TUBERCULOSIS

GENERAL

Tuberculosis (TB) kills 1,700,000 annually worldwide.

"The Captain of all the men of death that came to take him away was the consumption, for it was that which brought him down to the grave."
John Bunyan, 1680

Famous victims in their intellectual prime:
Chopin, Paganini, Thoreau, Keats, Elizabeth Browning, Brontës

One-third of the world's population have been infected.

Synergy with the HIV/AIDS pandemic.

Mounting problems with multi-drug resistant tuberculosis (MDRTB)

Before antibiotics, the case-fatality rates for tuberculosis were 40% - 60%.

30 million active cases of disease.
8 million new cases of tuberculosis appear each year.
95% are in developing countries.
5% are in industrialized countries.
Highest incidence in Africa.

Factors contributing to spread include
Ignorance
Poverty
Overcrowding
Poor hygiene
War and economic depressions

No useful serologic test for TB.
New T-cell assays promising.

Two closely related agents cause similar disease.
Mycobacterium tuberculosis (lung)
Mycobacterium bovis (gut)

CLINICAL FEATURES

TB is a slow progressive disease.
The organism elicits a granulomatous response.
Characterized by high infectivity and low virulence.

Two patterns of disease
- Primary tuberculosis
- Reactivation tuberculosis

Primary TB
- Usually pulmonary (starts at periphery or mid-zone of lung)
- Tubercle bacilli in alveoli are engulfed by macrophages.
- Macrophages carry infection to hilar lymph nodes.
- Multiplication of bacilli proceeds with a minor inflammatory reaction.
- Bacilli may travel to other tissues via lymphatic circulation.
  - Liver
  - Spleen
  - Kidney
  - Bone
  - Brain and meninges
  - Lung apices

- Symptoms are usually absent to minimal (mild flu-like illness).
- Cell-mediated immunity develops after 2 - 6 weeks of infection.
- Formation of microscopic granulomas
  - Multi-nucleated giant cells and cell necrosis (central area)
  - Lymphocytes (peripheral area)

- Most primary infections are controlled by host immune response
  - Mycobacterial multiplication stops in the granulomas
  - Most organisms slowly die
  - Granulomas scar (fibrosis) and calcify
  - In some granulomas, mycobacteria can remain viable for years
  - Basis for reactivation

- 5% of primary infections progress
  - Dissemination with active milliary disease
  - Necrotic tubercle eroding into small blood vessel

Reactivation TB

- ~10% develop reactivation sometime during lifetime.
- In Western countries, usually occurs after age 50 years.
- In developing countries, less defined age pattern.
- Reactivation increases with
  - Malnutrition
  - Alcoholism
  - Diabetes
  - Older age
  - Severe stress (loss of spouse)
  - HIV/AIDS (reactivation rate increased by 200 - 300 fold)

- Reactivation site
  - Often in the lung apex
  - Higher oxygen concentration
  - Less blood perfusion
  - Less lymphatic drainage

- Lesions are slow spreading
  - Coalescing tubercles
  - Enlarging region of tissue necrosis
  - Small blood vessels eroded (blood in sputum)
  - Pulmonary cavities

- Symptoms or reactivation
  - Chronic fevers
  - Weight loss
  - Night sweats
  - Productive coughs with blood

- Dissemination to other organs (especially with HIV/AIDS patients)
  - Kidneys
  - Bones
  - Lymph nodes
  - Brain and meninges
  - Bone marrow
  - Bowel

EPIDEMIOLOGY

Transmission modes

- #1 Respiratory (breathing droplet nuclei)
- #2 Gastrointestinal (eating contaminated milk or meat)
- #3 Skin (direct contact)

TB's ID-50 is undefined

- Infection is a stochastic process
- Single cough produces 1,000,000 infectious droplet nuclei
- No clear threshold of organisms required to produce infection.

Factors for acquiring infection

- Number of bacilli in sputum
- Frequency and efficiency of coughs
- Closeness of contact
- Degree of ventilation in contact area

Industrialized countries

- 80% of cases are in people ≥50 years
- Most cases are due to reactivation.
- Few cases are due to recent exposure.

Developing countries

- Infection involves all age groups.
- 75% of cases are in people <50 years
- 80% of impact on economically productive years.
- 26% of avoidable deaths.

Age < 15 years

- 1,300,000 cases
- 450,000 deaths

Epidemiological patterns of tuberculosis
Annual Risk of Infection

Area	Current level (%)	Annual decline (%)	Health Resources
Industrialized	0.1 - 0.01	>10	Excellent
Middle Income Latin America West Asia North Africa	0.5 - 1.5	5 - 10	Good
Middle Income East Asia South East Asia	1.0 - 2.5	< 5	Good
Low Income Sub-Saharan Africa Indian Subcontinent	1.0 - 2.5	0 - 3	Poor

United States (Case Study)

Early 1980 PPD-positive
- 5% overall population
- 1% children
- Higher among nonwhite and urban poor
- Most cases were in people ≥50 years (reactivation)
- Steady decline stopped in 1985

From 1985 - 1992
- 20% increase in active cases attributed to
- Immigrants
- Intravenous drug users
  - 6 - 7% annual conversion rates
- HIV/AIDS cases
  - Reactivation rates increased by 200 - 300 fold
  - 8% annual reactivation rate
- Single-source outbreaks
  - Classrooms
  - Homeless shelters
  - Nursing homes
  - Hospitals
  - Prisons

Impact of HIV infection
- Increases risk of reactivation disease
- Increases risk of disseminated infection

Worldwide Comparisons

In 1992
- 10 - 12 million HIV infected adults worldwide
- 3.0 million HIV/TB co-infections worldwide.
- 2.4 million HIV/TB co-infections in Sub-Saharan Africa alone.

In 2000
- 30 - 50 million HIV infected adults worldwide
- 75% of HIV transmissions occurring where TB is common

PATHOGEN'S FEATURES

Characteristics

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*
- Gram positive bacilli
- Slim rod-shaped organism
  - 0.2 - 0.4 um diameter
  - 2 - 10 um length
- Non-motile
- Does not form spores
- Strictly aerobic
- Does not produce exotoxin or endotoxin

- Slow growing at 37C
- Does not grow at room temperature
- Mean generation time of 12 - 24 hours
- Colonies appear after 3 - 6 weeks of incubation
- Organisms require rich media
- Growth enhanced by 5 - 10% CO2
- Heat sensitive (killed by pasteurization at 30 minute and 62C)

Cell Wall

- Unique glycoprotein
  - N-glycolymuramic acid
  - Most bacteria contain N-acetylmuramic acid
- Hydrophobic cell wall
  - 60% lipid content
  - Causes bacteria to clump which inhibits permeability of nutrients
  - Grows more slowly than most other human pathogenic bacteria
- Acid-fast and alcohol-fast bacilli (AFB)
  - Difficult to stain but once stained difficult to decolorize
  - Cell wall resists decolorization with 3% HCl and 95% ETOH
  - Distinguishing feature of Mycobacteria

Pathogenicity

- No single virulence gene has been identified.
- The basis for virulence is not clear.
- Disease results from delayed-type hypersensitivity reactions to proteins
- Purified protein derivative (PPD)

Immunity
- Differences in immunity reflect extent of exposure of forebears
- Recently exposed populations
  - Native Americans and Eskimos
  - Higher morbidity
  - Higher mortality

Diagnosis
- Clinical symptoms
- Chest X-rays
- Skin tests
- Sputum smears
- Cultures

Delayed-type hypersensitivity to proteins
- Purified protein derivative (PPD)
- Score reactions 48 - 72 hours later

- Positive PPD
  - Indicates prior exposure and immune reaction
  - *Mycobacterium tuberculosis*
  - *Mycobacterium bovis*

- Negative PPD
  - No previous exposures
  - Pre-hypersensitive stage of infection
  - Loss of sensitivity over time
  - Loss of sensitivity (anergy)
    - AIDS
    - Steroids or immune suppressive drugs
    - Measles

T-cell-based assays (ELISPOT)
- Some promise

Smears
- Sputum: 65% culture-positive samples are smear-positive
- Contamination by other mycobacteria may yield false-positive results
- PCR probes are being developed and used but are expensive.

Cultures

- Typical samples include
  - Cerebrospinal fluid
  - Bone marrow
  - Pleural fluid
  - Sputum

- Treat with (alkali, acid, detergents) to kill normal flora but not TB
  - Solid media requires 3 weeks or longer to show visible colonies
  - Liquid media cuts detection times in half (14C-labeled palmitic acid)

- Biochemical tests — identify the specific organism
  - DNA/RNA probes
  - Gas chromatography

- Drug susceptibility tests require 1 - 2 weeks

Drug therapies

Most countries do not have ways to monitor treatment outcomes.
Patients are non-infectious after 1 - 2 weeks of therapy

First-line drugs

- ISONIAZID
- ETHAMBUTOL
- RIFAMPIN
- PYRAZINAMIDE
- STREPOTYMCIN

Second-line drugs

- PARA-AMINOSALICYLIC ACID
- ETHIONAMIDE
- CYCLOSERINE
- FLUROQUINOLINES (CIPRO)
- KANAMYCIN

Typical therapies

- Start with 2 - 4 agents (before susceptibility testing)
- ISONIAZID + RIFAMPIN (9 months)
- ISONIAZID + RIFAMPIN+ PYRAZINAMIDE (6 months)

Typical Outcomes

< 50% patients are cured.

25% of patients do not complete 6 months of treatment within one year

Model Outcomes

≥ 80% in Malawi, Mozambique, Nicaragua, Tanzania

Feasible to achieve 90% cure rates with existing technology and drugs

Drug Prophylaxis

ISONIAZID

Usually used as single agent

Indications

- Radiological evidence of active primary complex
- Close contact of infectious case
- Recent PPD conversion
- Immunosuppression and PPD-positive

Drug Resistance

Mutation

1 per 10^7 to 10^{10} organisms

Body burdens $\geq 10^{10}$ organisms

Resistance develops when one drug is used for treatment

Treat infections first with 2 - 4 drugs

Reduce number of drugs over time

Selection

Global Patterns 1994 - 1997

Drug resistance (ISONIAZID, RIFAMPIN, STREPTOMYCIN, ETHAMBUTOL)

No prior treatment

- 9.9% of isolates resistant to at least 1 drug
- 1.4% of isolates resistant to 2 or more drug

Prior treatment

- 36% of isolates resistant to at least 1 drug
- 13% of isolates resistant to 2 or more drug

Overall averages

- 12.6% of isolates resistant to at least 1 drug
- 2.2% of isolates resistant to 2 or more drug

PREVENTION

Worldwide status of TB control programs.
Three goals of WHO TB program
- Reduce mortality
- Reduce prevalence
- Reduce incidence

1960 - 1979 WHO policy
- Based on case-finding
- Treatment of sputum smear-positive cases
- BCG vaccination at birth

Outline of new WHO TB control program
- Improvement of cure rate
- Target 85% in developing countries
- Target 95% in industrialized countries

Cost-effectiveness of short-course chemotherapy
- Standard chemotherapy costs $15 per patient
- Short-course chemotherapy costs $30 - 40 per patient
  - Higher cure rates
  - More cost effective than standard chemotherapy
  - Combined ISONIAZID/RIFAMPIN tablets

Expansion of TB services
- Microscopic services
- X-ray equipment

Vaccines
- BCG (Bacille Calmette-Guérin)
- Introduced in 1921
- Derived from *Mycobacterium bovis* after repeated subculture
- Intradermal injection of live bacillus
  - BCG contraindicated for AIDS patients
  - Used only in PPD-negative subjects
- Results in loss of PPD as marker of new exposures
- WHO sponsored vaccination programs

Meta-analysis of 12 case-controlled studies
- 50% efficacy in preventing TB infections.
- 78% efficacy in preventing disseminated TB infections.
- 64% efficacy in preventing TB meningitis
- 67% efficacy in preventing TB deaths.
- Age of vaccination was not a predictor of efficacy.

Recommended uses of BCG
- Persons with continuous exposure to ISONIAZID and RIFAMPIN resistant TB
- Persons who cannot tolerate ISONIAZID
- Risk groups with TB infection rates >1% per year.

BOTTOM LINES

MDRTB strains increasing very little data available for world.

Clear need to expand TB programs

Clear need to increase cure rates.

HIV/AIDS makes it more difficult to control TB.

READING

• Pablos-Méndez et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. New Engl J Med 1998; 338: 1641-1649.

• Mukherjee JS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004; 363: 474 - 481.

• Elzinga G, et al. Scale up: meeting targets in global tuberculosis control. Lancet 2004; 363: 814 - 819.

• Liebeschuetz S, et al. Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. Lancet 2004; 364: 2196 - 2203.

• Cobelens FGJ, et al. Risk of infection with Mycobacterium tuberculosis in travelers to areas of high tuberculosis endemicity. Lancet 2000; 356: 461 - 465.

FIGURE 1

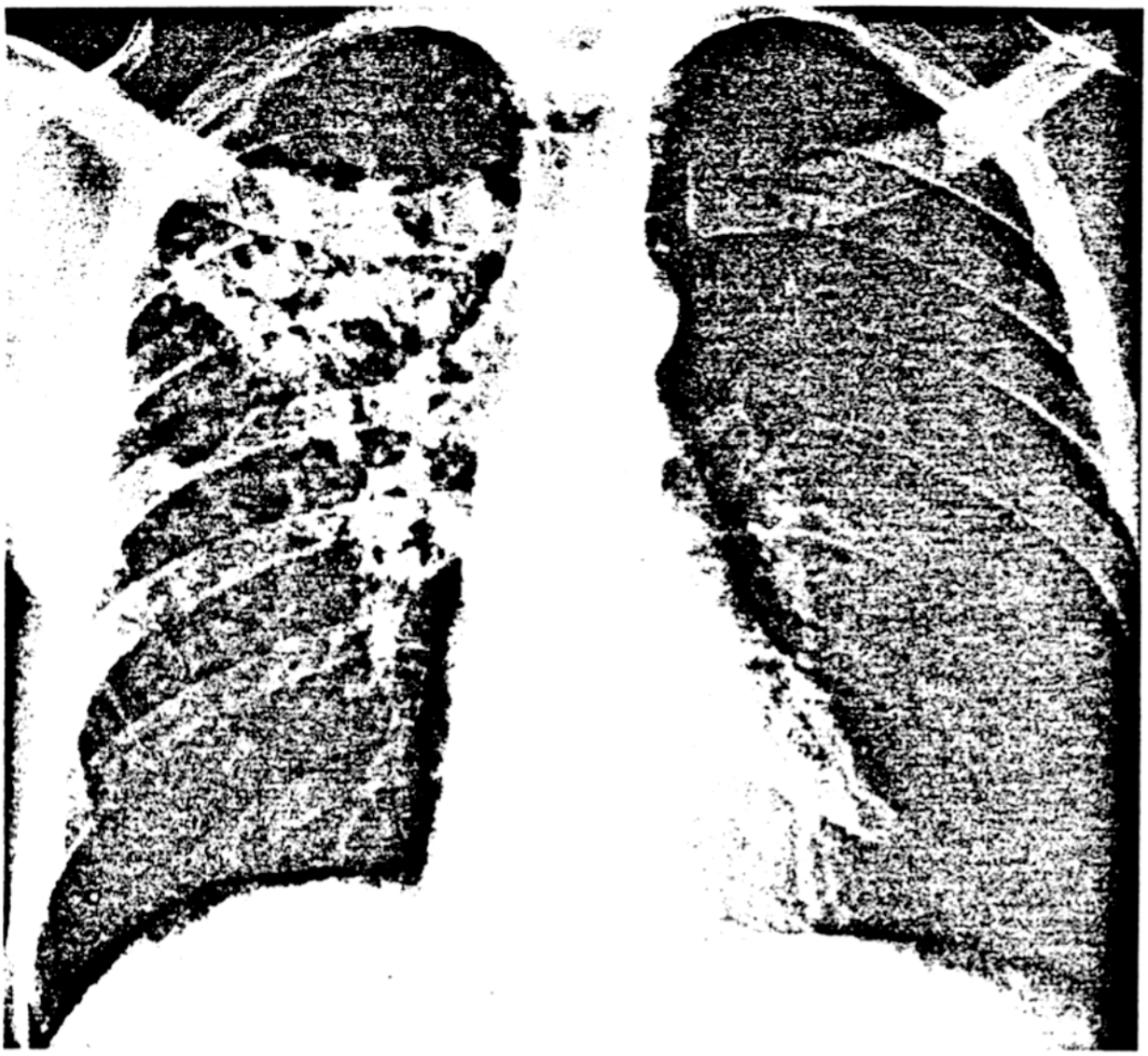
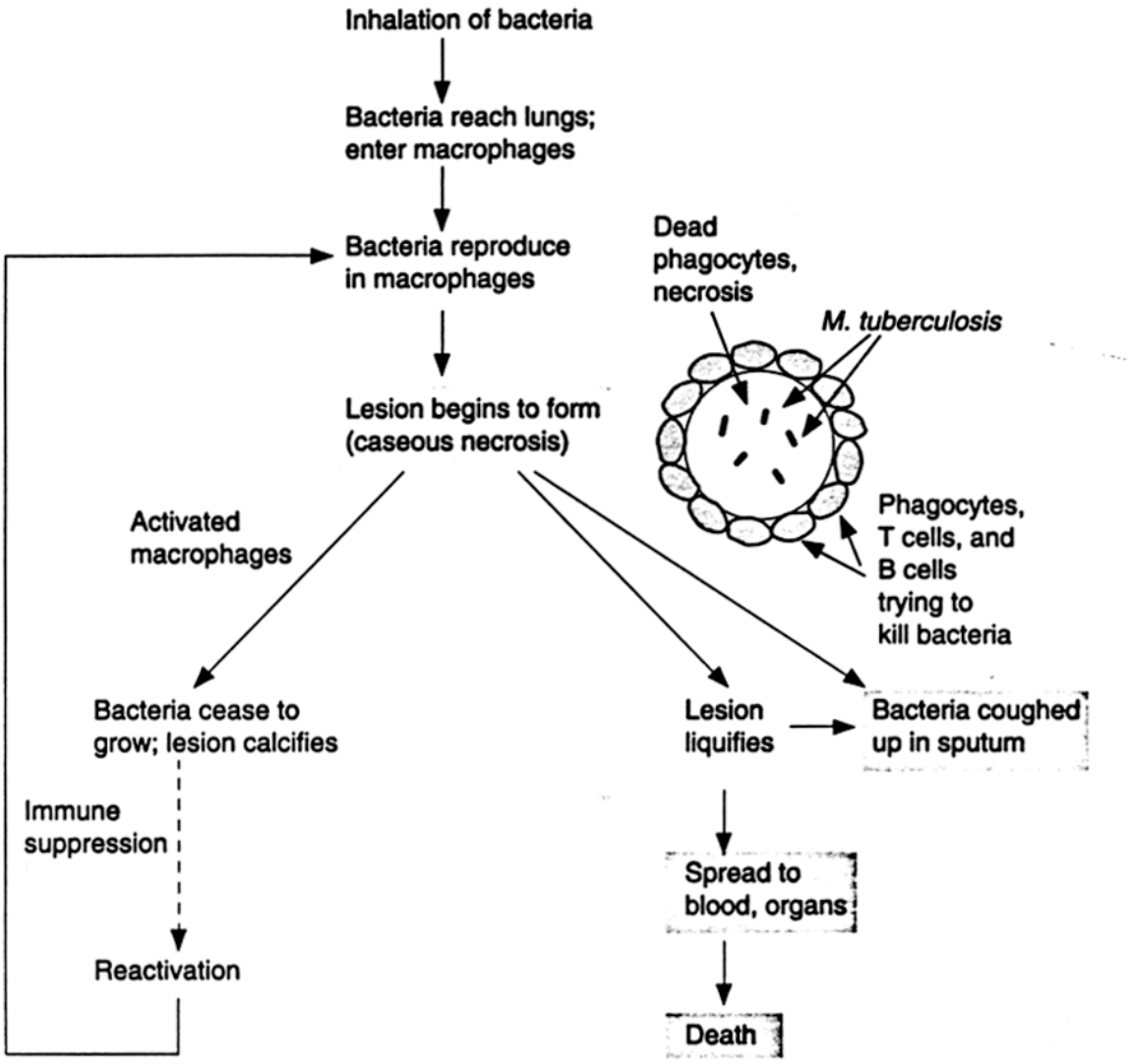


FIGURE 2



Steps in the pathogenesis of TB.

FIGURE 3

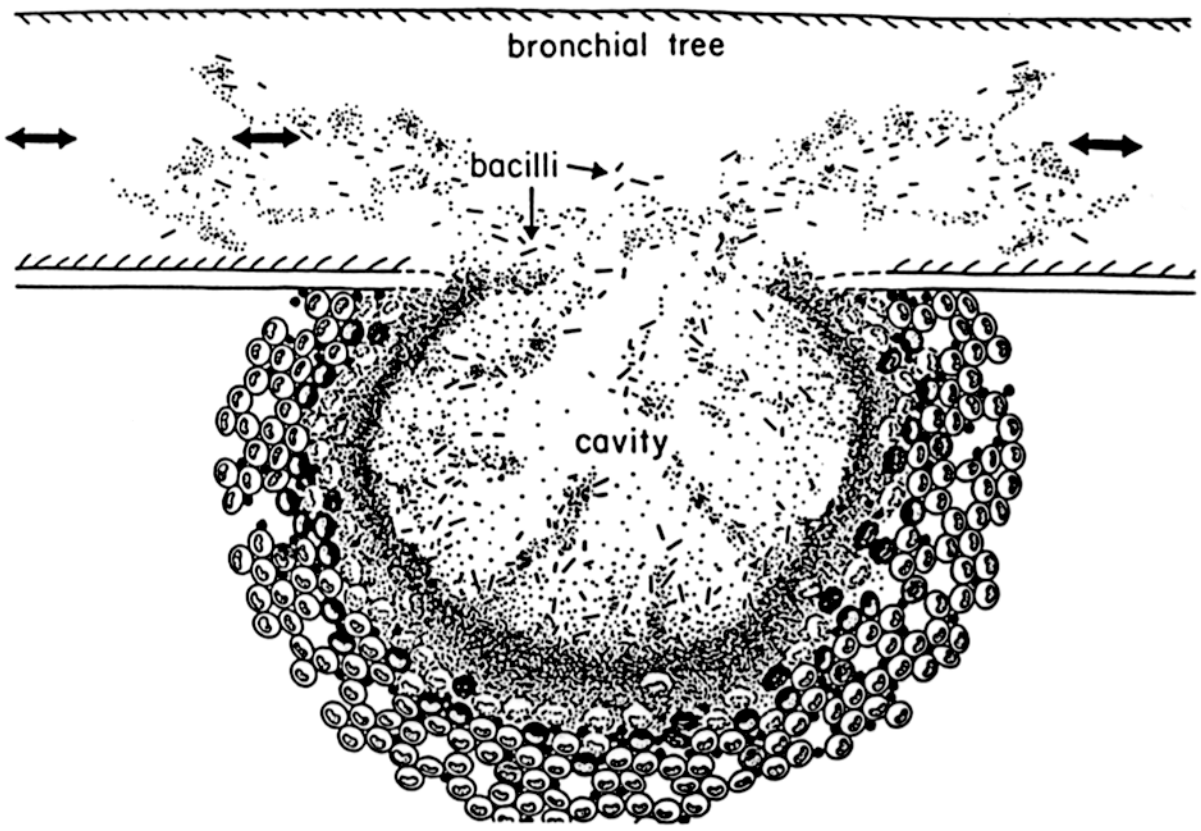


FIGURE 4

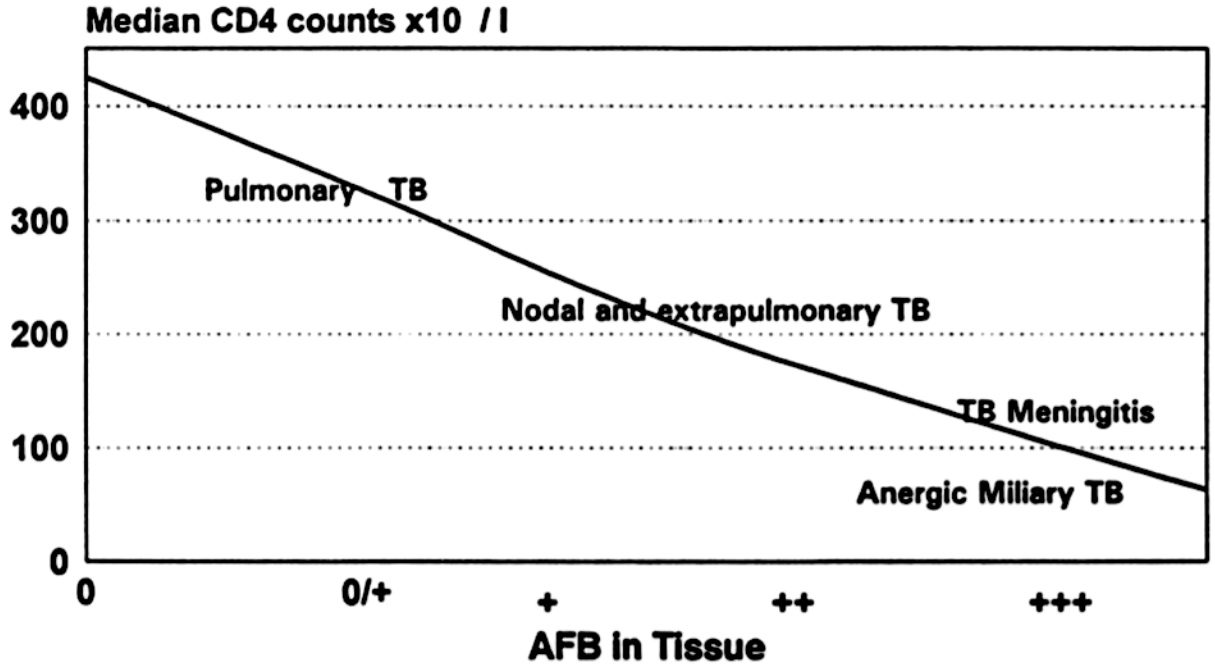

Median CD4 counts x10 / l
400
300
200
100
0
Pulmonary TB
Nodal and extrapulmonary TB
TB Meningitis
Anergic Miliary TB
0
0/+
+
++
+++
AFB in Tissue

FIGURE 5

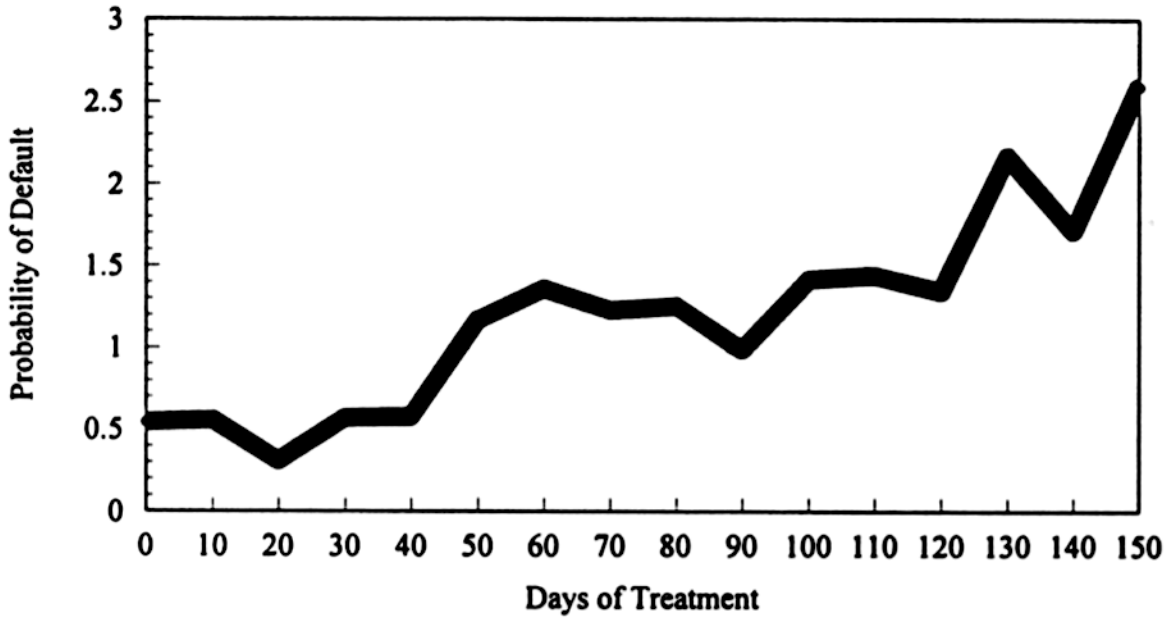

Probability of Default
3
2.5
2
1.5
1
0.5
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Days of Treatment

FIGURE 6

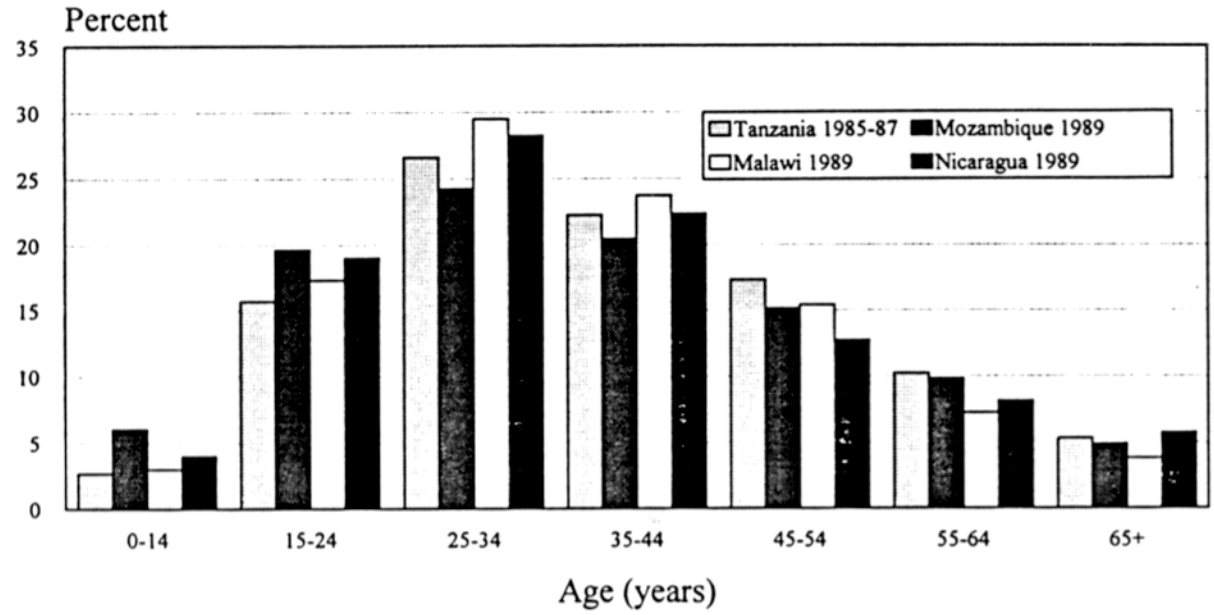

Percent
35
30
25
20
15
10
5
0
Tanzania 1985-87
Mozambique 1989
Malawi 1989
Nicaragua 1989
0-14
15-24
25-34
35-44
45-54
55-64
65+
Age (years)

FIGURE 7

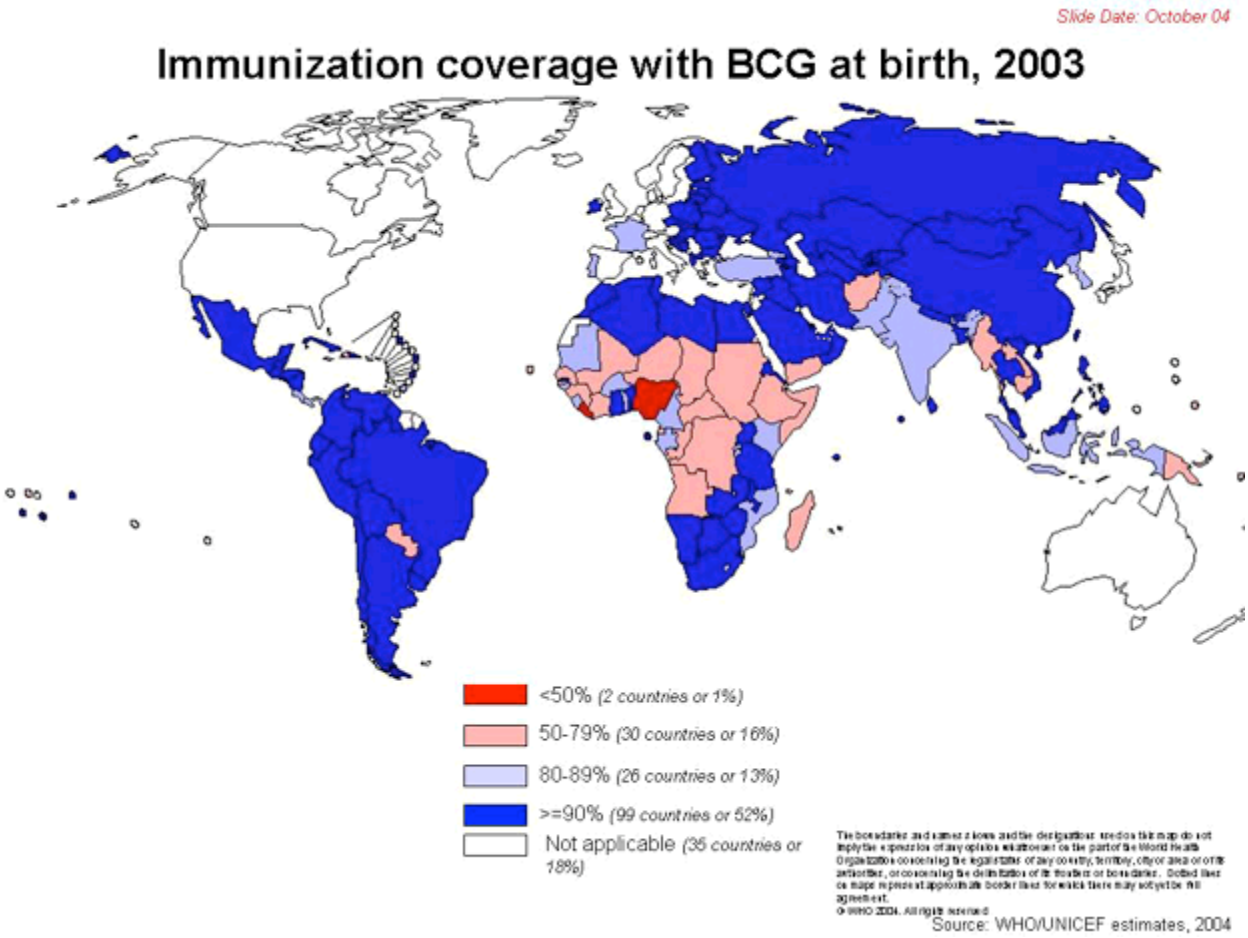
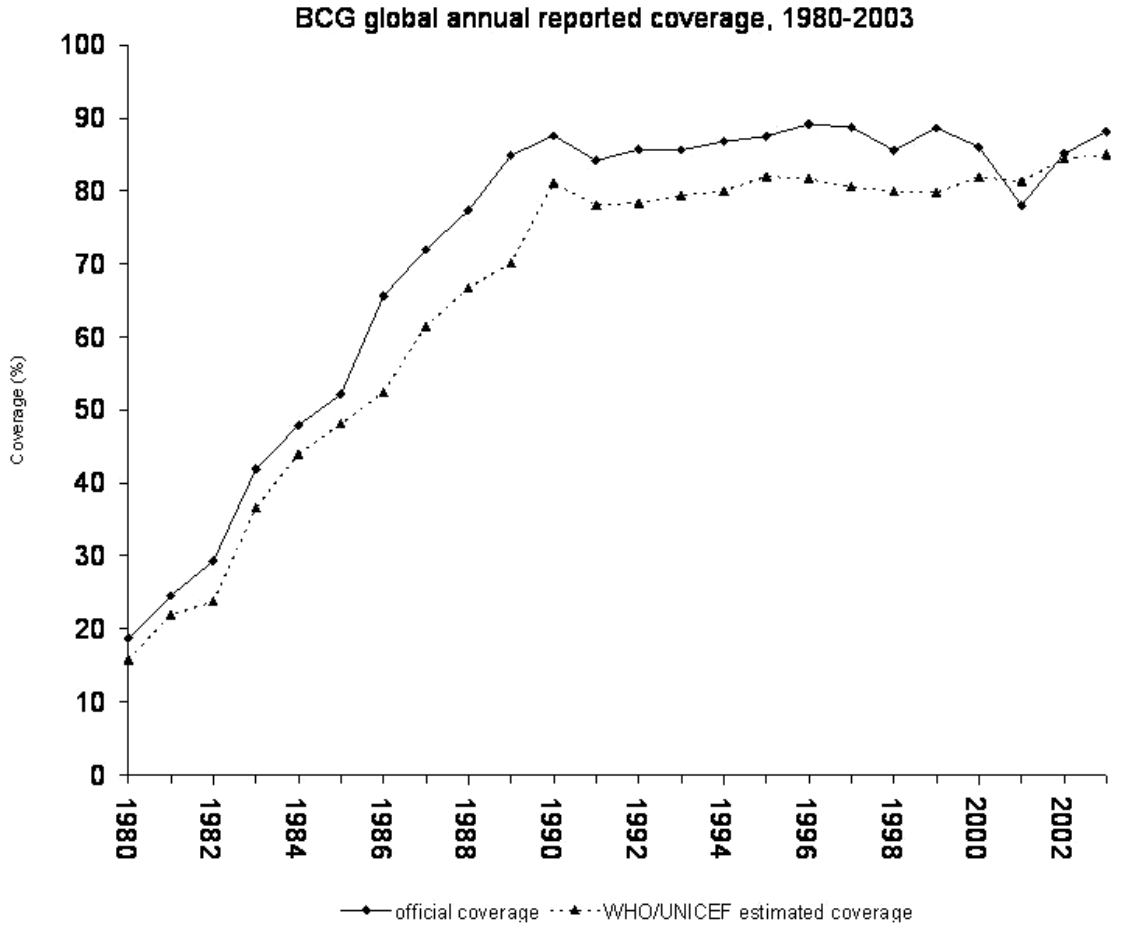

Slide Date: October 04
Immunization coverage with BCG at birth, 2003
<50% (2 countries or 1%)
50-79% (30 countries or 16%)
80-89% (26 countries or 13%)
>=90% (99 countries or 52%)
Not applicable (35 countries or 18%)
Source: WHO/UNICEF estimates, 2004

FIGURE 8


BCG global annual reported coverage, 1980-2003
Coverage (%)
100
90
80
70
60
50
40
30
20
10
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
official coverage
WHO/UNICEF estimated coverage