Tuberculosis Overview: TB – Yesterday, Today, and Tomorrow

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Chief, Division of Infectious Diseases and Global Medicine
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“The Lord shall smite thee with a consumption and with a fever, and with an inflammation . . . and they shall pursue thee until thou perish.”

Deuteronomy 28:22
“The captain of all these men of death that came against him to take him away was the Consumption, for it was that that brought him down to the grave.”

The Life and Death of Mr. Badman
John Bunyan
1672
## TB epidemiology

<table>
<thead>
<tr>
<th></th>
<th>GLOBAL</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected cases</td>
<td>1.7 billion (33% population)</td>
<td>10 million (4% population)</td>
</tr>
<tr>
<td>Case incidence</td>
<td>8-10 million/year</td>
<td>~ 10,000/year</td>
</tr>
<tr>
<td>Case prevalence</td>
<td>40-50 million</td>
<td>~12,000</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.9 million/year</td>
<td>1,000 – 1,500/year</td>
</tr>
<tr>
<td>MDR</td>
<td>Up to 15% (DR and Ecuador)</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
A Silent Global Epidemic

- One-third of the world’s population infected
- Eight million new cases of active disease per year
- Two to three million deaths per year
- One person is newly infected every second and one person dies every 10 seconds
- Rising incidence of drug-resistant disease
- Billions of dollars in lost productivity
9m cases annually
>1/3 in populous India and China

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Highest TB rates per capita are in Africa linked to HIV/AIDS
TB cases falling in 6/9 regions of the world

Incidence rate (/100K/yr)

- SE Asia
- W Pacific
- E Mediterranean
- Latin America
- C Europe
- Est Mkts

TB cases have been rising in Africa and E Europe.
Reported TB Cases
United States, 1982–2011*

*Updated as of June 25, 2012.
TB Case Rates,* United States, 2011

*Cases per 100,000.

>3.4 (2011 national average)

<3.4
Percentage of TB Cases Among Foreign-Born Persons, United States*

2001

2011

*Updated as of June 25, 2012.
Reported TB Cases by Age Group, United States

- 25–44 yrs (34%)
- <15 yrs (6%)
- 15–24 yrs (11%)
- 45–64 yrs (30%)
- >65 yrs (20%)
TB Case Rates by Age Group and Sex, United States
Reported TB Cases by Race/Ethnicity*
United States

- Hispanic or Latino (29%)
- Black or African-American (25%)
- Asian (28%)
- White (16%)
- American Indian or Alaska Native (1%)
- Native Hawaiian or Other Pacific Islander (1%)

*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.
Trends in TB Cases in Foreign-born Persons, United States, 1989–2009*

*Updated as of July 1, 2010.
Countries of Birth of Foreign-born Persons Reported with TB
United States

- Mexico: 23%
- Philippines: 12%
- India: 8%
- Vietnam: 8%
- China: 5%
- Guatemala: 3%
- Haiti: 3%
- Other Countries: 38%
Estimated HIV Coinfection in Persons Reported with TB, United States, % Coinfection

*Updated as of July 1, 2010.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.
Pathogenesis and Transmission
Pathogenesis
Pathogenesis

• Droplet nuclei of 5µm or less are generated by individuals with TB and these contain 1-10 bacilli
• A single bacillus can cause disease, but 5-200 are needed to cause human infection
• Once inhaled, the bacilli become lodged in distal sub-pleural foci usually in the lower lobes
Pathogenesis

- Once deposited in the alveolar space, the bacilli are ingested by non-activated alveolar macrophages
- The bacilli are either destroyed here or multiply
- The logarithmic multiplication of bacilli is followed by cell-mediated immunity in 3-4 weeks
Pathogenesis

- During the first several weeks after infection, tubercle bacilli hematogenously spread gaining access through pulmonary lymphatics.
- Spread is preferential to areas of high oxygen tension.
- Usually the primary focus is eradicated within weeks or months but if progression continues – progressive primary disease.
Pathogenesis

- Exposure to a person with active TB results in infection in about one third of those without HIV
- Of those infected, 3-5% develop TB within one year and an additional 3-5% develop TB at some point thereafter
Transmission
Transmission

- It is hard to believe that there was much doubt as to the airborne nature of TB transmission.
- It was not until classic studies by Riley in Baltimore in the late 1950s confirmed and quantified airborne transmission.
- The studies were conducted in a ward at the VA where all the effluent air was passed through a series of cages with guinea pigs.
Transmission

- Calculated that there was one infectious dose in 11,000 to 12,500 cubic feet of air.
- Infectivity of patients was very heterogeneous with eight out of 130 patients accounting for almost half of all infections.
- Untreated patients with drug-susceptible TB were much more infectious.
- Drug susceptible disease is four to eight times more infectious than resistant disease.
- UV light is very effective in preventing infection.
Transmission of Tuberculosis

Dissemination of Tuberculosis

Expulsion
Droplets containing M. tuberculosis coughed or sneezed into air
Droplets remain suspended in air for an hour or two
Sterilized by sunlight and/or dispersed by winds
Infectious mycobacteria preserved in darkness and moisture from hours to months

Introduction into host
Inhalation
Ingestion (infected milk)

Implantation
Lungs (initial infection anywhere in lung). Drainage to hilar lymph nodes
Tonsil Drainage to cervical lymph nodes
Lymph nodes
Intestine (most commonly in lower ileum and cecum). Drainage to mesenteric lymph nodes
Finger Drainage to axillary lymph nodes

Secondary dissemination to other organs
Laboratory accident
Transmission

Factors related to transmission are going to be related to either

Characteristics of the index patient

OR

Characteristics of contacts
Index Patient Characteristics

- Extent of disease
- Duration that source case and the contact are together and this includes proximity
- Local air circulation
- Other factors that may be important but have not been substantiated include, infective burden of MTB, previous exposure and infection, virulence, and a contact’s intrinsic predisposition for infection.
Characteristics of Contacts

- The most important characteristics determining disease progression once infected are age and immune status.
- Younger children are more likely to progress to active disease and are more likely to have short latent periods followed by potentially lethal forms of the disease.
- Therefore children under five are high priority for therapy after exposure to a case.
Immune Status

- HIV's effects are well-known with rates of progression to active disease after infection of 35-162 per 1,000 person years.
- Other forms of immune suppression are important with progression including steroid therapy with prednisone equivalent of > 15mg per day for > 4 weeks, organ transplantation anti-rejection drugs, cancer therapy, and TNF-α antagonists.
- Other medical conditions have a lesser effect on progression after exposure.
Exposure and Transmission

• In an enclosed space the volume of air, the circulation, and the exhaust rate of the air are important predictors of transmission.

• The commonly used terms of “close” and “casual” are not defined and should be avoided.

• New contact guidelines recommend using size as a way to grade exposure settings.
Likelihood of Infection

• Dependent on intensity, frequency, and duration of exposure

• Examples include:
  – Airline passengers seated for eight hours or more in the same or adjoining row as a person who is contagious are more likely to be infected than others.
  – One set of criteria includes a monthly hourly total for exposure to non-cavitary cases before infection occurs (120 hours total).
Tuberculosis Infection – No Disease

- Can not spread to others
- Not considered a TB case
- Positive skin test reaction
- X-ray negative
- No symptoms
- Potential for active disease
Progression from Infection to Disease is Increased by . . .

- HIV infection
- X-ray evidence of old, untreated TB
- Substance abuse, injecting drug use
- Silicosis, diabetes
- Certain therapies
- Certain cancers
- Underweight by 10% or more
Disease Progression

- Progression from infection to disease caused by an inability to contain infection
- 5-10% of all HIV(-) will progress from infection to disease
- Up to 8% per year of TST(+), HIV(+) patients will progress from infection to disease
- The average patient with active TB infects 30 other individuals
Transmission and Pathogenesis of TB

- Tuberculosis is spread by airborne droplets (“droplet nuclei”)
- Most persons exposed to a person with tuberculosis do not become infected
- Close contacts are at high risk of acquiring infection
- Ten percent of infected persons will develop clinical tuberculosis
- Persons with tuberculosis infection but no disease are not contagious
- Cavitary or smear positive patients are more infectious than noncavitary or smear negative patients
Diagnosis of Active TB Disease

Key:

THINK TB
Signs and Symptoms of TB Disease

- Often of long duration
- General
  - Fatigue, malaise, weight loss, fever, night sweats
- Pulmonary
  - Prolonged cough, coughing up blood
- Extrapulmonary
  - Depends on site
Diagnosis of TB Disease

- Chest x-ray
  - 95% of HIV(-) cases with upper lobe infiltrates and/or cavities
Characteristics of Chest Radiographs

- 47 patients
  - 17 with AIDS and 30 without AIDS

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>PATIENTS WITH AIDS</th>
<th>PATIENTS WITHOUT AIDS</th>
<th>P VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilar and/or mediastinal adenopathy</td>
<td>10 (59%)</td>
<td>1 (3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Localized pulmonary infiltrates involving middle or lower lung fields</td>
<td>5 (29%)</td>
<td>1 (3%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Localized pulmonary infiltrates involving upper lobes</td>
<td>3 (18%)</td>
<td>29 (97%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pulmonary cavities</td>
<td>0</td>
<td>20 (67%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No pulmonary infiltrates</td>
<td>6 (35%)</td>
<td>0</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Adopted with permission from Am Rev Respir Dis. 1985;131:393-396.
Diagnosis of TB Disease

- Up to 30% of HIV(+), active TB cases will have no infiltrates or cavities
Extra-pulmonary TB

- ~10% in HIV(-)
- HIV(+)
  - 33% with extrapulmonary alone
  - 33% with pulmonary alone
  - 33% both pulmonary and extrapulmonary (many with negative CXRs)
- Any organ has been noted to be involved
  - Pleural dx most common
  - Lymph nodes
  - GU
  - Bone (Need to prolong therapy)
  - Abdominal
  - CNS (Need to prolong therapy)
TB Disease Diagnosis

- Smear
  - Cheap & rapid
  - Only 40-60% positive in cases of active TB
  - The Standard for Diagnosis of TB in most of the world
TB Diagnosis

- **Culture**
  - Takes 6-8 weeks by conventional
  - Takes 1-3 weeks by liquid media
  - Need ~100 organisms/ml to get 1 colony
  - Sensitivity-Positive in 80% of CDC Verified Cases
  - Specificity- 1-2% False Positive

- **Susceptibility**
  - Takes 1-2 weeks after positive culture
  - Molecular Techniques have the ability to give more rapid results

Most of the world does not have access to these critical laboratory tests!!!
TB Diagnosis
Nucleic Acid Amplification

- Results within eight hours
  99% specificity on smear (+) cases
- Up to 80% sensitivity on three samples
- $30 to $50 per test
- Approved by the FDA for smear-positive and -negative, untreated cases
- May have a rule in non-pulmonary samples
“CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations.”
Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Beekhuis, M.D., Pamela Nabetta, M.D., Doris Hilkemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krupp, M.D., Jenny Allen, B.Tech., Rasim Tahir, M.D., Robert Blakemore, B.S., Rosana Rustomjee, M.D., Ph.D., Ana Milovic M.S., Martin Jones, Ph.D., Sean M. O’Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Rausch-Grades, M.D., Eduardo Gotuzzo, M.D., Carmela Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

ABSTRACT

BACKGROUND
Global control of tuberculosis is hampered by slow, invasive diagnostic methods, particularly for the detection of drug-resistant forms and in patients with human immunodeficiency virus infection. Early detection is essential to reduce the death rate and in-treatment transmission, but the complexity and infrastructure needs of sensitive methods limit their accessibility and effect.

METHODS
We assessed the performance of Xpert Mtb/RIF, an automated molecular test for Mycobacterium tuberculosis (Mtb) and resistance to rifampin (RIF), with fully integrated sample processing in 1,790 patients with suspected drug-sensitive or multidrug-resistant pulmonary tuberculosis. Eligible patients in Peru, Azerbaijan, South Africa, and India provided three sputum specimens each. Two specimens were processed with N-acetyl-L-cysteine and sodium hydrosulfite before microscopy, solid and liquid culture, and the Mtb/RIF test, and one specimen was used for direct testing with microscopy and the Mtb/RIF test.

RESULTS
Among culture-positive patients, a single, direct Mtb/RIF test identified 541 of 564 patients with smear-positive tuberculosis (95.2%) and 124 of 171 with smear-negative tuberculosis (72.5%). The test was specific in 608 of 689 patients without tuberculosis (90.2%). Among patients with smear-negative, culture-positive tuberculosis, the addition of a second Mtb/RIF test increased sensitivity by 12.6 percentage points and a third by 5.1 percentage points, to a total of 96.2%. As compared with phenotypic drug-susceptibility testing, Mtb/RIF testing correctly identified 290 of 295 patients (98.0%) with rifampin-resistant bacteria and 504 of 514 (98.2%) with rifampin-sensitive bacteria. Sequencing resolved all but two cases in favor of the Mtb/RIF assay.

CONCLUSIONS
The Mtb/RIF test provided sensitive detection of tuberculosis and rifampin resistance directly from untreated sputum in less than 2 hours with minimal hands-on time. (Funded by the Foundation for Innovative New Diagnostics.)

From the Foundation for Innovative New Diagnostics, Geneva (C.C.B., M.D., M.D.); Forschungsinstitut zur Bekämpfung der Tuberkulose (K.F.), the Department of Clinical Laboratory Sciences, University of Cape Town, and National Health Laboratory Service, Cape Town (A.M., A.M.); and the Unit for Clinical and Biomedical TB Research, South African Medical Research Council, Durban (J.A., K.P.) — all in South Africa; P.D. Hinduja National Hospital and Medical Research Centre (M.G.), Mumbai, India (S.S., C.A.); Institute Maladies Respiratoires et Maladies Infectieuses, Université Paris-Nord, Côteaux, France (C.G.); Specialized Treatment Institution, Baku, Azerbaijan (M.T.), the Division of Infectious Diseases, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark (R.D.G.L.C., C.P.B., C.P.B., S.L., O.M.P.); and the Department of Epidemiology and Biostatistics, Delft University Medical Center, Delft, The Netherlands. Address reprint requests to Dr. Blakemore at the Foundation for Innovative New Diagnostics, Anafora Building 18, 1300 Gamman, Switzerland, or catharina.blakemore@finddiagnostics.org.

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## Molecular testing:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>% mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF</td>
<td>rpoB</td>
<td>&gt;96%</td>
</tr>
<tr>
<td>INH</td>
<td>katG</td>
<td>40-60%</td>
</tr>
<tr>
<td>INH-ETH</td>
<td>inhA</td>
<td>15-43%</td>
</tr>
<tr>
<td>PZA</td>
<td>pncA</td>
<td>72-97%</td>
</tr>
<tr>
<td>F-quinolones</td>
<td>gyrA</td>
<td>75-94%</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>tlyA</td>
<td>unknown</td>
</tr>
</tbody>
</table>

GenoType MTB-DR (Hain Lifescience)
Removing TB suspects from respiratory isolation: Efficiency of a single sputum NAAT compared to serial smears

Processing: 7 days; NAAT 6 days; broth medium monitored 7 days
NAAT (first specimen) - AFB and culture (3 specimens) - 493 pt [46 TB]

<table>
<thead>
<tr>
<th></th>
<th>Tuberculosis (46)</th>
<th>No TB (447)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Sputum NAAT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High ROTT (35)</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Low ROTT (11)</td>
<td>0</td>
<td>447</td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

ROTT = Risk of TB transmission
NAA Testing in Florida

Usefulness of NAA testing in Florida:

- Smear sensitivity around 40%, not specific for M. tuberculosis.
- At state lab, 1/2 of positive smears yields nontuberculous mycobacteria, including M. avium complex, M. kansasii, M. abscessus.
- Rapid results may have a role in determining if the patient has or does not have TB.
- Useful for infection control, management of isolation, contact investigation decision.
NAA Testing

• Culture must be done as an adjunct
  – This is quality assurance for the NAA test
  – Must have culture for subsequent susceptibility test
Frederic Chopin
Mallorca

“I have been sick as a dog the last two weeks; I caught cold in spite of
18 degrees C. of heat, roses, oranges, palms, figs and
three most famous doctors on the island.
One sniffed at what I spat up,
the second tapped where I spat it from,
the third poked about and listened how I spat it.
One said I had died,
the second that I am dying,
the third that I shall die.”
“How the battle against TB was won . . . and almost lost.”

1944 Streptomycin Introduced
1946 Youmans recognizes SM resistance
1951 Need for multi-drug therapy
1952 PZA introduced
1952 INH introduced
1961 EMB introduced
1966 Rifampin introduced

“The Lord hath created medicines out of the earth and he that is wise will not abhor them.”

Ecclesiasticus 38:4
Waksman Noble Prize 1952
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action
Development of Resistance

INH

INH

RIF

INH

RIF

INH

INH

INH

INH

INH

INH
“More bugs – more drugs!!!!!”

J. Sbabaro
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action
- Slow or intermittent growth of mycobacterium which permits the persistence of viable organisms despite prolonged antibiotic treatment, because only actively replicating organisms are killed by antibiotics
Treatment of Active TB Disease

- Start with 4 drugs in all patients
  - INH, RIF, PZA and EMB or SM until sensitivities return
  - If pansensitive, D/C EMB or SM
  - After 2 months of therapy, D/C PZA
  - Continue INH & RIF for 4 more months for total of 6 months
- Must have culture conversion by 2 months
- 6 month regimen good for HIV(-) and (+)
- Can use BIW regimen
  (TIW ? RIF Monoresistance in HIV pts after daily for first 2 months )
- Monitor adherence and toxicity
- DOT preferred, Combination pills for self administered
Determinants of Response to Therapy

- Clinical signs
  - Improved cough usually within two weeks
  - Fever usually within two weeks
    - However – can last four to six weeks
  - Weight gain and improved appetite
- Decreased organisms seen on smear
  - Usually markedly decreased within three to four weeks
    - However – can last for months
- Decreased counts on cultures
  - 90% convert in two months on INH/RIF/PZA
ATS/CDC/IDSA Treatment Guidelines 2003

- **Responsibility** for successful treatment is clearly assigned to the public health departments
- **Strong recommendations** for initial patient centered case management and DOT
- **Recommend getting sputum cultures** at two months to identify potential relapse
- **Extended treatment** for those still with positive cultures at two months and cavities on CXR
- **Role** for rifabutin, rifapentine and fluoroquinolones
- **Treatment completion** defined by number of doses as well as duration of therapy
Likelihood of Infectiousness

- Probably infectious
  - Positive sputum smears with viable AFB
  - Presence or induction of coughing
  - Not treated or recently started
  - Poor clinical or bacteriologic response to prescription

- Not infectious
  - Receiving effective therapy and responding
  - Three daily negative sputums
Causes of Inadequate Response to Therapy

- Non adherence!!!!!!!!!!!!!!!!!!!!
  - DOT
  - Involuntary detention
- Increased drug resistance/incorrect sensitivities
- Malabsorption/increased metabolism
- Inability of drugs to penetrate effected tissues
Clinical Significance of Resistance

- If pansensitive > 95% chance of cure
- If resistant to INH > 90% chance of cure
- If resistant to rifampin > 70% chance of cure
- If resistant to INH and RIF ~ 50% chance of cure
- Before chemotherapy ~ 50% chance of cure
Assure the treatment until cure of every tuberculosis patient!
DOT therapy works!

- 95% of patients with TB will be cured by DOT
  - Decreases morbidity and mortality and cost (~ $1500/patient)
  - Decreases spread of disease
    - Average patient with TB infects 30 other individuals
  - Decreases resistance
    - MDR costs ~ $250,000 to cure with only ~ 80% success
- 5% of patients with active TB will be unable to complete therapy requiring legal interventions and facilities to cure them
  - In S.F. one non-compliant patient with MDR-TB was responsible for 40 other cases
Infection Control

- Think TB, isolate, and start meds
- Six to eight air exchanges/hour
- Negative pressure
- Doors closed
- All entering room wear N95 mask
- Keep in isolation until three negative smears, on medications and responding clinically
## Nosocomial HIV-Related Multidrug-Resistant Tuberculosis Outbreaks

### As of August 1992

<table>
<thead>
<tr>
<th>Facility</th>
<th>Location</th>
<th>Time Period</th>
<th>Total Cases</th>
<th>Resistance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td>Miami</td>
<td>1988-91</td>
<td>65</td>
<td>INH, RIF (EMB, ETA)</td>
</tr>
<tr>
<td>Hospital B</td>
<td>NYC</td>
<td>1989-91</td>
<td>35</td>
<td>INH, SM (RIF, EMB)</td>
</tr>
<tr>
<td>Hospital C</td>
<td>NYC</td>
<td>1989-92</td>
<td>70</td>
<td>INH, RIF, SM (EMB, ETA, KM, RBT)</td>
</tr>
<tr>
<td>Hospital D</td>
<td>NYC</td>
<td>1990-91</td>
<td>29</td>
<td>INH, RIF (EMB, ETA)</td>
</tr>
<tr>
<td>Hospital E</td>
<td>NYS</td>
<td>1990-91</td>
<td>7</td>
<td>INH, RIF, SM, (EMB, ETA, KM, RBT)</td>
</tr>
<tr>
<td>Hospital F</td>
<td>NYC</td>
<td>1990-91</td>
<td>16</td>
<td>INH, RIF, SM, (EMB, ETA, KM, RBT)</td>
</tr>
<tr>
<td>Hospital I</td>
<td>NJ</td>
<td>1990-92</td>
<td>13</td>
<td>INH, RIF (EMB)</td>
</tr>
<tr>
<td>Prison System*</td>
<td>NYS</td>
<td>1990-92</td>
<td>42</td>
<td>INH, RIF (SM, EMB, ETA, KM, RBT)</td>
</tr>
</tbody>
</table>

**Total Cases**: 277

*24 Prison cases are also counted with Hospital C

INH = isoniazid; RIF = rifampin; SM = streptomycin; EMB = ethambutol; ETA = ethionamide; KM = kanamycin; RBT = rifabutin
## HIV Prevalence and Mortality of Multidrug-Resistant Tuberculosis Patients As of August 1992

<table>
<thead>
<tr>
<th>Facility</th>
<th>HIV Infection</th>
<th>Mortality</th>
<th>Median Interval TB Dx to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td>93%</td>
<td>72%</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Hospital B</td>
<td>100%</td>
<td>89%</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Hospital C</td>
<td>95%</td>
<td>77%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hospital D</td>
<td>91%</td>
<td>83%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hospital E</td>
<td>14%</td>
<td>43%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hospital F</td>
<td>82%</td>
<td>82%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hospital I</td>
<td>100%</td>
<td>85%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Prison System</td>
<td>98%</td>
<td>79%</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>
What factors contributed to the outbreak?

Breakdown of Source Control

- Convergence of highly susceptible, immunosuppressed patients with patients with active tuberculosis
- Delayed recognition of tuberculosis
- Delayed recognition of multidrug resistance
- Delayed initiation of **effective anti-tuberculosis therapy**
- Lapses of infection control practices
  - Delayed isolation
  - Poor ventilation
  - Lapses in respiratory isolation
  - Inadequate duration of isolation
  - Inadequate precautions for cough-inducing procedures
Negative air pressure is required for patient respiratory isolation rooms. It is created when the flow of air coming into the room from the regular source (blue) is less than the flow outward through vents and ducts (red). This allows air to come in from the corridor (purple). In-flow greater than outflow (not shown) creates positive pressure, which allows air to escape from the isolation room, increasing the danger of spread of infection.
Common Obstacles

Adherence

HIV  TB

Resistance
Common Future

Vaccine

HIV

TB
Assure the Treatment Until Cure of Every Tuberculosis Patient!
We may have won a battle but the war is far from over.
“U” Shaped Curve of Concern

Disease Rates High
Concern High

Disease Rates declines
Concern declines

Concern Declines
Disease Rates Rise

- Reichman 1991
Southeast National TB Center
Hotline
1-800-4TB-INFO