Tuberculosis in the U.S. 
An Epidemic Moving Toward Elimination

- 13,299 cases (4.4/100,000) in 2007
- Fifteenth year of decline (down 3.3% from 2006)
- 98 cases (0.9%) of MDR-TB in 2007 compared to 450,000 new cases around the world
- 26 states meet year 2000 elimination target (< 3.5/100,000)
- Completion of therapy exceeds 90%
Drug Resistant TB
Global Issues

- Updated *Global Plan to STOP TB* calls for culture and DST of all re-treatment patients by 2010 and universal DST for all newly diagnosed culture positive TB patients by 2015
- Global XDR TB Action Plan calls for the wide implementation of rapid assays for MDR TB in collaboration with FIND

Drug Resistant TB:
Human Resource Challenges

- It is estimated that one culture/DST capable laboratory will be needed per 5 million population
- It is also estimated that fewer than 5% of TB patients worldwide have access to first line DST
- If scale up of laboratory capacity is achieved, the overall requirements for testing will be somewhere between 5-10 million per year

Global laboratory capacity gap:
USD 2.6 billion required over next 7 years
The need for new diagnostic tests and strategies

- Case detection rates increasing slowly
- Some settings: <50% of estimated cases detected in DOTS programs
- Smear microscopy not sensitive
- Culture slow, resource intensive
- Culture-based drug susceptibility testing even slower, technically challenging

Progress in past 5 years

- Global Plan to Stop TB 2006-2015: provides framework to make new diagnostics accessible to high burden settings
- Stop TB Partnership Task Force on Retooling to stimulate adoption, introduction, implementation
- FIND & partners: catalyzing development, facilitating availability of new tests

New Diagnostics in the Pipeline

- There are at least twenty different technologies in various stages of development and evaluation
- Distinct target areas are being evaluated including growth and detection as well as molecular assays
- Liquid cultures with rapid species identification and line probe assays were endorsed by the WHO in 2007-2008
Cost per valid test result
(Cape Town data)

- From sputum (n=581):
  - Total cost of MTBDRplus testing from sputum = $581 * $18.00 = $10,458.00
  - Proportion of interpretable results from sputum = 97.1% (567/581)
  - Cost per valid MTBDRplus result from sputum = $19.66

- From culture (n=1104):
  - Total cost of testing from culture = $28,272 * $31 = $880,192
  - Proportion of interpretable results from culture = 94.5% (1043/1104)
  - Cost per valid MTBDRplus result from culture = $26.32

- For MGIT culture + DST (n=1686):
  - Total cost of testing = $1095 x $24.55 = $26,265.25
  - Proportion of interpretable results = 79.2% (1343/1686)
  - Cost per valid DST result = $37.12

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Current Methods for Diagnosing Drug Resistant TB
Diagnosis of TB Drug Resistance

Epidemiological Characteristics
- Previous treatment for TB disease (*recent? Self-administered?)
- History of exposure to an individual with MDR-TB
- Recent emigration from a geographic region with a high prevalence of resistance to tuberculosis therapy (former USSR, China, Korea, Honduras, Peru)

Clinical Characteristics
- Lack of sputum culture conversion to negative after 2 months of therapy for TB
- Progressive clinical and/or radiographic findings while on TB therapy
- Travel to a region with high rates of drug resistant TB
- Residence or work in an institution or setting in which drug-resistant TB is documented
- HIV

So, how good are these risk factors in predicting drug resistant TB?
- Retrospective, case control study to identify risk factors for MDR-TB and analyze impact of testing for rifampin resistance by rpoB gene mutation identification
- Of 42 confirmed MDR-TB cases that were evaluated almost half (43%) of patients did not have any of the conventionally recognized risk factors for MDR

Diagnosis of TB Drug Resistance

- Conventional methods: (indirect/proportion method?)

- Molecular Beacon Testing:
  - Real-time PCR test
  - Performed directly on AFB+ smears or on growth on solid media or MGIT tube
  - INH resistance: *katG, inhA* (85%)
  - RIF resistance: *rpoB* core region (>95%)

Diagnosis of TB Drug Resistance

- Line Probe Assays
  - commercially available in Europe - not cleared yet by FDA
  - Hain: detects presence of TB complex and gene mutations associated with Rifampin resistance (*rpoB*) and INH resistance (*katG* and *inhA*)
  - In smear positive specimens:
    - Rifampin resistance: Sensitivity (98.9%) Specificity (99%)
    - INH resistance: Sensitivity (94%) Specificity (99%)
  - Turnaround times: 1-2 days

How Do We Innovate the Diagnosis and Management of TB in a Cost Cutting Environment?
DX OF TB DRUG RESISTANCE

- 4 TB Regional Training and Medical Consultation Centers (RTMCCs)
- Regionally assigned to cover all 50 states
- Provide training, technical assistance and medical consultation to TB programs and medical providers.

What is a “HAINS” test

- What is it?
- How is it done?
- How sensitive? Specific?
- FDA status

Methodology

- The MTBDRplus is based on DNA STRIP technology and permits the molecular genetic identification of the MTB complex and its resistance to rifampin and or isoniazid from cultivated samples or pulmonary smear positive direct patient material.
- The identification of rifampin resistance is enabled by the detection of the most significant mutations of the rpoB gene.
- The identification of high level INH resistance the katG gene is examined and for low level INH resistance the inhA gene is examined.
HAIN PILOT PROJECT

- Partnership with Dr. Max Salfinger and grant through the Virginia TB Foundation

- Hain Pilot Project:
  - Physicians managing MDR suspects call 1800 TB hotline, in consultation with a clinical expert, they obtain permission to order test and shipping instructions
  - SNTC administrator coordinates transport of specimen to lab

Hain Study Protocol

- **Aim 1**: To determine the mean time from date of Hain test request to date of Hain test report.

  **Hypothesis**: The molecular drug susceptibility testing will reduce the amount of time to identify presence or absence of drug resistance in a patient with active tuberculosis.

Hain Study Protocol

- **Aim 2**: To identify any programmatic obstacles that contribute to delays in the testing or reporting of the specimen

  **Hypothesis**: Regionalization of innovative diagnostic tools for TB has the potential to be a powerful strategy that would significantly improve current standard of care even in the context of cost-cutting measures that are being imposed upon TB programs across the country. Obstacles that create delays in reporting to consultants must be identified and minimized to improve upon future program implementation
Hain Study Protocol

Aim 3: To analyze clinician response to the Hain test.

Hypothesis: Clinicians with improved confidence are more likely to use molecular DST in the future. Earlier detection of non-resistant strains will result in patients taking fewer drugs and thereby having less adverse side effects. If resistance is detected than patients will be started on appropriate medication at an earlier time decreasing transmission, results will also impact the priority of subsequent contact investigations.

The test is restricted to cases of patients who were considered to be at risk for MDR based on signs, symptoms, risk factors, TST, and chest radiograph. Pt had to have at least one clinical risk factors for drug resistance:
- Previous treatment for TB disease
- Exposure to an individual with MDR-TB
- Recent emigration from a geographic region with a high prevalence of resistance to tuberculosis therapy
- Progressive clinical and/or radiographic findings while on TB therapy
- Lack of sputum culture conversion to negative after 2 months of therapy for TB
- Travel to a region with high rates of drug resistant TB
- Residence or work in an institution or setting in which drug resistant TB is documented

Questionnaire for Clinicians:

1. How high is your clinical suspicion for MDR-TB?
   - High (>75%) __
   - Moderate (50-74%) __
   - Low (25-49%) __
   - Very low (<25%) __

2. Indicate the criteria for MDR risk (1-7) all that apply:
   a. previous treatment for TB disease
   b. exposure to an individual with MDR-TB
   c. recent emigration from a geographic region with a high prevalence of resistant TB
   d. progressive clinical and/or radiographic findings while on TB therapy
   e. lack of sputum culture conversion to negative after 2 months of therapy for TB
   f. travel to a region with high rates of drug resistant TB
   g. residence in an institution or setting in which drug resistant TB is documented
Questionnaire for Clinicians

3. At the time of specimen collection did you start treatment with anti TB drugs?

4. Which drugs did you use? (List options and specify all that apply)

5. If no, did access to the HAIN test influence your decision to wait to start medication until the results were received?

6. What do you as a clinician think is an appropriate time frame to have HAIN results?

7. Were you satisfied with the length of time it took to get the HAIN test result: very satisfied/ satisfied/ not satisfied/ 

Questionnaire for Clinicians

8. Did the result of the DST change your clinical management of the patient?

9. Did you start new drugs-specify/ stop drugs/ no change?

10. If yes, specify what new drugs were added and which were stopped.

11. Did the DST (HAIN) result aid in contact investigation?

12. Did the DST (HAIN) result alter your confidence in clinical diagnosis and management of suspected MDR?

13. Will you plan to order DST (HAIN) again in the future if clinical case suspicious for MDR?

HAIN’S Regional Project

- 57 requests made from our region between April 1, 2008 and March 31, 2009
- Hain performed on 35
- 22 not included in study and did not have Hain due to:
  - 10 were MTD negative
  - 3 lacked clinical information
  - 1 specimen not received by lab
  - 1 specimen in which sensitivities known by the time Hain request was made
  - 1 specimen received as paraffin block
  - 6 Hain requested for reasons other than outlined in study
States that made requests:
- Florida 39
- Georgia 1
- South Carolina 1
- Louisiana 2
- North Carolina 3
- Tennessee 2
- Virginia 8
- Kentucky 1
Average number of days from time of request to time to report: 8

Resistance Patterns:
- 9 cases were either INH or Rif resistant
- 4 cases of Rifampin monoresistance (risk factors included 1 from Haiti, 1 clinical worsening on treatment, 2 had hx of prior tx or TB)
- 2 MDR (risk factors included 1 from Haiti, 1 had hx of prior TB treatment)
- 3 cases of INH monoresistance (risk factors included 1 recent arrival from Nepal, 1 prior tx for TB in Philippines, 1 recent arrival from Soviet Union)

Discussion:
- Consultants more likely to delay initiating regimen until test result available (when pt is clinically stable)
- Test result provided reassurance to consultants who did not start an empiric expanded regimen despite pt risk factors for MDR: in low incidence region, the strength of test will be in its ability to rule-out MDR-TB
- Early cessation of EMB?

New State-Wide Recommendations:
- All AFB positive specimens will be processed for HAIN test and all Rif resistant cases are referred to the TB-Physicians Network
Case 1

- Pt was diagnosed with pulmonary with smears AFB 3+ positive and MTD+ and was started on standard 4-drug RIPERIPE
- Sputum became smear negative within 2 weeks
- One month later, the patient developed fevers as high as 104 and smears were positive again.
- Patient was hospitalized in isolation.
- Because she does not appear to be clinically responding to treatment, we would like to test for drug resistance with the Hains test.

Case 2

- 54 year old male is HIV positive and has a new diagnosis of pulmonary MTB (MTD is positive)
- He is a contact to INH resistant case
- He has received 2 weeks of Rifampin monotherapy for LTBI (the MD did not think he had active disease at the time)

Case 3

- Patient is US born and volunteers in a daycare center with very young children
- She was treated for pansensitive MTB in 2005
- She now present with cough, weight loss and lower lobe infiltrates
Hain Study Protocol

• Discussion:
  – What about cases that are contacts to vulnerable populations (infants, HIV etc)?
  – What about cases presenting with life-threatening forms of MTB (meningitis, disseminated)?
  – What about cases intending to travel long distances?
  – Can we stop EMB early?

Where are we now?

• Surveys for participating consultants to assess clinician’s response to test
• Analyze complete data from April 2008-March 2009
• Assess factors that impede rapid turnaround:
  – Release from requesting state (hospital/state labs)
  – Fed-Ex pick-up and delivery
  – Florida State lab : processing and reporting

Future Directions

• Role of Florida State Lab
• All AFB + specimens?
• All AFB/ MTD + specimens?
• New assays to detect XDR-TB?