

Tuberculosis in 2000

*can we build a vaccine for the
white plague?*

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Bio 160 March 1 2000

History
Epidemiology
Pathogen
Infection
Disease
Treatment
Drug Resistant TB
Immunity?
Existing Vaccines
Future Vaccines

Tuberculosis

History

- Neolithic skeletons show TB changes (5000 BC)
- Egyptian mummies from 2400 BCE show definite pathological signs of tubercular decay.
- The term phthisis, consumption, appears first in Greek literature.
- Sylvius' *Opera Medica* (1679), identified actual tubercles and progression to abscesses and cavities.
- Manget described the pathological features of miliary tuberculosis in 1702.

TB history ...

- In 1720, the physician Benjamin Marten conjectured that TB was caused by "minute organisms" and was transmissible by close and prolonged contact.
- Sanatoria cures began in 1854: mountains, good nutrition, exposure to continuous fresh air.
- 1865, Dr. Jean-Antoine Villemin demonstrated that consumption could be passed from humans to cattle and from cattle to rabbits.
- 1882, Robert Koch discovered a staining technique that enabled him to see *Mycobacterium tuberculosis*.
- X rays invented in 1895.

Tuberculosis

... recent history

- 1890's Calmette and Guerin used bile to passage *M bovis*. BCG introduced in 1927 (does not prevent adult TB).
- Medications for TB first developed in 1945 (Waxman, fungi, Merck) and 1960.
- No new drugs approved since 1966.
- The World Health Organization declared tuberculosis a *global health crisis* in 1993: "DOTS" proposed as solution.

Tuberculosis

Recent history

- Transmission dependent on crowding
- Sporadic and romanticized
- Epidemic and stigmatized
- Failure to eradicate where access to health care is poor and crowding is common
- Diagnostic tools date from 1800's
- No new funding: No new drugs, tests, or vaccines

Race/ethnicity/social class of TB affected – the only epidemic caused by a disease for which there is a cure!

Tuberculosis

Epidemiology

- 1/3 of the world population, or 2.1 billion people infected with *Mtb*
- 10% of these infected individuals, or 200 million people, will progress to fulminant tuberculosis
- 3 million people die yearly = 1/4 of preventable adult deaths
- Between 1993 and 1996 there was a 13 percent increase in TB world wide
- > 70 million people projected to die in the next two decades.

Tuberculosis

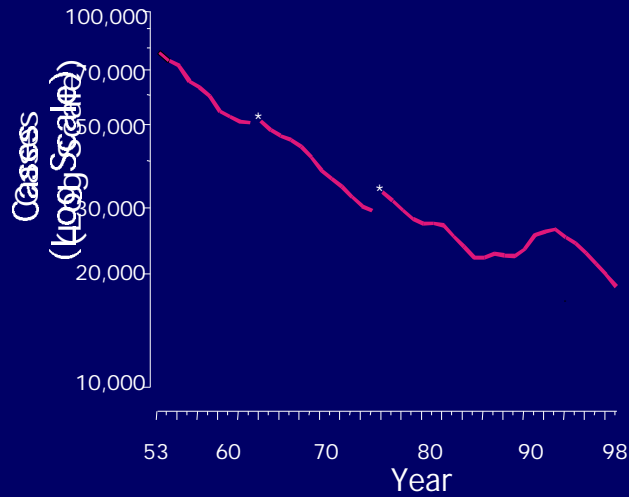
Regional Epi



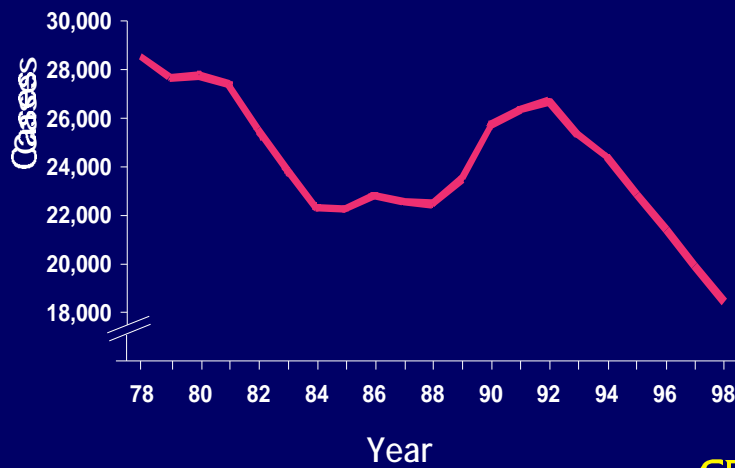
USA

- 1980: Elimination of TB scheduled for 2010
- 1985: HIV epidemic begins
- 1990-1992: Outbreak of TB in NY, FLA, NJ (prisons)
- 1994: Renewed control efforts bring NY under control
- 1996: “Strain w” spreads beyond NY state borders
- 1999: New concerns about “TB immigration”
- 2000: Revised estimates of “eradication” to 2040 or beyond

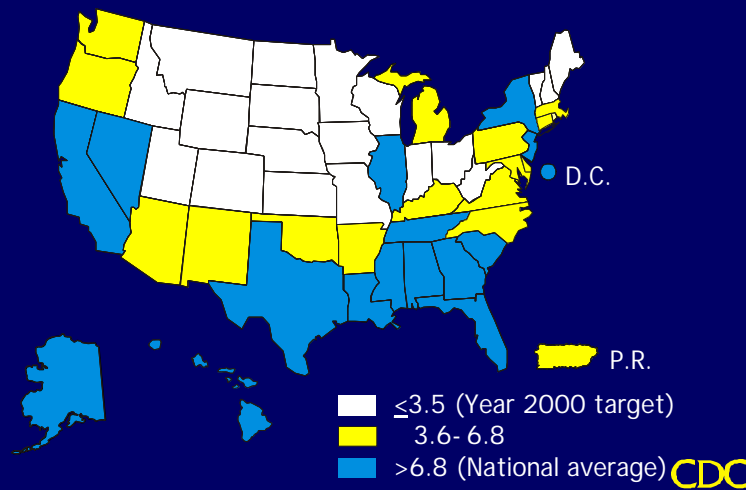
Reported TB Cases United States, 1953-1998



Reported TB Cases United States, 1978-1998



TB Case Rates by State United States, 1998



Change in TB Cases by State United States, 1985, 1992, and 1998

State	% Change	
	1985vs. 1992	1992vs. 1998
New York	+84.4	-56.3
California	+54.2	-28.4
Texas	+32.7	-27.5
Florida	+19.8	-23.7
Illinois	+6.5	-33.1
All Others	-4.2	-24.0

CDC

Change in TB Cases by Race/Ethnicity United States, 1985, 1992, and 1998

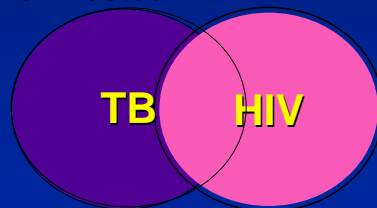
Race/Ethnicity	% Change	
	1985vs. 1992	1992vs. 1998
White, nonHispanic	-9.9	-41.0
Black, non-Hispanic	+26.8	-39.4
Hispanic*	+73.5	-24.6
Asian/Pacific Islander	+46.4	-0.7
American Indian/ Alaskan Native	-23.3	-15.4

*Persons of Hispanic origin may be of any race



Tuberculosis Epidemiology / HIV

- HIV is accelerating the TB epidemic
- TB is the leading cause of death from AIDS (30% of AIDS deaths world wide)
- Of 31 million people world wide who were HIV positive in 1997, 1/3 were infected with TB.



Tuberculosis

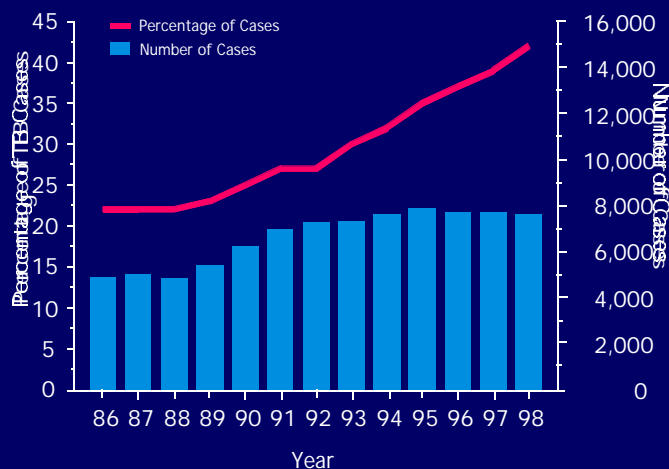
Epidemiology / Travel

- Movement is accelerating the TB epidemic
- Air travel has increased 17 fold since 1960
- In 1994, there were 804,000 legal immigrants entering the US, and 97 million air passengers
- In 1997, there were 1448 million passengers worldwide.
- 2 billion are forecasted for the year 2005.

“Medical examination of millions of people travelling by air world wide [is] not possible” (WHO, 1999).

In March 1999, a Ukrainian man traveling to Philadelphia infected with a strain of drug resistant tuberculosis infected 13 of the 40 people in his immediate seating area.

Trends in TB Cases in Foreign-born Persons, United States*, 1986-1998



* Comprises the 50 states, the District of Columbia, and New York



Tuberculosis

Regional Epi

India

"...5 million Indians are infected with HIV, a number greater than that found in any other country in absolute terms..."

India moved up on CDC list of priorities as a result of the explosion of [HIV] infections.

Studies show that an estimated 14 million Indians have TB, including 3.5 million with infectious [tuberculosis] disease."

AIDS Alert—International Supplement (05/99) Vol. 14, No. 5, P. 1

Tuberculosis

Regional Epi

Russia

Epidemic MDR-TB in prisons.

overcrowded conditions, poor nutrition of inmates; lack of adequate medical facilities; lack of drugs .

most inmates inappropriately treated with single drugs or inadequate quantities of the appropriate drugs.

bacteria became resistant to the first-line anti-tuberculosis drugs, and now there are many isolates from these prisons that are resistant to all known anti-tuberculosis drugs.

MDR-TB-infected individuals are now sequestered in separate prisons and simply allowed to die.

outside the prisons, infected guards and service personnel, and even pardoned tuberculous prisoners, return to their home communities.

Farmer, P. 1999. TB superbugs: the coming plague on all our houses. *Natural History*, April 1999, p. 46-53.

Global incidence / prevalence of TB in 1998

(Thousands)

	EME	FSE	LAC/MEC	Asia	SSA	World
New smear-pos	68	51	279	1,854	780	3,032
New, all types	151	112	621	4,121	1,734	6,739
Smear-pos prev	37	63	469	4,765	1,806	7,140
Prev, all types	86	134	1,195	10,896	4,404	16,715

EME: Established Market Economies: U.S. Western Europe, Australia and Japan;

FSE: the Formerly Socialist Economies of Europe, including Russian Republics;

LAC/MEC: Latin America and the Caribbean, the Middle Eastern Crescent, countries of North Africa; **SSA:** sub-Saharan Africa; **Asia:** China, Southeast Asia, India, and Korea.

Estimated incidence of TB: top countries, 1997

Country	Population x 1000 (1997)	incidence thousands	Incidence rate/10 5
India	960 178	1 799	187
China	1 243 738	1 402	113
Philippines	70 724	219	310*
South Africa	43 336	170	392*
Russian Federation	147 708	156	106
Uganda	20 791	66	320*
Peru	24 367	65	265*
22 high burden countries total	3 657 421	6 361	174
Global total	5 849 389	7 963	136

Source: Dye C, Scheele S, Dolin P, Pathania V & Raviglione MC.

Global burden of tuberculosis: estimated incidence, prevalence and mortality by country in 1997.

TB Trends in 1997



The graph displays three data series: Western Europe (green line), Eastern Europe (red line), and SSA (purple line). The Western Europe line starts high and trends downwards. The Eastern Europe line starts lower than Western Europe, dips, and then rises sharply. The SSA line starts low and shows a steady upward trend.

Western Europe

Eastern Europe

SSA

Mycobacterium tuberculosis

...the pathogen



Tuberculosis

Transmission

- Transmission is by aerosol:
Coughing, sneezing, talking, singing
- An individual with active tuberculosis infects, on average, 10-15 new people each year that they remain infectious and untreated
- Transmission is increased in a closed environment (classroom, airline, bus, or train)



Tuberculosis

...pathogenesis

- inhalation (or ingestion) of *Mtb*
- colonization of macrophages (lung)
- bacteria grow slowly, resist WBC killing
- granuloma formation
- Bacteria in the nodules can remain viable for decades.
- Reactivation event: (aging, cancer chemotherapy, HIV, stress, malnutrition) impairs defenses, bacteria spread.
- Symptoms:coughs, severe weight loss, fever, "night sweats" and fatigue.
- 80% chance of death if not treated.

Tuberculosis

...pathogenesis

- Infection vs disease
- Location of disease
- 90% do not get disease (immune state?)
- Relevant antigens?
- Correlates of immunity?

Tuberculosis

Diagnosis

- Skin Testing (PPD)
- Chest X Ray
- Symptoms
- Risk Factors

Tuberculosis

Treatment history

year	drug	target
1945	Streptomycin	ribosome
1945	PAS	
1952	Isoniazid	mycolic acid and other targets
1952	PZA	?
1963	ethambutol	cell wall and others
1967	rifampicin	RNA polymerase
1993	sparfloxacin	DNA gyrase

Tuberculosis

Treatment of Infection

INH prophylaxis x 1 year

PZA and rifampin x 2 months

Cure rate?

Tuberculosis

Treatment of Disease

DOTS: Directly observed treatment, Short course

four drugs for six months
cure rates of 95% are possible
six month supply costs \$11

Only 12% of all TB patients receive DOTS
95 out of 212 countries have adopted DOTS
DOTS is likely to fail.

Tuberculosis

WHO approach to TB

DOTS: Directly observed treatment, Short course

- 1) political commitment
- 2) microscopy services
- 3) drug supplies
- 4) monitoring systems
- 5) DOT

Where are the weak links??

Tuberculosis

Vaccines

...much of the developed world erroneously believes that there is a vaccine for TB

Tuberculosis

vaccines: BCG

(bacille Calmette-Guerin)

- BCG first introduced on a national scale in 1927
- Over 80% of the world's children are vaccinated with BCG.
- It has significantly reduced mortality due to tuberculosis meningitis and miliary tuberculosis in children.
- **BUT** BCG has not had an impact on deaths due to adult pulmonary tuberculosis since the vaccine was introduced.
- It does not prevent infection, so vaccinated children can acquire latent disease through exposure to *M. tuberculosis* and may, with immunosuppression due to malnutrition or other infections, develop pulmonary disease as adults.

Tuberculosis

...vaccines

- **Live attenuated vaccines**

Genetically-modified BCG that express *M. tuberculosis*-specific antigens; genetically engineered mutants of *M. tuberculosis* that are attenuated; live attenuated vectors (viruses or bacteria) that express *M. tuberculosis* genes.

- **Subunit vaccines**

Protein, peptide, lipid, or carbohydrate antigens, with or without adjuvants.

- **Naked DNA vaccines**

DNA encoding whole proteins or peptide epitopes of *M. tuberculosis*.

Tuberculosis

...vaccines

Prophylactic?

Post infection prophylaxis?

Therapeutic?

stages in vaccine development

- identify disease
- identify pathogen
- determine risk group
- means of testing for presence of infection
- understand correlates of immunity/ immune state
- identify protective antigens
- create vaccine - bench
- animal model
- preclinical safety testing
- FDA approval
- commercialization and distribution

TB Vaccine Milestones

1927 BCG is introduced

1996 The NIAID, NIH Workshop in the report entitled a Blueprint for Tuberculosis Vaccine Development

1998 Advisory Council for the Elimination of Tuberculosis in the report entitled Development of New Vaccines for Tuberculosis, MMWR 47:1-6.

2000 WHO admits defeat (unofficially) of DOTS and begins vaccine effort

2001 Several TB genomes will be available (BCG already available)

2005? Brown University undergraduate research assistants develop vaccine for TB