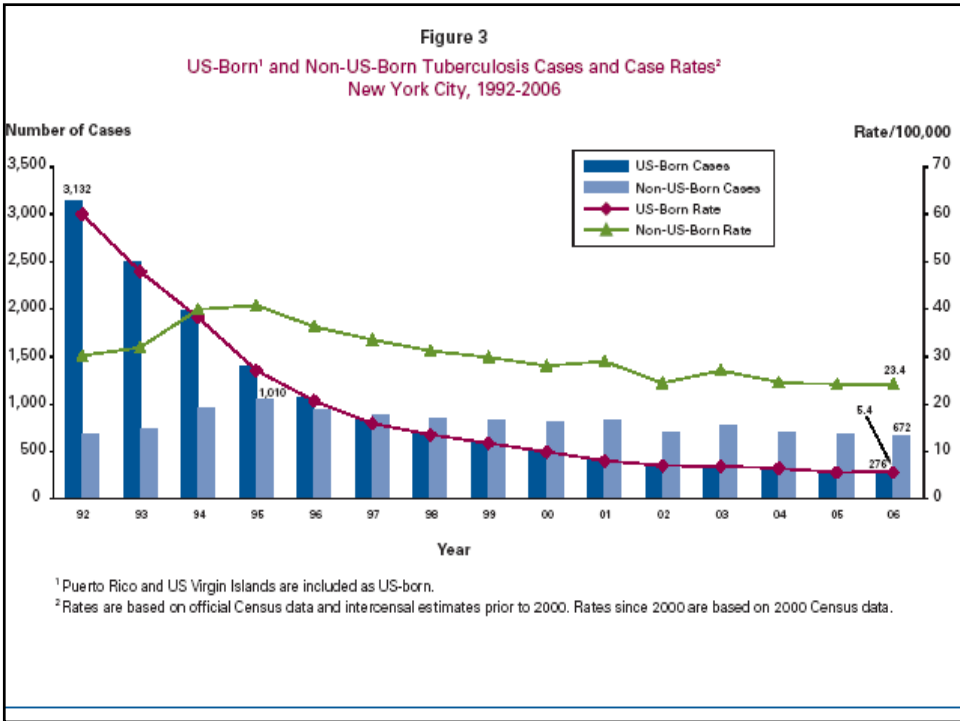
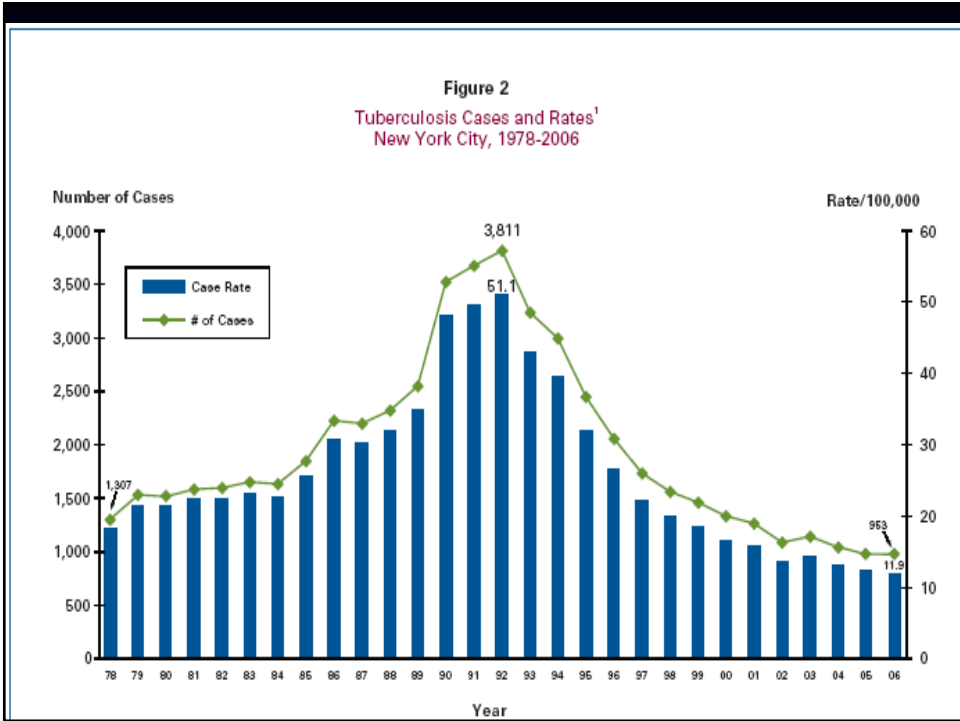
**Crack Use Pervades Life in a Shelter**

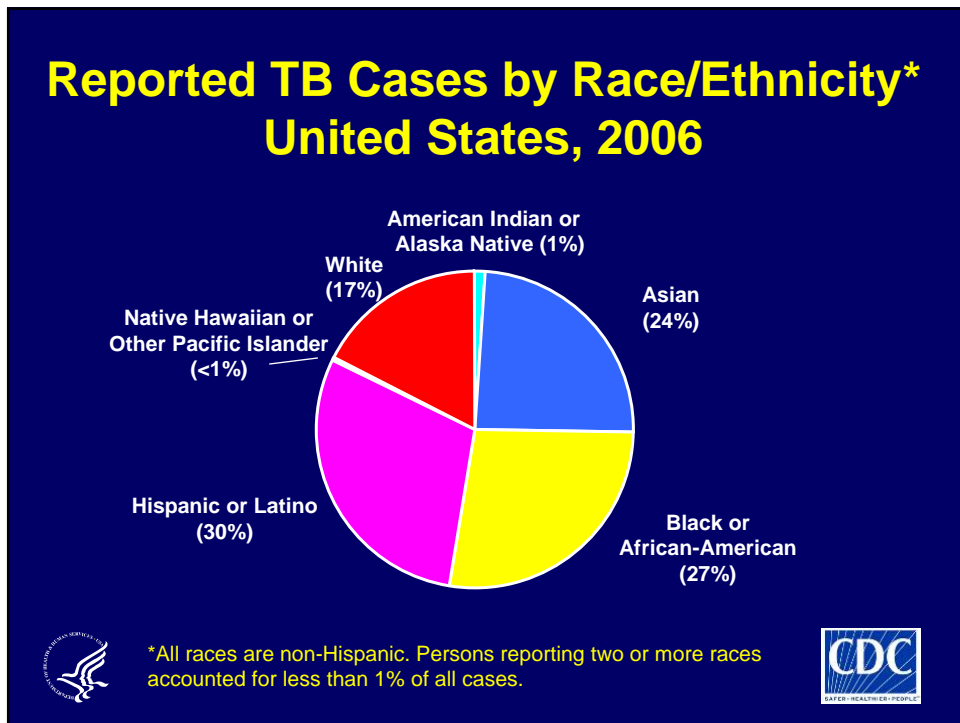
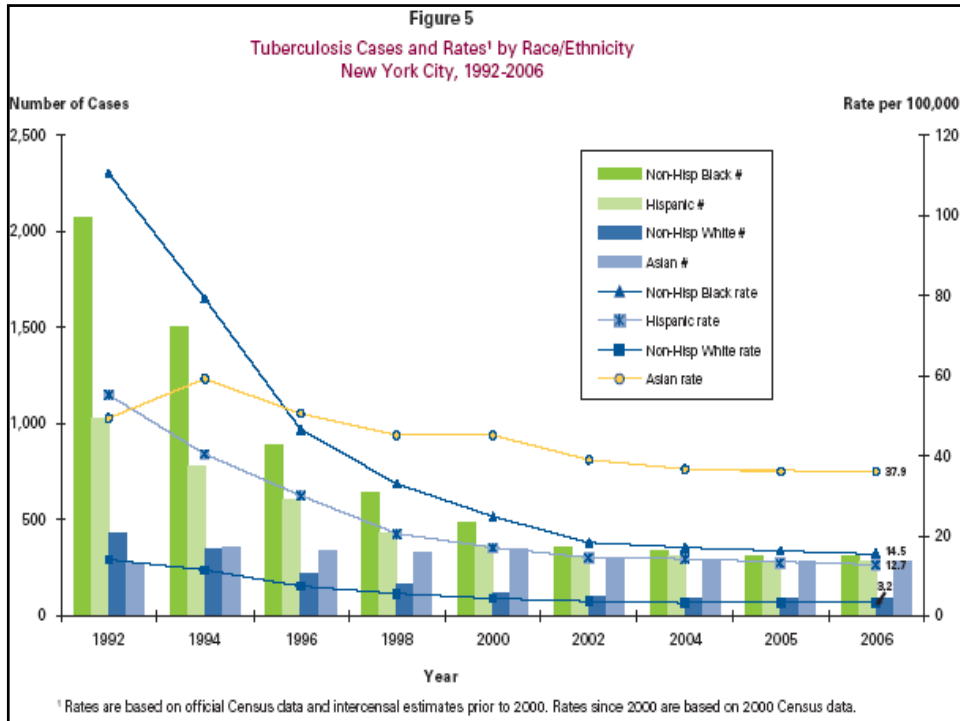
The New York Times - Ruby Washington

Beds for 850 men are set up on the floor of the Fort Washington Armory in upper Manhattan.

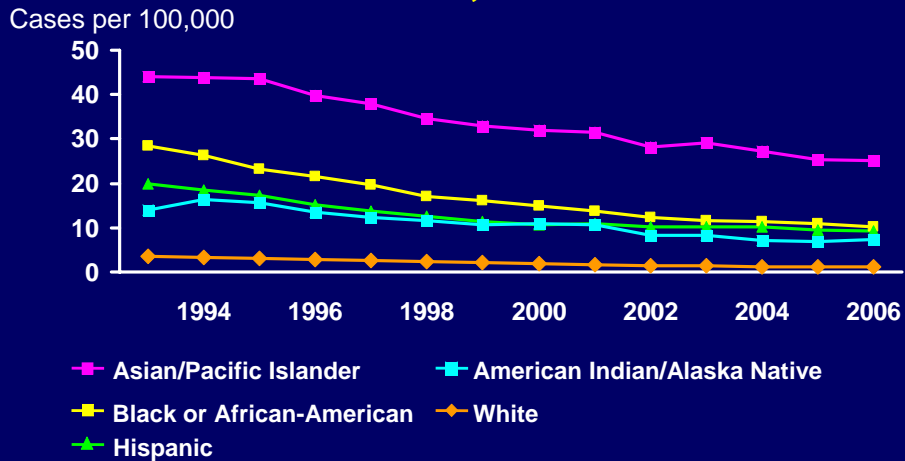
By JOSH BARRANEI







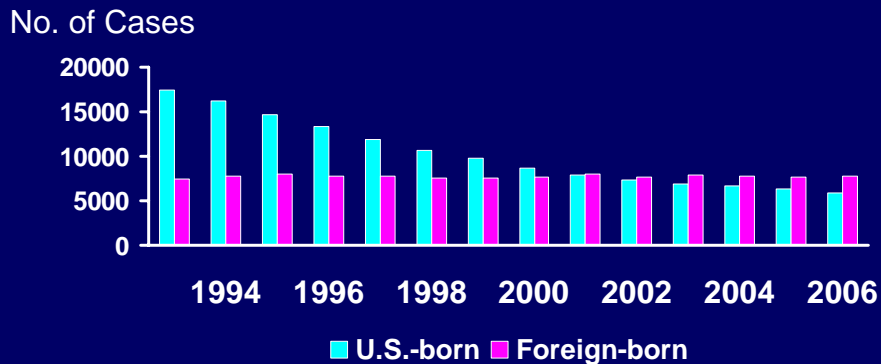
## TB Case Rates by Race/Ethnicity\* United States, 1993–2006\*\*



\*All races are non-Hispanic. In 2003, Asian/Pacific Islander category includes persons who reported race as Asian only and/or Native Hawaiian or Other Pacific Islander only.  
 \*\*Updated as of April 6, 2007.



## Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993–2006\*



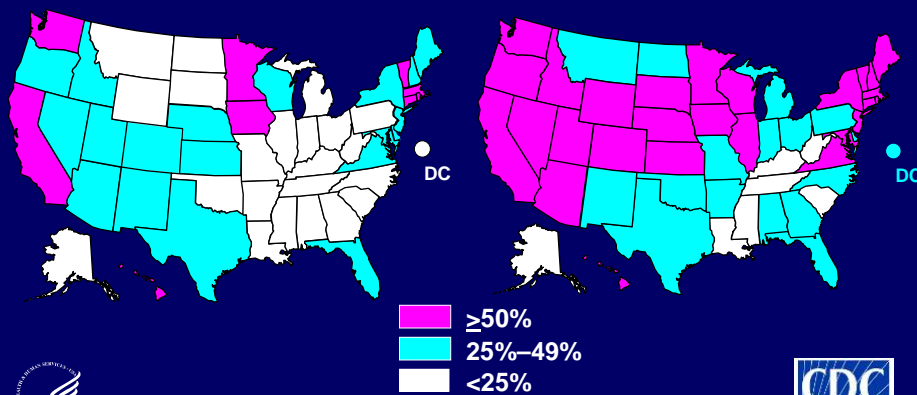
\*Updated as of April 6, 2007.



## Percentage of TB Cases Among Foreign-born Persons, United States\*

1996

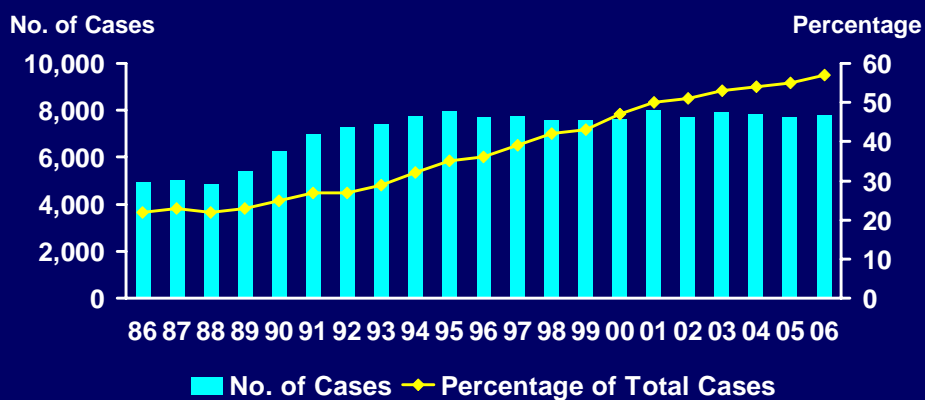
2006



\*Updated as of April 6, 2007.



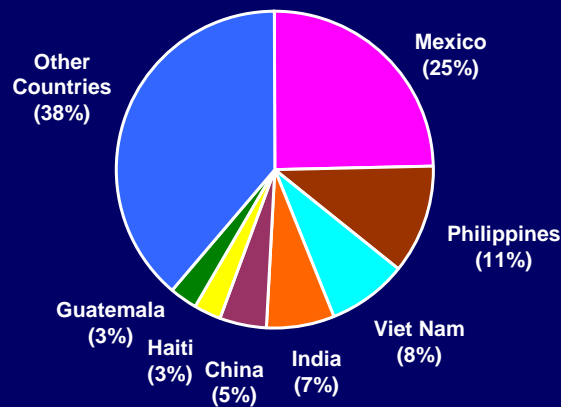
## Trends in TB Cases in Foreign-born Persons, United States, 1986–2006\*



\*Updated as of April 6, 2007.



## Countries of Birth of Foreign-born Persons Reported with TB United States, 2006

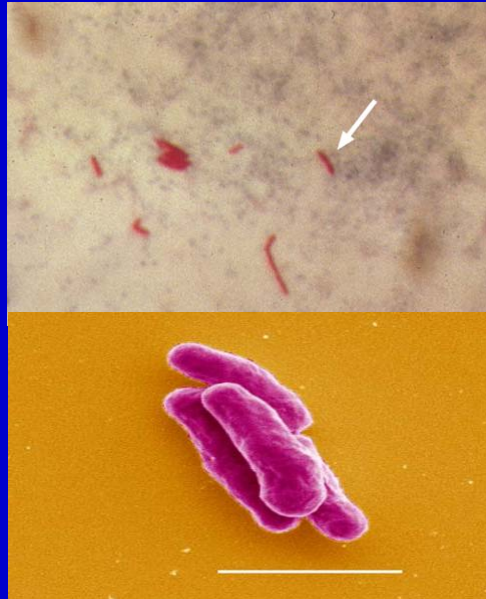


## M. Tuberculosis complex

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*: unpasteurized milk/cheese
- *Mycobacterium africanum & canetti*
- *Mycobacterium microti* : rodents

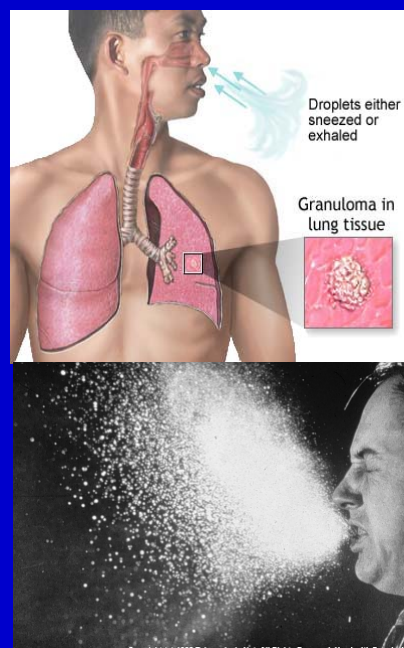
## THE BACILLUS

- CELL WALL CONTENT=LIPIDS
- SLOW GROWTH:
- 20 hours vs. 20 minutes for E.Coli
- Length of RX



## TRANSMISSION

- Lungs=entry portal
- Inhalation of droplet nuclei
- Coughing: 3000 droplet nuclei/cough
- Talking: 5 minutes
- Sneezing: BEST



## TRANSMISSION ENHANCERS

### INOCULUM SIZE:

- AUTOPSY SUITE TRANSMISSIONS

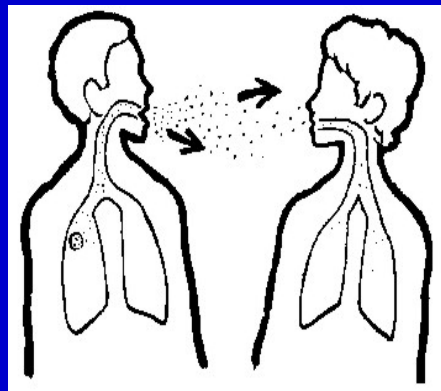
### STRAIN VARIABILITY/VIRULENCE:

- KENTUCKY OUTBREAK

### VENTILATION: BACILLUS LONGEVITY & INFECTIVITY IN AIR

### Primary Infection: BEFORE IMMUNE RESPONSE

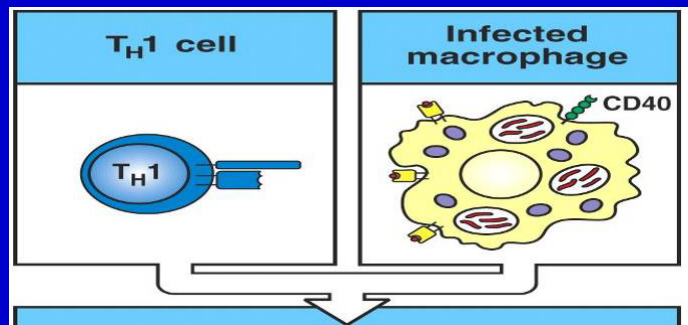
- TB reaches alveoli
- Replicates extracellularly and intracellularly
- Lack of immediate host immune response



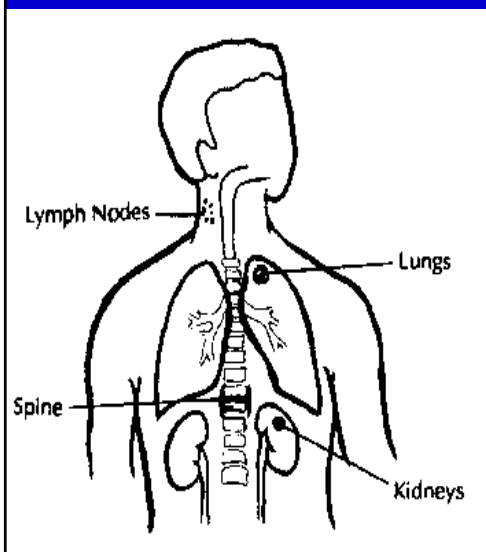
## REPLICATION

- Intracellularly=within alveolar macrophage
- MTB prevents acidification of phagosome
- MTB multiplies for weeks in alveolar macrophages

AND



## DISSEMINATION



- Metastatic foci established in regional nodes
- Seed blood
- Travel to tissues favoring multiplication

## Development of Immune Response: 6-12 weeks

- Alveolar macrophage infected with TB secretes Interleukins 12 & 18
- These attract CD 4 cells
- CD 4 cells meet TB antigen macrophage presents to them
- Transformation of CD 4 cells

## TRANSFORMED CD 4 CELLS:

- **PROLIFERATE:** production of clones of similarly reactive CD 4 cells
- **CUTANEOUS HYPERSENSITIVITY:** big enough population of transformed CD4 allows delayed rxn to tuberculin
- **RELEASE INTERFERON GAMMA**

## INTERFERON GAMMA

- CD4 cells release interferon gamma
- Interferon gamma stimulates additional macrophage phagocytosis of *M. tuberculosis*
- Interferon gamma stimulates macrophage to release tumor necrosis factor alpha (TNF Alpha)

## Tumor Necrosis Alpha (TNF alpha)

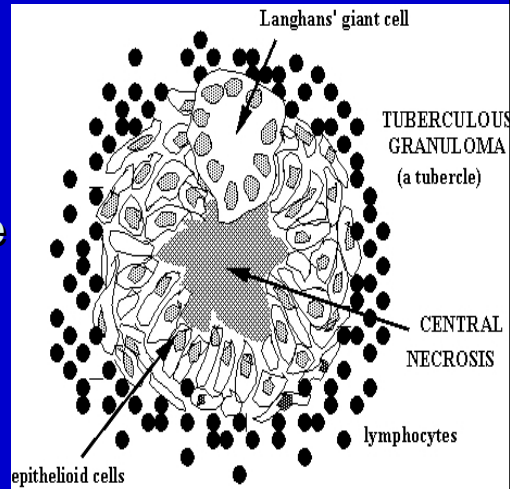
- TNF alpha increases macrophage ability to kill *M. tuberculosis*
- TNF alpha required for granuloma formation
- Granulomas sequester mycobacteria and prevent uncontrolled dissemination

## PATHOLOGY OF A GRANULOMA

Macrophages secrete lytic enzymes which cause tissue necrosis

Epithelioid cell=highly stimulated macrophage

Langhans Giant Cell=fused macrophages with multiple nuclei

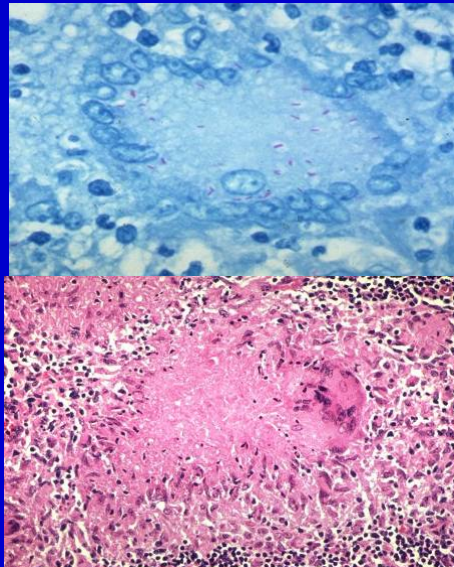


## GRANULOMA = SUCCESSFUL TISSUE REACTION & HEALING

Small antigen load & high hypersensitivity= **Epithelioid cells, giant cells etc.**

Large antigen load & high hypersensitivity= **Necrosis & Caseation**

Small or large antigen load & no hypersensitivity=few cells  
**No granuloma & huge #s of bacilli: AIDS patients**



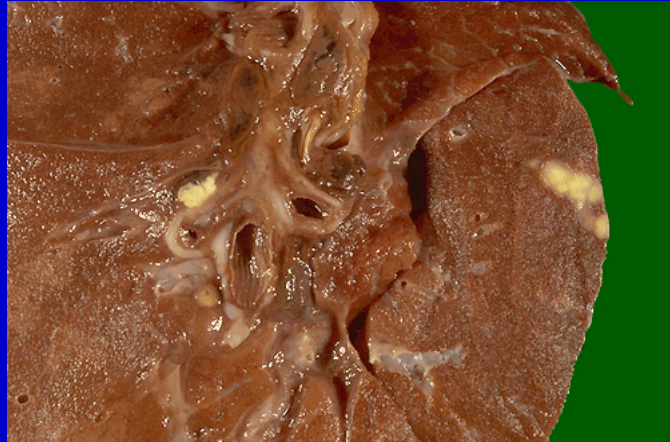
## Lack of TNF Alpha

- Murine experiments:
  - Blockade of TNF alpha resulted in reactivation, high bacillary burden, persistent tuberculosis and death
  - TNF alpha knock-out mice infected with *M. tuberculosis* followed similar course

## Primary Infection with Resolution: 85% of Cases

- **Patient asymptomatic/viral syndrome**
- **Enlargement of hilar/ peri-bronchial nodes**
- **Ghon complex: hilar node calcification**
- **Positive PPD 6-12 weeks**





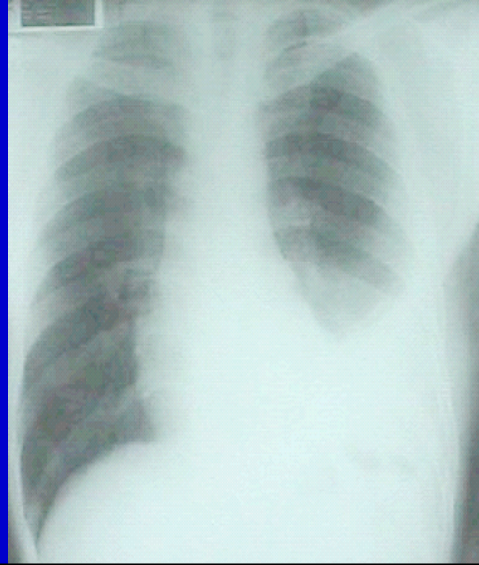
## Primary Infection with Progression

### Progressive Primary Disease

- Young children <5- cannot resolve initial infection :Progression to active disease, miliary or disseminated, CNS involvement
- Almost always developing world where TB is endemic

## TUBERCULOUS PLEURISY

- **HYPERSENSITIVITY REACTION**
- **EXUDATIVE PLEURAL EFFUSION**
- **CULTURE NEGATIVE- FEW BACILLI**
- **WW II STUDIES: 65% RELAPSE TO ACTIVE TB IF UNTREATED**



## PRIMARY INFECTION- ADOLESCENCE/YOUNG ADULTS

**Develop cavitory disease:**

**23% age 15-19**

**13% age 20-24**

**4% 25-29**

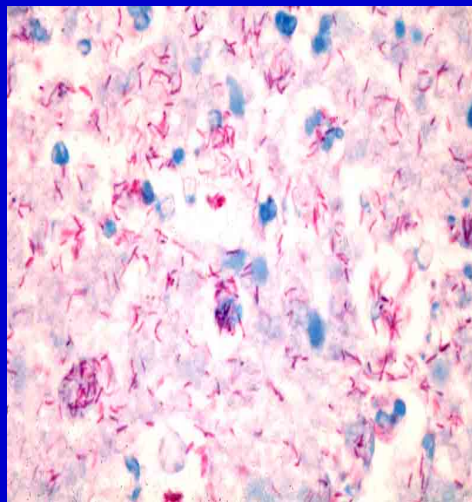


## PRIMARY INFECTION: AIDS NOSOCOMIAL OUTBREAKS

- Multiple nosocomial outbreaks of TB in AIDS wards, homeless shelters and prisons in late 1980s-1990s
- Undiagnosed patient with active TB in AIDS ward where all patients CD4<50
- No CD4s to mobilize so no interferon gamma & no macrophages stimulated to phagocytose or secrete interferon gamma

## OVERWHELMING TB

- **No immunologic control of bacillus**
- **Rapid dissemination**
- **MDR strains killed scores in AIDS wards**



Reactivation: 10-15% of those infected

- **Persistence of viable organisms**
- **Containment of infection, lack of active disease**
- **Viable organisms remain alive, dormant for years**
- **Disease occurs when cellular immune system can no longer contain MTB**

## CAUSES OF REACTIVATION

- **Iatrogenic immunosuppression**  
– Transplant; Rheumatologic Rx
- **Immunocompromising diseases**
- **Malnutrition**
- **Old Age**
- **Unknown: ?hormonal ?stress**

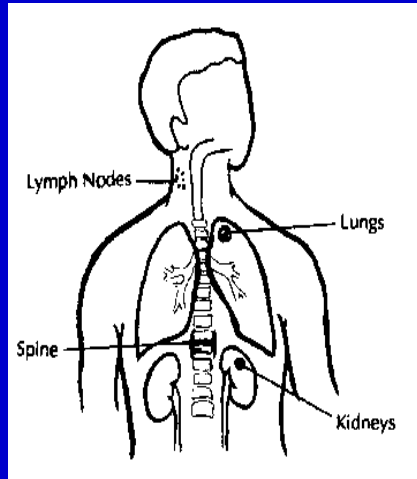
## 85% Reactivation=Lungs

- **Caseating necrosis, liquefaction, drainage into the bronchial tree**
- **Cavity formation**



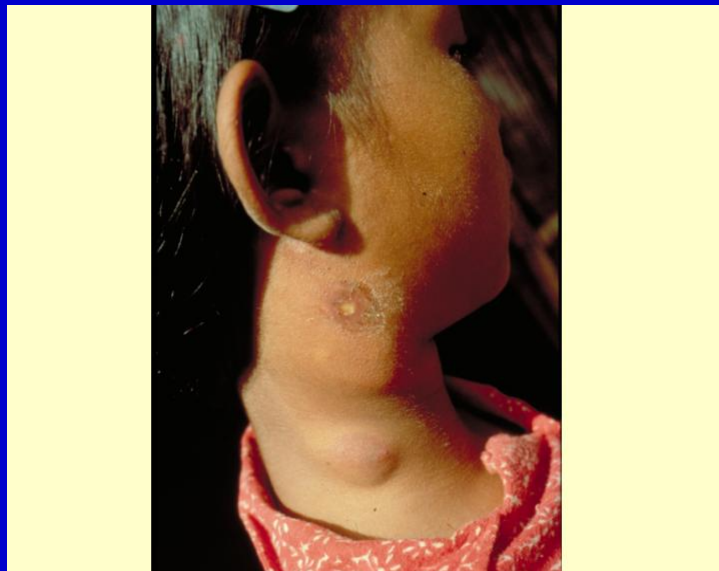
- **Cavity favors bacillary multiplication to huge #s:  $10^9$ - $10^{10}$  organisms / GM tissue**
- **5-6 logs greater than # organisms in non-cavitary disease= MOST CONTAGIOUS**
- **Implications for development of drug resistance**

## EXTRAPULMONARY TB



- Viable organisms remain alive for years
- Most common organs to which disseminated during primary infection

## LYMPH NODES: SCROFULA Most frequent form of extrapulmonary TB



Usually Cervical



Or Supraclavicular



Can also be axillary



## BONES

- **ONE THIRD INVOLVE SPINE From:**
- **Hematogenous spread from initial infection**
- **Lymphatic spread from pleural disease**
- **Contiguous disease**



## POTTS DISEASE

- Earliest focus:  
Anterior superior or  
inferior angle of  
vertebral body
- Spreads to  
intervertebral disk  
& adjacent  
vertebra



## RENAL TUBERCULOSIS

- HEMATOGENOUS SPREAD  
AFTER PRIMARY INFECTION  
SEEDS GLOMERULI & FORMS  
GRANULOMAS
- LATER, CASEOUS NECROSIS,  
FIBROSIS & CALCIFICATION
- ASYMPTOMATIC UNTIL  
CALYX/PELVIS ULCERATED
- STERILE PYURIA: MUST SEND  
FOR MTB CULTURE
- USUALLY EVIDENCE OF  
PULMONARY TB PRESENT
- 25% MILIARY HAVE POSITIVE  
URINE CULTURE FOR MTB

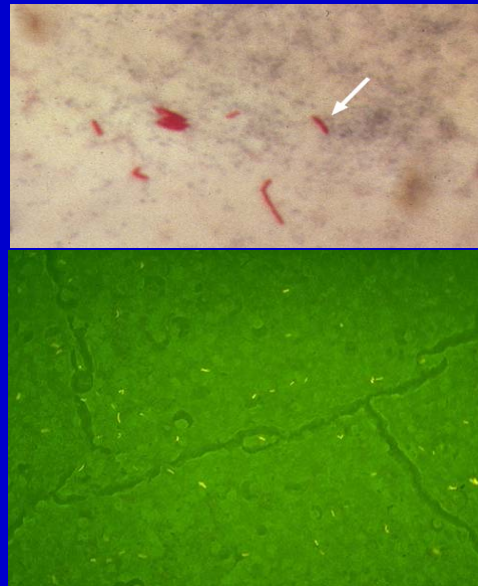


## Diagnosis: Symptoms

- Systemic symptoms non-specific: fever, fatigue, night sweats, weight loss
- Pulmonary symptoms: cough, productive or dry
- Hemoptysis: can be emergency
  - Suggests bronchial wall erosion

## DIAGNOSTIC PROCEDURES

- **SPUTUM SMEAR:**
  - Acid fast=all mycobacterial species
  - Ziehl-Neelsen stain
  - Auramine
  - **SMEAR POSITIVE MEANS AT LEAST 10,000 ORGS/ML**



## CULTURE=GOLD STANDARD

Available in most of world  
in WHO reference labs

**SOLID MEDIA=Slow growth**  
=3-8 weeks; Lowenstein  
Jensen (LJ slant) =egg  
based or Middlebrook  
7H11=agar based

**LIQUID MEDIA=Rapid growth**  
= 1-3 weeks; Middlebrook  
7H12



## CULTURE CONT'D

- **LIQUID: RAPID GROWTH:**  
1-3 weeks in Middlebrook 7H12  
broth media
- **IDENTIFICATION FROM CULTURE**
  - DNA PROBES – **MTB complex,**  
***M.avium complex, M. kansasii, M.***  
***gordonae***
  - **BIOCHEMICAL TESTS** – Niacin,  
Nitrate, Catalase, etc. to identify  
other mycobacteria



## WHAT IS MTB COMPLEX?

*M. tuberculosis* Complex (MTBC) can include:

- *M. tuberculosis*
- *M. bovis*, *M. bovis* BCG
- *M. africanum*
- *M. microti*
- *M. canetti*

## BIOCHEMICAL TESTS NECESSARY TO DISTINGUISH THESE

***M. bovis* ALMOST ALWAYS RESISTANT TO PYRAZINAMIDE**

Nucleic Acid Amplification:  
Can detect MTB in fresh sputum

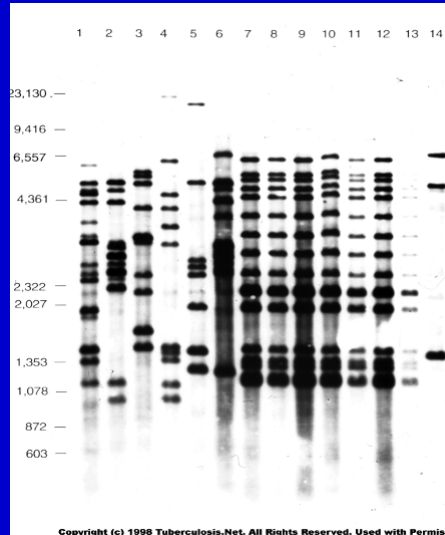
- Sensitivity intermediate between acid fast smear and culture
- AFB smear negative, nucleic acid amplification=40-77% sensitive
- AFB smear positive, nucleic acid amplification=95% sensitive & 100% specific
- **LUXURY OF DEVELOPED WORLD**

## RFLP=Restriction fragment Length Polymorphism

Restriction endonuclease makes DNA fragments

Separate fragments by electrophoresis

IS 6110 as DNA probe=  
Insertion sequence occurring repeatedly at highly variable locations on MTB chromosome



## DNA FINGERPRINTING

- MOLECULAR EPIDEMIOLOGIC TOOL TO IDENTIFY DIFFERENT TB STRAINS
- FIRST USED BY DUTCH IN EARLY 1990S TO QUANTIFY SOURCE OF LOCAL TB STRAINS
- USED TO IDENTIFY NOSOCOMIAL OUTBREAKS IN AIDS WARDS, SHELTERS
- LUXURY OF DEVELOPED WORLD

## Chest X-Ray

- Upper lobe infiltrate with or without cavity
- Hilar adenopathy with or without infiltrates
- Pleural effusion, exudative
- Lower lobe infiltrate
- Miliary pattern

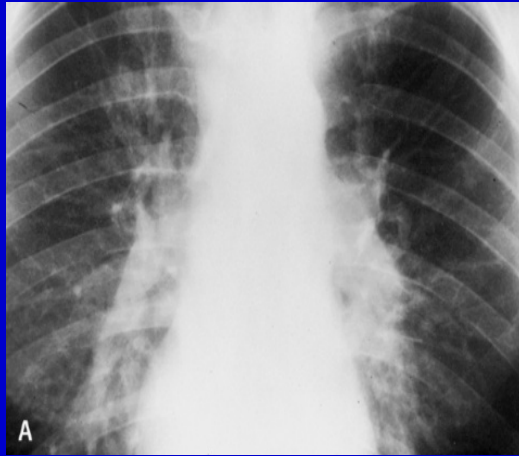
## UPPER LOBE INFILTRATE



- Apical or sub-apical
- Most common in reactivation disease if immune system intact
- Radiologic extent of disease reflects tissue damage
- Tissue damage reflects host's ability to have hypersensitivity reaction

## HILAR ADENOPATHY

- Most common chest X-ray in patients with AIDS (CD4 <200)
- Reflects minimal cellular immune response



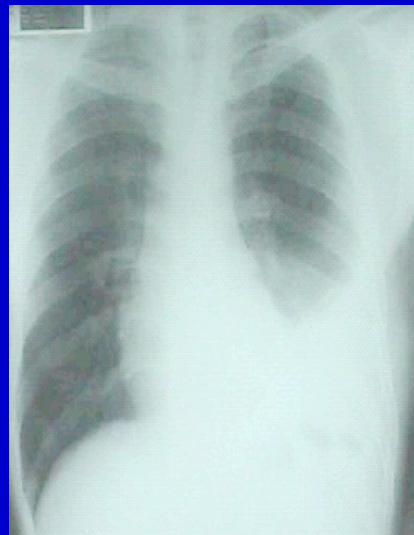
## PLEURAL EFFUSION

Seen in post-primary as above: scant orgs

Smear negative but culture positive 25%

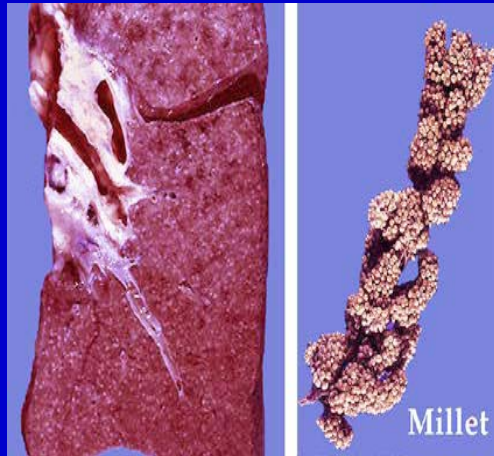
Seen as complication of reactivation TB: more likely to have orgs

Smear positive 50% & culture positive 60-70%



## MILIARY PATTERN

- From description of pathologic lesions as “millet seeds”
- Chest x-ray shows 0.5-1.0 mm nodules



## MILIARY PATTERN

**Following childhood infection and progression**

**Immunocompromising diseases:**

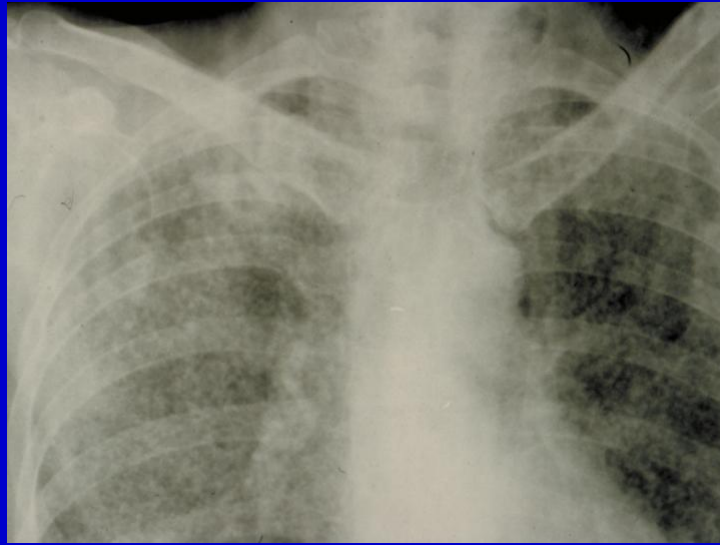
-alcoholism

-cirrhosis

-rheumatologic diseases

-Rx with immunosuppressive





## DIAGNOSIS DIFFICULT

- May have multiple organ involvement
- Millet seed granulomas in tissue
- Transbronchial biopsy=highest yield for diagnosis



## TREATMENT: GENERAL PRINCIPLES

- ALWAYS USE AT LEAST 2 DRUGS:
  - Begin with 4 pending sensitivities
  - Natural incidence of spontaneous resistance to any 1 drug= 1 in 10,000 organisms
  - Bacilli resistant to 1 will be killed by others
  - Natural resistance to 2 drugs spontaneously= 1 in  $10^{10}$
- Prolonged Length of Rx: 6-9 months
- **D**irectly **O**bserved **T**herapy

## Prophylaxis: LTBI

**Targeted Testing: PPD is NOT a general screen**

### Immunocompromised patients:

- HIV infected, chemotherapy, organ transplant, immunosuppressive RX for autoimmune diseases
- Close contacts of infectious cases
- Previously untreated patients with Chest x-ray evidence of old disease (NOT just granuloma)
- Recent Immigrants (in US <5 years)
- People who work in high exposure institutions

## POSITIVE PPD: DEFINITION

- 5 mm: HIV infected, close contacts of infectious cases, Chest XRay evidence of old disease
- 10 mm: everyone else



## ELISPOT (Enzyme-linked immunospot)

- T-cell based assay from blood: Need 1 tube of blood
- *M. tuberculosis* genes NOT present in *M. bovis BCG*
- Early secretory antigen target-6 (ESAT-6)=gene product specifically produced by *M.tuberculosis* and not by *M. bovis BCG* or any other mycobacteria

## Will this replace PPD?

- T cells specifically target this antigen (ESAT-6) and can be detected by ELISPOT obtaining 1 tube of blood
- TB outbreak in high school in UK showed ELISPOT higher sensitivity and specificity than PPD skin test
- Licensed & available as Quantiferon Gold but discordance with PPD in numerous studies; significance not yet clear

### **BOX 4. Conditions requiring caution in interpreting negative QuantiFERON®-TB Gold test results**

- Human immunodeficiency virus infection or acquired immunodeficiency syndrome
- Immunosuppressive drugs, including those used for managing organ transplantation
- TNF\* $\alpha$
- Diabetes mellitus
- Silicosis
- Chronic renal failure
- Certain hematological disorders (e.g., leukemias and lymphomas)
- Other specific malignancies (e.g., carcinoma of the head, neck, or lung)

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\* Tumor necrosis factor.

## BCG: Most Widely Used and Most Controversial Vaccine in World

- **M. Bovis strain attenuated through serial passage no standardized strain or procedure to make one largest study: India = no protection from TB infection other studies: England = protection from TB infection prevalence of non-TB mycobacteria may interfere**
- **All agree: highly effective for infants & small children against dissemination & meningitis**

## BCG Used in Countries Where TB Endemic

- BCG may be indicated for infants and small children continuously exposed to MDR patient
- BCG at birth should not give positive PPD as adult
- Boosting: 2 step testing for all those with BCG

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