Building Specialized Knowledge: Tuberculosis

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Objective: provide background for understanding the importance of tuberculosis as a public health problem, the rationale for current control strategies, and the status of tuberculosis and tuberculosis control today.

Outline of talk:
• The basics
  – the organism
  – transmission
  – infection and disease
  – diagnosis
  – treatment
• Epidemiology: current status globally, in US and Brazil
• Current strategies for control
• Discussion

Topics for discussion
• What do you know about the tuberculosis control programs in the United States and Brazil?
• Should strategies that are currently employed in only one country be introduced into the other (e.g., BCG, INH preventive therapy)?
• In this talk, we focus on strategies and interventions for tuberculosis control. How would you evaluate implementation of the strategies? Specifically, what might you consider during visits to centers during your time in São Paulo?
• Can tuberculosis be eradicated? Eliminated as a public health problem? By 2050?
Robert Koch

“The struggle [against tuberculosis] has caught hold along the whole line and enthusiasm for the lofty aim runs so high that a slackening is no longer to be feared. If the work goes on in this powerful way, then the victory must be won.”

Mycobacterium tuberculosis: the tubercle bacillus, Koch’s bacillus (BK), acid-fast bacillus (AFB)

Stop TB Strategy (2006)

- Vision: A TB-free world
- Targets
  - By 2015: Halt and begin to reverse the incidence of TB (Millenium Development Goal 6c)
  - By 2015: reduce prevalence of and deaths due to TB by 50% compared with a baseline of 1990
  - By 2050: eliminate TB as a public health problem

Mycobacterium tuberculosis

- The organism
- Transmission
Tuberculosis: the organism

- *Mycobacterium tuberculosis:*
  - human beings the reservoir; *M. bovis*, other species less important
  - different strains (distinguished by molecular methods)
- Aerobic: requires high levels of oxygen
- Slow generation time (15-20 hours)
- High cell wall content of lipids
  - Prevents digestion by macrophages
  - Interferes with many antibiotics
  - Staining characteristics (acid-fast)

Tuberculosis: transmission

- Persons with tuberculosis: increased infectiousness
  - Sputum smear positive
  - Culture positive
  - Cavitation on chest x-ray, laryngeal TB
  - Coughing, sneezing > talking
- Environmental risk for transmission
  - Indoors (UV light kills TB bacilli)
  - Small, enclosed spaces
  - Poor ventilation
- Increased risk for infection
  - Greater exposure to infectious person (duration, frequency, proximity)
  - Increased susceptibility (e.g., immunosuppression)
Tuberculosis: infection and disease

Bacilli that reach alveoli multiply freely in alveoli and alveolar macrophages; small numbers spread throughout body via bloodstream

Replication proceeds for ~2-8 weeks until cellular immunity develops; activated lymphocytes and macrophages surround and contain bacilli.

Infection during this stage often asymptomatic. Chest x-ray may show healed lesions that can contain viable organisms.


• Persons with intact immunity are able to form granulomas, control infection, contain surviving bacilli in dormant healed lesions, and eliminate bacilli that periodically reactivate

• Persons with latent tuberculosis infection (LTBI):
  – have no symptoms and are not infective to others
  – usually have a positive tuberculin skin test or blood test that measures cellular immunity to M. tuberculosis (interferon-gamma release assay)
  – May develop active tuberculosis sometime later in life, either by reactivation of old infection or exogenous reinfection (though less susceptible than uninfected persons)
• If the immune system cannot contain the tubercle bacilli, they multiply and produce **active tuberculosis (disease)**

• Overall, active tuberculosis develops in only 5-10% of persons infected with *M. tuberculosis*

• Persons may develop
  – Primary progressive tuberculosis (more common in children)
  – Reactivation or reinfection tuberculosis (more common in adults)

• Infection may be pulmonary (most common), extrapulmonary or disseminated (miliary)

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**Symptoms of active tuberculosis**

• Fever, sweats, loss of appetite, weight loss

• Pulmonary: cough, sputum, bleeding, chest pain

• Other organ systems:
  – Nervous system
  – Lymph nodes
  – Musculoskeletal
  – Genitourinary
  – Gastrointestinal
  – Cardiac

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**Persons at increased risk for progression of latent tuberculosis infection to active tuberculosis (disease)**

• Age: infants, < 5 years, 15-25 years, elderly

• Recently infected (~5% within 1st 2 years)

• Infected with HIV (7-10%/year)

• Diabetes (30% over lifetime)

• Silicosis, chronic renal failure, malignancies, gastrectomy, malnutrition

• Receiving immunosuppressive therapy

• Cigarette smoking, abuse of alcohol or drugs

• Heavily exposed, exposed to more virulent strain

• Medically underserved, low income

• Genetics
Tuberculosis: tools for prevention and control

- Diagnosis
  - Infection
  - Disease
- Treatment
  - Infection
  - Disease
- Prevention
  - Disease
  - Infection

Tests for tuberculosis infection

<table>
<thead>
<tr>
<th>Tuberculin skin test</th>
<th>Interferon-gamma release assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person has been infected with M. tuberculosis</td>
<td>Blood is drawn for testing; test measures the immune response to the TB bacteria in whole blood</td>
</tr>
<tr>
<td>Requires two or more patient visits to conduct the test</td>
<td>Requires one patient visit to conduct the test</td>
</tr>
<tr>
<td>Results are available 48 to 72 hours later</td>
<td>Results can be available in 24 hours depending on the batching of specimens by the laboratory and transport</td>
</tr>
<tr>
<td>Can cause booster phenomenon</td>
<td>Does not cause booster phenomenon</td>
</tr>
<tr>
<td>Reading by HCW may be subjective</td>
<td>Laboratory test not affected by HCW perception or bias</td>
</tr>
<tr>
<td>IGRA vaccination can cause false-positive result</td>
<td>IGRA vaccination does not cause false-positive result and infection with most non-tuberculosis mycobacteria does not cause false-positive result</td>
</tr>
<tr>
<td>A negative reaction to the test does not exclude the diagnosis of LTBI or TB disease</td>
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</table>

cdc.gov

Active tuberculosis (disease): laboratory confirmation of clinical and radiological diagnosis

Smears
- Carbol-fuchsin methods (Ziehl-Neelson, Kinyoun), direct microscopy
- Auramine-rhodamine, fluorescent microscopy
- 5000-10,000 bacilli/mL needed for detection
- Rapid
- Does not distinguish M. tuberculosis from other mycobacteria

Culture (gold standard)
- Solid media (Lowenstein-Jensen, others); 3-8 wks
- Liquid media (e.g., Middlebrook 7H12); 1-3 wks
- Detects 10-100 bacilli/ml
- Provides organisms for speciation, susceptibility testing, stain identification
- Liquid systems can be automated
Diagnosis of active tuberculosis (disease): nucleic acid amplification

- Several commercially available assays that target amplified DNA or ribosomal RNA
- Sensitivity intermediate between that of smears and cultures
- For smear positive sputum, sensitivity and specificity >95%; for smear negative, culture positive, sensitivity 40-77%, specificity 95%
- Complements smears and cultures

Xpert MTB/RIF test

- Fully-automated molecular test.
- Simultaneously detects TB and rifampin drug resistance
- Provides accurate results in less than two hours so that patients can be offered proper treatment on the same day
- Has minimal bio-safety requirements, training, and can be housed in non-conventional laboratories

WHO RECOMMENDATIONS

- Strong recommendation: should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB
- Conditional recommendation: may be used as a follow-on test to microscopy in settings where MDR-TB and or HIV is of lesser concern, especially in smear-negative specimens

EXPECTED IMPACT

- 3-fold increase in the diagnosis of patients with drug-resistant TB
- Doubling in number of TB/HIV cases diagnosed in areas with high rates of TB and HIV (compared to microscopy diagnosis)
Antituberculosis Drugs

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide

**Second-Line Drugs**
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*
- Moxifloxacin*
- Gatifloxacin*

*Not approved by US FDA for the treatment of TB

Treatment of latent tuberculosis infection

- International Union Against Tuberculosis trial: 6 and 9 months of INH reduced progression from latent tuberculosis infection to active tuberculosis by 68 and 93%, respectively
- Current regimens in US (after ruling out active tuberculosis):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily or 2x/wk *</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily or 2x/wk</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
</tr>
<tr>
<td>Isoniazid and rifapentine</td>
<td>Once weekly</td>
<td>Once weekly*</td>
</tr>
</tbody>
</table>

*Use directly observed therapy (DOT)

Treatment of active tuberculosis

- Before effective treatment became available, 50% of patients with active pulmonary tuberculosis died in 2 years and only 25% were cured
- Barriers to successful treatment
  - Drug resistance
  - Inappropriate regimen
  - Nonadherence to therapy (underscores importance of directly observed therapy)
- Principles of treatment
  - Active tuberculosis must be treated for at least 6 months (most bacilli killed in the first 2 months, but a few bacilli survive longer and treatment needed for several more months)
  - Treatment regimens must continue multiple drugs to which the organism is susceptible because treatment with a single drug can lead to the development of resistance
Spontaneous mutations develop as bacilli proliferate to $>10^8$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>$10^{-8}$</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>$10^{-6}$</td>
</tr>
</tbody>
</table>

Typical lung cavity has ~100 million ($10^8$ bacilli)

Rationale for multi-drug therapy

Drug-resistant mutants in large bacterial population

Multidrug therapy: No bacteria resistant to all 3 drugs

INH

RIF

PZA

Monotherapy: INH-resistant bacteria proliferate

INH

Spontaneous mutations develop as bacilli proliferate to $>10^8$

INH resistant bacteria multiply to large numbers

INH

RIF

INH mono-resist. mutants killed, RIF-resist. mutants proliferate $\rightarrow$ MDR TB
Treatment Regimens for Active Tuberculosis

- Initial phase: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months, (except one regimen that excludes PZA)
- Continuation phase: additional 4 months or (7 months for some patients: those with positive smears at 2 months, cavitary lesions or silicosis)
- Four regimens recommended for treatment of culture-positive TB, with different options for dosing intervals in continuation phase

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuous Phase</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>6 days/week for 20 doses (8 weeks)</td>
<td>12 (6+6)</td>
</tr>
<tr>
<td></td>
<td>7 days/week for 10 doses (5 weeks)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

- Treatment Monitoring

  - Serial sputum smears every 2 weeks to assess early response
  - Monthly sputum for AFB smear and culture (until 2 consecutive cultures negative)
  - Additional drug-susceptibility tests if culture-positive after 3 months of treatment
DOTS (WHO 1993):
Directly observed therapy
• Commitment of governments to a national tuberculosis programme
• Detection of cases through case finding by sputum smear microscopy examination of patients with suspected tuberculosis in general health services
• Standardised short course chemotherapy with the first line drugs isoniazid, rifampicin, pyrazinamide, and ethambutol (or streptomycin) for, at least, all smear positive cases of tuberculosis under proper conditions of case management
• Regular, uninterrupted supply of all essential antituberculosis drugs
• A monitoring system for programme supervision and evaluation.
  In addition:
• Mycobacterial cultures and drug susceptibility testing are not required
• Treatment is started on the basis of symptoms or a positive smear
• Second line drugs are not used
• Three categories of treatment regimens exist; all are directly observed
• In the developing world, mycobacterial cultures and susceptibility testing are generally not performed, so drug resistance is not detected even if it is present

Treatment Failure
• Defined as positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured
• Single new drug should never be added to a failing regimen; it may lead to acquired resistance to the added drug
• Add at least three new drugs (e.g., fluoroquinolone, ethionamide, and an injectable drug: SM, amikacin, kanamycin, or capreomycin) to the existing regimen being cognizant of the possibility of drug resistance

Drug resistance: Definitions
• Primary drug resistance:
  – Infected with TB which is already drug resistant
• Secondary (acquired) drug resistance:
  – Drug resistance develops during treatment

MDR TB (multi-drug resistant): TB isolate that is resistant to both isoniazid and rifampin

XDR TB (extensively resistant): MDR + resistance to fluoroquinolone and 1 of the 3 injectable drugs (amikacin, kanamycin, capreomycin)

TDR TB "Totally resistant": not clearly defined, but cases of resistance to all 1st and 2nd line drugs or all drugs tested
DOTS-Plus

- Second line antituberculosis drugs (more toxic and expensive, and less effective, than first line drugs) are used. The regimen includes two or more drugs to which the isolate is susceptible, including one drug given parenterally for six months or more. Total duration of treatment 18-24 months; treatment is directly observed
- Treatment regimen is either:
  - Individualised according to drug susceptibility test results of the \textit{M} \textit{tuberculosis} isolate identified on culture; or
  - Given as a standardised regimen to patients who fail supervised re-treatment (for example, when culture and drug susceptibility testing are not performed).
- Mycobacterial cultures and drug susceptibility testing may be performed.

Death of XDR TB Cases Defined on Initial DST (drug sensitivity testing), 1993–2007

<table>
<thead>
<tr>
<th>Status</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead at Diagnosis</td>
<td>2</td>
</tr>
<tr>
<td>Died During Therapy</td>
<td>15</td>
</tr>
</tbody>
</table>

**Total Deaths** 17

- **Percent of Death Among Total XDR Cases (17/48)** 35%
- **Percent of Death Among XDR Cases with a Known Outcome\(^a\) (17/33)** 52%

\(^a\) Known Outcomes are cases who died or completed therapy
Bacillus Calmette-Guérin (BCG)

- Current vaccine for tuberculosis
- Live attenuated strain of *Mycobacterium bovis*; original strain subcultured every 3 weeks x 13+ years;
- Subsequently maintained by continuous subculture in different laboratories
- First used as vaccine in 1921
- Currently produced by several laboratories using lyophilized seed lots
- At best, 60-85% effective in preventing TB for 5-15 years
- At worst, no effect
- Variable efficacy in part depends on geography; efficacy lower closer to the equator

BCG

- Efficacy greatest in preventing TB meningitis and miliary TB; variable in preventing pulmonary TB
- Never used in US
- UK (1953-2005): universal immunization of all school children at age 13, immunization of high risk infants
- Brazil: universal BCG immunization introduced 1967-8; given again to health care professionals, close contacts of patients
Epidemiology:
Current status globally, in Brazil and in US

Global Epidemiology of Tuberculosis
• *M. tuberculosis* infects 1/3 of the world’s population
• Tuberculosis ranks as the eighth leading cause of death and low-and middle-income countries; among adults aged 15-59 years, it is the third cause of death, after HIV/AIDS and ischemic heart disease
• 8.6 million fell ill with tuberculosis in 2012, including 1.1 million persons with HIV infection (but only 5.8 million were reported)
• In 2012, 1.3 million people died from tuberculosis, including 320,000 persons with HIV/AIDS
• Tuberculosis is one of the top killers of women, with 250,000 deaths among HIV-negative and 160,000 deaths among HIV-positive women

Tuberculosis-2012 Global Report
• 22 “high-burden” countries account for 80% of the world tuberculosis cases
• Globally, absolute number of cases is increasing slowly, but the number of cases per capita has falling by around 2% a year
• Highest burden in Africa and India
• India and China account for 38% of the world’s TB cases
• 60% of cases in South-East Asian and Western Pacific regions
• African Region has 24% of world’s cases and the highest rate of cases and deaths per capita
• Worldwide 3.6% of new cases and 20.2% of previously treated cases were estimated to have MDR-TB
• 84,000 cases were reported, but this is only 1/5 of the estimated 450,000 estimated incident cases of MDR-TB
• The highest proportions of TB patients with MDR-TB are in Eastern Europe and central Asia
• Approximately 9.6% of MDR-TB cases have XDR-TB; XDR-TB reported in 92 countries

Tuberculosis/HIV facts: 2013
• At least one third of the 35.3 million people living with HIV worldwide is infected with tuberculosis (latent tuberculosis infection). Persons co-infected with tuberculosis and HIV are 21-34 times more likely develop active TB in persons without HIV
• Tuberculosis the most common presenting illness among people living with HIV, including those were taking antiretroviral therapy. They were estimated 1.1 million HIV positive new tuberculosis cases globally in 2012. Approximately 75% of these were in sub-Saharan Africa.
• Tuberculosis is the leading cause of death among people living with HIV, accounting for 1 in 4 HIV-related deaths. In 2012, approximate 430,000 people died of HIV-associated tuberculosis.
• Persons with HIV are facing emergent threat of drug-resistant tuberculosis, including MDR-TB and XDR-TB.

Estimated burden of disease caused by TB, Brazil 2012 (WHO 2013)
• Population 198,656,000
• Prevalence 120,000 (51-210,000); rate 59/100,000
• Incidence 92,000 (76-110,000); rate 46/100,000
• Mortality: 4,900 (4.6-5.2,000); rate 2.5/100,000
• HIV-positive incident cases 16,000 (13,000-19,000)
• Of the 22 “high-burden” countries, Brazil has the 4th largest population, the 7th lowest number of prevalent cases, the 3rd lowest number of incident cases, 3rd lowest numbers of deaths and the lowest prevalence, incidence and mortality rates!
**Reported TB Cases**
United States, 1982–2012*

- *Updated as of June 10, 2013.*

**TB Morbidity**
United States, 2007–2012

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>13,282</td>
<td>4.4</td>
</tr>
<tr>
<td>2008</td>
<td>12,895</td>
<td>4.2</td>
</tr>
<tr>
<td>2009</td>
<td>11,520</td>
<td>3.8</td>
</tr>
<tr>
<td>2010</td>
<td>11,163</td>
<td>3.6</td>
</tr>
<tr>
<td>2011</td>
<td>10,517</td>
<td>3.4</td>
</tr>
<tr>
<td>2012</td>
<td>9,945</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*Cases per 100,000. Updated as of June 10, 2013.*

**Tuberculosis in US: 2012**

- Population: 310.5 million persons in 2012
- 9,945 in 2012, a 5.4% decrease from 2011; rates/100,000 decreased 5.9% (3.4 to 3.2/100,000)
- California, Texas, New York and Florida accounted for >50% of cases
- TB case rate was 1.4 per 100,000 for US born persons and 15.9 for foreign-born persons
- 1.1% of cases had 1<sup>st</sup> multidrug resistance; 2 cases had XDR-TB
- Asians exceeded all other racial or ethnic groups with the largest percentage of total cases (30%); those born outside of the US accounted for 29% of the national total
- 7% of persons with TB who reported HIV status were HIV-positive
TB Case Rates by Age Group and Sex, United States, 2012

Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2012*

Countries of Birth of Foreign-born Persons Reported with TB, United States, 2012
Tuberculosis: prevention and control

Strategies for control of tuberculosis

- Detection and treatment of cases
- Treatment of latent cases
- Vaccination
- Modification of risk factors
- Infection control

2015 Targets (from MDGs)
- >70% with infectious TB will be diagnosed
- >85% of those will be cured
- By 2015, global prevalence of TB will be reduced to 50% of 1990 levels
- By 2050, global incidence will be <1/million population
Stop TB Strategy (WHO)

- pursue high-quality DOTS expansion and enhancement;
- address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations;
- contribute to health system strengthening based on primary health care;
- engage all care providers;
- empower people with TB, and communities through partnership; and
- enable and promote research.

1. Pursue high-quality DOTS expansion and enhancement
   a. Secure political commitment, with adequate and sustained financing
   b. Ensure timely case detection and diagnosis through quality-assured bacteriology
   c. Provide standardised treatment, with supervision, and patient support
   d. Ensure effective drug supply and management
   e. Monitor and evaluate performance and impact

2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations
   a. Scale up collaborative TB/HIV activities
   b. Scale up prevention and management of MDR-TB
   c. Address the needs of TB contacts, and of poor and vulnerable populations

3. Contribute to health system strengthening based on primary health care
   a. Help improve health policies, human resource development, financing, supplies, service delivery, and information
   b. Strengthen infection control in health services, other congregate settings and households
   c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health
   d. Adopt successful approaches from other fields and sectors, and foster action on the social determinants of health

4. Engage all care providers
   a. Involve all public, voluntary, corporate and private providers through Public-Private Partnerships (PPP) approaches
   b. Promote use of the International Standards for Tuberculosis Care

5. Empower people with TB, and communities through partnership
   a. Pursue advocacy, communication and social mobilisation
   b. Foster community participation in TB care, prevention and health promotion
   c. Promote use of the Patients’ Charter for Tuberculosis Care

6. Enable and promote research
   a. Conduct programme-based operational research
   b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines

STOP TB: achievements (2012)

STOP TB: achievements (2012)

- 1995-2012: 56 million patients treated according to WHO’s strategy, 41 million successfully; 22 million lives saved
- Case detection/notification rate rates ~66% in 2012
- Treatment success rate for new smear-positive cases of pulmonary tuberculosis reached 87%
- Percentage of tuberculosis patients tested for HIV reached 40% (and 69% in the African region)
- 75% of HIV positive TB patients were given SMP-TMX, and 48% were receiving antiretroviral treatment
- Approximately 50,000 MDR-TB patients were enrolled for treatment
- Xpert MTB/RIF test was rolled out in 95 countries; price was reduced 41%
- 11 vaccines to prevent TB are moving through development in stages

STOP TB 2011-2015: Anticipated results

- Diagnosis and treatment of 32 million people with TB using Stop TB/DOTS approach, successfully treating 28 million
- Testing 7 million people for MDR-TB, confirming 1 million cases and treating them
- HIV testing for almost 30 million TB patients; screening 71 million people living with HIV for TB
- 4 million HIV-TB coinfected patients receiving both TMP-SMX and antiretroviral therapy
STOP TB 2011-2015
Research and development: anticipated results

- Point of care tests for diagnosing active TB, latent TB (and projecting risk of progression to TB disease), detecting drug resistance- >50 companies involved
- New, 4-month TB treatment regimen for patients with susceptible infection
- At least one new drug on the market for treatment of drug-resistant tuberculosis; 10 new drugs in late stages of development
- Safer, higher efficacy regimen for treatment of latent tuberculosis infection
- New tuberculosis vaccine candidate: 10 (phase 1-2b), 4 in phase 3 clinical trials

WASHINGTON (AP) — Dec 31, 2012. The Food and Drug Administration on Monday approved a Johnson & Johnson tuberculosis drug that is the first new medicine to fight the deadly infection in more than four decades.

The agency approved J&J's Sirturo, for use with older drugs to fight a hard

STOP TB: 2011-2015

- Total cost of plan: 2011-2015: $47 billion
  - $37 billion for implementation, 10 billion for research
  - 48%: implementation of the DOTS component
  - 15% interventions to manage drug-resistant TB
- 2013-2015: funding gap is up to $3 billion/year

If no improvements in tuberculosis control are made from 2011-15, approximately 10,000,000 people will die from tuberculosis by 2015.
Topics for discussion

• What do you know about the tuberculosis control programs in the United States and Brazil?
• Should strategies that are currently employed in only one country be introduced into the other (e.g., BCG, INH preventive therapy)?
• In this talk, we focus on strategies and interventions for tuberculosis control. How would you evaluate implementation of the strategies? Specifically, what might you consider during visits to centers during your time in Sao Paulo?
• Can tuberculosis be eradicated? Eliminated as a public health problem? By 2050?