Tuberculosis from a Clinician's Perspective

Epidemiology and Laboratory Priorities

Charles L. Daley, M.D.
University of California, San Francisco
F. J. Curry National TB Center

Tuberculosis from a Clinician's Perspective

● Epidemiology
● Transmission and Pathogenesis
● Diagnosis and Treatment of Tuberculosis
● Diagnosis and Treatment Latent TB Infection (LTBI)
● Laboratory Priorities-A Clinician's Perspective

The Global Resurgence of Tuberculosis

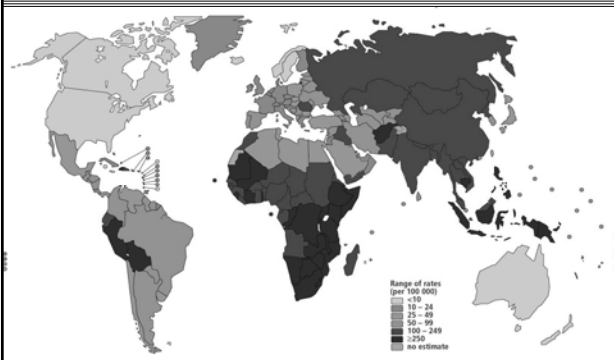"The microbe is nothing:
the terrain, everything."

– L. Pasteur, 1822-1895

Magnitude of Tuberculosis

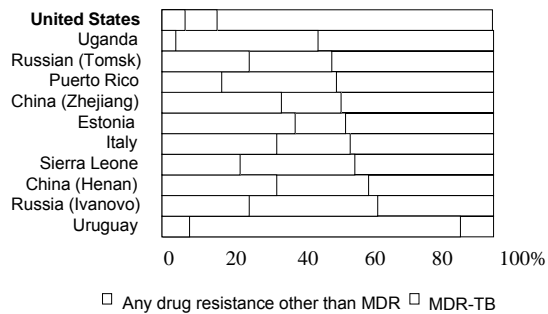|	
Prevalence of infection	2 billion
Annual number of new cases	8 million
Annual case rate	60.6/100,000
Tuberculosis deaths*	2 million
% preventable deaths	26

*Does not include TB/HIV deaths

Estimated TB Incidence Rates, 1997

Range of rates
(per 100 000)
<10
10 – 24
25 – 49
50 – 99
100 – 249
≥250
no estimate

WHO Global Project
Prevalence of MDR-TB in Previously Treated

United States
Uganda
Russian (Tomsk)
Puerto Rico
China (Zhejiang)
Estonia
Italy
Sierra Leone
China (Henan)
Russia (Ivanovo)
Uruguay

0   20   40   60   80   100%

☐ Any drug resistance other than MDR ☐ MDR-TB

Global Distribution Of HIV/MTB

5,000
84,000
62,000
107,000 2,364,000
307,000
440,000 7,302,006

GLOBAL TOTAL: 10.7 MILLION
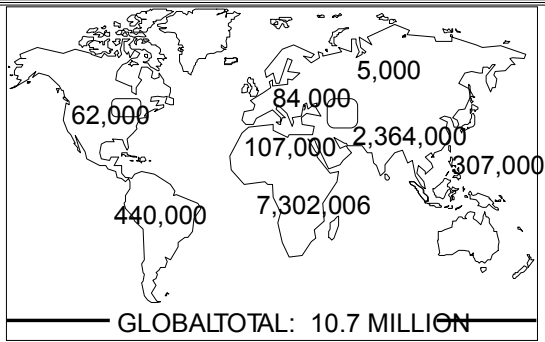
Tuberculosis Cases in the U.S.
1980-2000

30,000
25,000
20,000
TB Cases
15,000
10,000
5,000
0

80 82 84 86 88 90 92 94 96 98 0

Years

Source: CDC

TB Case Rates in the U.S, 2000

O D.C.

□ ≤ 3.5 (year 2000 target)
□ 3.6 - 5.8
Rate: cases per 100,000   □ > 5.8 (national average)
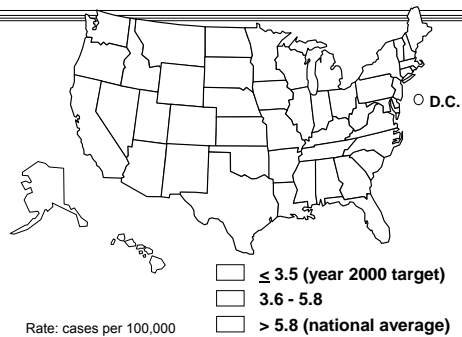
Number of TB Cases
US-born vs. Foreign-born , 1992-2000

No. of Cases (y-axis): 0, 5000, 10000, 15000, 20000

Years (x-axis): 1992 1993 1994 1995 1996 1997 1998 1999 2000

Legend: US-born, Foreign-born
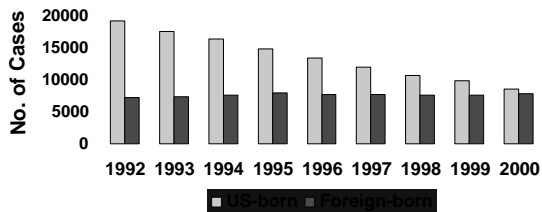
TB Cases In The United States
Age 24-44, by HIV Status, 1998

Reporting Area	Total Cases	Cases with HIV Status		% HIV +
		No.	%	
Alabama	107	85	79.4	12.9
Florida	544	457	84.0	46.8
Georgia	228	174	76.3	29.9
Louisiana	132	103	78.0	18.4
Maryland	112	92	82.1	28.3
New York City	652	548	84.0	39.6
Oregon	71	60	84.5	13.3

Source: CDC

Transmission and Pathogenesis of TB

```
                    ┌──────────────────┐
                    │ No infection (70%)│
                    └──────────────────┘
              Adequate
              ↗        ╭─────────────╮   ┌────────────────────┐
┌────────┐  ╱         │Non-immunologic│──│Early progression (5%)│
│Exposure│─┤          │   defenses    │  └────────────────────┘
└────────┘  ╲         ╰─────────────╯          Inadequate
              Inadequate                         ↗
              ↘  ┌────────────┐  ╭───────────╮  ┌──────────────────┐
                 │Infection (30%)│ │Immunologic│──│Late progression(5%)│
                 └────────────┘  │ defenses  │  └──────────────────┘
                         ╲       ╰───────────╯       Inadequate
                    Adequate                          ↗
                         ↘  ┌──────────────┐  ╭───────────╮
                            │Containment (95%)│ │Immunologic│
                            └──────────────┘  │ defenses  │
                                              ╰───────────╯
                                                   Adequate
                                                    ↘  ┌──────────────────────────┐
                                                       │Continued containment (90%)│
                                                       └──────────────────────────┘
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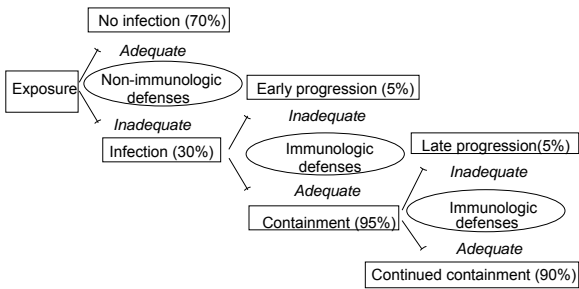
Diagnosis of Tuberculosis

- 400 B.C.   Clinical observation and deduction - Hipprocates
- 1761   Percussion - Anenbrugger
- 1819   Ausculation - Laennec
- 1882   Microscopic examination and culture - Koch
- 1895   Xrays - Rontgen

Sensitivity and Specificity
A Laboratory Perspective

- Sensitivity - The percentage of patients with the disease who have a positive test
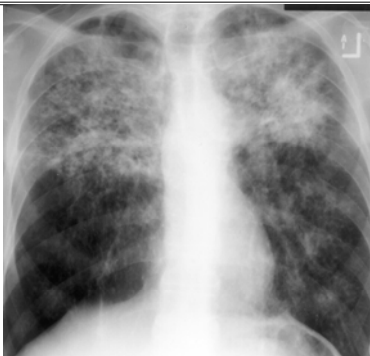- Specificity - The percentage of patients without disease who have a negative test

Predictive Values
A Clinician's Perspective

- Positive predictive value (PPV) - The percentage of patients with a positive test who have the disease
- Negative predictive value (NPV) - The percentage of patients with a negative test who do not have the disease
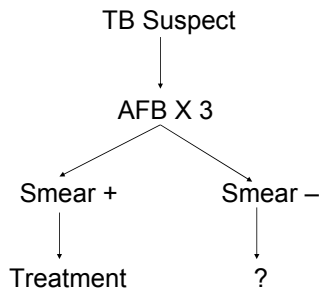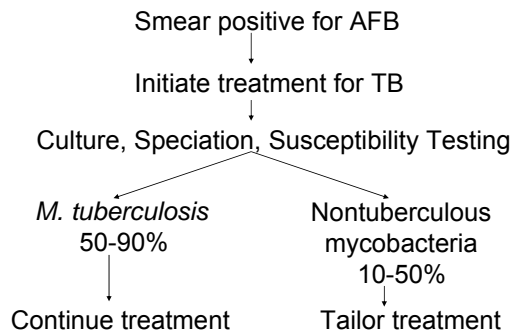
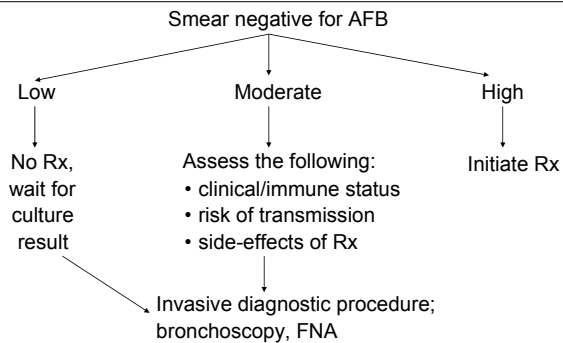## Prevalence of Disease vs. Predictive Value
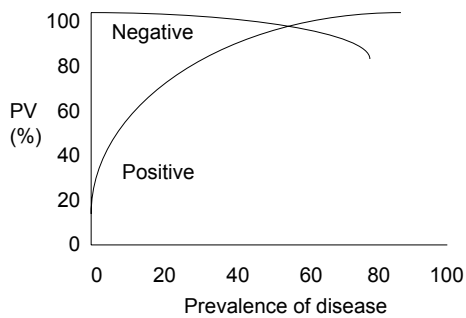
TB or Not TB?

Diagnostic Work-Up of TB Suspect

TB Suspect
↓
AFB X 3
↓ ↘
Smear +   Smear –
↓   ↓
Treatment   ?

Predictive Value of a Positive AFB Smear

Smear positive for AFB
↓
Initiate treatment for TB
↓
Culture, Speciation, Susceptibility Testing
↙   ↘
M. tuberculosis   Nontuberculous
50-90%   mycobacteria
                      10-50%
↓   ↓
Continue treatment   Tailor treatment

Clinical Decision Making with Negative AFB Smears

Smear negative for AFB
↙   ↓   ↘
Low   Moderate   High
↓   ↓   ↓
No Rx,   Assess the following: Initiate Rx
wait for   • clinical/immune status
culture   • risk of transmission
result   • side-effects of Rx
                      ↓
        Invasive diagnostic procedure;
        bronchoscopy, FNA

Direct Amplification Tests
Smear Positive Specimens

AFB Smear +

Perform DAT

Positive DAT   Negative DAT

MTB   NTM   MTB   NTM
100%   0%   10%   90%
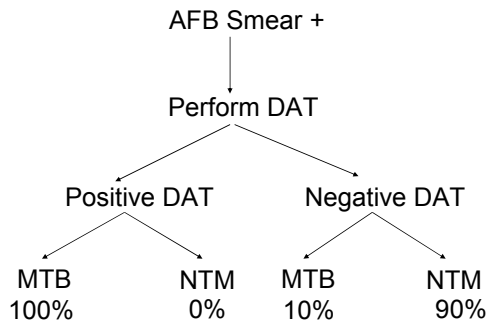
Diagnosis of Tuberculosis
Role of Clinical Suspicion

- Prospective multicenter trial
  - » 7 sites (6 in U.S. and 1 in Switerzland)
- 338 TB suspects were enrolled
- Patients were stratified by clinical investigators to be at:
  - » Low (≤ 25%)
  - » Intermediate (26-75%)
  - » High (>75%) risk of TB

Catanzaro A, et al. JAMA 2000;283:639

Diagnosis of Tuberculosis
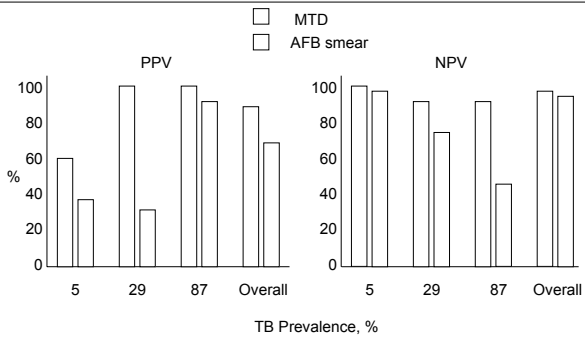### Role of Clinical Suspicion

- Among 338 suspects, 72 had TB
  - 45 (63%) had ≥ 2 positive cultures
  - 20 (28%) had one positive culture
  - 7 (10%) had not positive cultures

	Low (n= 224)	Intermediate (n=68)	High (n=46)
Prevalence of TB	5%	29%	87%
Started on drugs	11%	49%	98%

Catanzaro A, et al. JAMA 2000;283:639

Diagnosis of Tuberculosis
Role of Clinical Suspicion

Treatment of Tuberculosis
Unscientific and Probably Ineffective

- Wolf's liver boiled in wine
- Flesh of a she-ass with broth
- Smoke of dried cow dung
- Elephant's blood
- Woman's milk
- Mice boiled in salt and oil

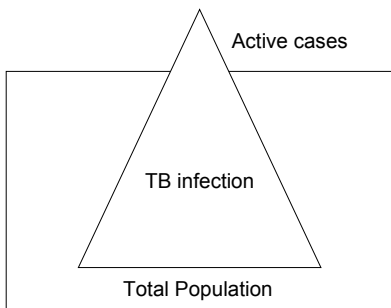## Treatment of Tuberculosis
San Francisco General Hospital

Treatment of Tuberculosis
Standard Regimen

	Initial Phase	Continuation Phase
Isoniazid		
Rifampin		
Pyrazinamide		
Ethambutol*		

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0    1    2    3    4    5    6
              months
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*Streptomycin may be substituted

Tuberculosis
Tip of the Iceberg

Active cases

TB infection

Total Population

Tuberculin Skin Testing
Mantoux Method

Quanti-FERON-TB® Test

Collect blood ——→ Dispense blood into wells

Add simulation antigens to blood

Nil antigen | Hu PPD | Av PPD | Rec antigens | Mitogen control

Specific T cells respond and produce gamma-interferon ——→ ELISA
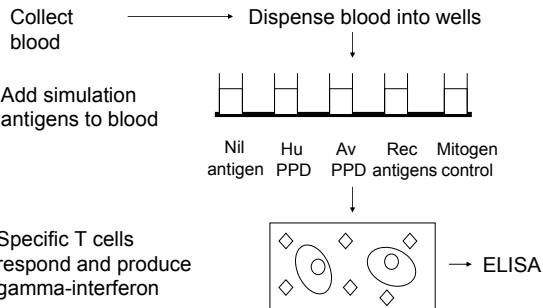
Quanti-FERON-TB® Test
Impact of BCG Vaccination

	Overall	% Agreement TST+	TST-	kappa
Total Population	84.7	64.8	90.2	0.55
Unvaccinated	88.1	64.5	91.3	0.50
Unk. Vaccination	82.2	72.1	88.0	0.61
BCG Vaccinated	70.1	61.5	81.8	0.41

Mazurek G, et al. JAMA 2001

Quanti-FERON-TB® Test
Discordance: +TST, –QFT

| Variable	Category	Relative Risk	P-value
Race	White	1.0	
	Hispanic	1.24	0.63
	Black	1.69	0.15
	Asian	2.33	0.03
	Other	0.61	0.66
History of BCG	None	1.0	
	Unknown	2.49	0.03
	Vaccinated	6.92	0.00
MAC by QFT	No	1.0	
	Yes	2.64	0.008

Mazurek G, et al. JAMA 2001

ESAT-6 ELISPOT Assay
Contacts Stratified by Exposure

•50 healthy contacts with well-defined degrees of exposure

•ESAT-6 correlated with degree of exposure

•ESAT-6 was not correlated with BCG status

Lalvani, et al. Lancet 2001;357:2017-21
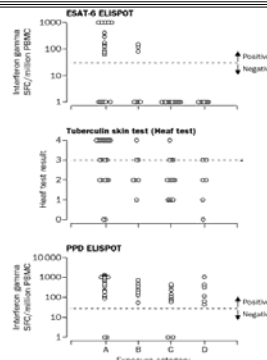
Treatment of LTBI
Drug Regimens

Regimen	Duration (months)	Interval
Isoniazid	9	Daily Twice-wkly
Isoniazid	6	Daily Twice-wkly
Rifampin-PZA	2 2-3	Daily Twice-wkly
Rifampin	4	Daily

ATS/CDC AJRCCM 2000

Laboratory Priorities
A Clinician's Perspective

● Services offered - The more the merrier
● Turn around time - The quicker the better
● Communication - It's a good thing
● Costs?

Laboratory Priorities
A Clinician's Perspective

Test	Positive characteristics	Negative characteristics
Smear	Rapid Inexpensive + Infectiousness	Not sensitive
Culture	Definitive diagnosis	Slow
Susceptibility tests	Identifies drug resist.	Slow
Amplification tests	Rapid Sensitive and specific	Expensive – Infectiousness

Drug Susceptibility Testing
Priorities

- Isoniazid
  - » Low and high concentrations?
- Rifampin
- Pyrazinamide
- Ethambutol
- ?Streptomycin?

Communication

- Communication is essential for patient care
- Speed of reporting results must be balanced against the reporting of accurate results
- In suspected cross-contamination, the clinician should be informed immediately

A Clinician' Laboratory Wish List

- Diagnosis and treatment of TB
  - » Rapid identification-species specific
  - » Correlate with infectiousness of patient
  - » Rapid drug susceptibility testing
  - » Determine response to therapy
- Diagnosis and treatment of LTBI
  - » Rapid and accurate determination of infection
  - » Test to predict progression to active TB

Genome of *M. tuberculosis*