How Much TB is out there?

- World Wide TB: 9 million new cases/yr
  2 million deaths per year
- US: 13,293 in 2007
  Just under 13,000 in 2008
- Virginia: 309 in 2007
  292 in 2008
  273 in 2009
- 1/3 of world’s population is infected with TB bacteria (latent TB Infection = LTBI)

Have germs, will travel…
Migrating populations in the 1990s

Compared to 1960-75, four-fold increase in migration

Source: Population Action International 1994
Estimated TB Incidence Rates, 2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>VA Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>350</td>
<td>5.5</td>
</tr>
<tr>
<td>1996</td>
<td>349</td>
<td>5.3</td>
</tr>
<tr>
<td>1997</td>
<td>349</td>
<td>5.3</td>
</tr>
<tr>
<td>1998</td>
<td>339</td>
<td>5.2</td>
</tr>
<tr>
<td>1999</td>
<td>334</td>
<td>4.9</td>
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<tr>
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<td>292</td>
<td>4.1</td>
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<tr>
<td>2001</td>
<td>366</td>
<td>4.3</td>
</tr>
<tr>
<td>2002</td>
<td>315</td>
<td>4.5</td>
</tr>
<tr>
<td>2003</td>
<td>332</td>
<td>4.6</td>
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<td>2004</td>
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<td>2005</td>
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<td>2006</td>
<td>332</td>
<td>4.3</td>
</tr>
<tr>
<td>2007</td>
<td>309</td>
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<tr>
<td>2008</td>
<td>292</td>
<td>3.8</td>
</tr>
<tr>
<td>2009</td>
<td>273</td>
<td>3.5</td>
</tr>
</tbody>
</table>
VA TB Cases: Urban vs. Rural, 2002-2005

- US born
- Foreign born

1 DOT trip = 6 miles, 20 traffic lights
1 DOT trip = 75 miles

~1150 VA cases
Jan 02-June 05

Number of Reported Foreign-Born vs. US Born TB Cases, VA 1996-2009

- US Born
- Foreign Born

TB Cases by Age:

VA, 2000-2009

- 0-14
- 15-24
- 25-44
- 45-64
- 65+

Number of Cases

Year

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
VDH TB Prevention and Control Policies and Procedures

- Based on USPHS/CDC, ATS, IDSA and Pediatric “Red Book” guidelines
- Adapted to address uniquely Virginia issues

Elements of a Tuberculosis Control Program

- Clinical Services
  - Medical evaluation and follow-up
  - Social services
  - Laboratory
  - Pharmacy
- Epidemiology and Surveillance
  - HIV testing and counseling
  - Data analysis, investigation, evaluation & planning
- Case Management
  - Contact investigation
  - Follow-up
  - Isolation, detention
- Federal TB Control Program
  - Guidelines
  - Technical assistance
- State TB Control Program
  - State statutes, regulations, policies, guidelines

M tuberculosis as causative agent for tuberculosis

Robert Koch ~1882
The Mycobacteria

Human pathogens

*M. tuberculosis* Complex

(*M. tuberculosis, M. bovis, M. microti,*
*M. africanum, M. canettii*)

*M. leprae*

Transmission of TB

- Spread person to person through the air

TB: Airborne Transmission

Person with active pulmonary TB

TB bacteria airborne

Person breathing TB bacteria
TB Invades/Infects the Lung

- Effective immune response
- Infection limited to small area of lung
- Immune response insufficient
- Active Disease

Probability of TB Transmission

- Transmission dependent on these factors
  - Infectiousness of the person with TB
  - Environment in which the transmission occurs
  - Duration of the exposure to TB bacteria
  - Virulence of organism
  - Immune system of person exposed

Pathogenesis of TB

- Infection begins when the inhaled droplets reach the lungs
- Tubercle bacilli multiply
- A small number of tubercle bacilli may enter the bloodstream and spread throughout the body (lungs, kidneys, brain, bone)
- Within 2-10 weeks, the immune system produces a capsule that surrounds the tubercle bacilli
Sites of TB Disease

- Pulmonary TB (TB of the lungs)
  - 80% of cases
  - Potential for transmission – infectious until proven otherwise
- Extrapulmonary TB (outside the lungs)
  - Can occur anywhere in body
  - Portal of entry through lungs
  - Typical sites include larynx, lymph nodes, the pleura, brain, kidneys, bones, or joints
  - Usually not infectious – always rule out pulmonary!

Likelihood of Developing TB Disease

- Once infected with tubercle bacilli
  - 90% chance of never developing the disease
  - 10% life time chance that TB disease will develop
    - Half the risk within the first 2 years
    - Risk lower after the first 2 years
  - Other personal health factors can influence risk
    - HIV infection - single highest risk for progress to active disease
      - 10% annual risk

Diagnosis of TB Infection and Disease

Signs and Symptoms
- TST
- CXR
- Bacteriology (positive sputa)
Diagnosis of TB Disease:

Symptoms

- Pulmonary TB Disease
  - Coughing
  - Pain in the chest when breathing or coughing
  - Coughing up sputum or blood

- General TB Disease
  - Weight loss
  - Fatigue
  - Malaise
  - Fever
  - Night sweats
  - Other symptoms specific to the site of the TB disease

Latent Infection vs. Active Disease

<table>
<thead>
<tr>
<th>Latent Infection</th>
<th>Active Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubercle bacilli in the body</td>
<td></td>
</tr>
<tr>
<td>Tuberculin skin test reaction usually positive</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray usually normal</td>
<td>Chest x-ray usually abnormal</td>
</tr>
<tr>
<td>Sputum smears and cultures negative</td>
<td>Sputum smears and cultures may be positive</td>
</tr>
<tr>
<td>No symptoms</td>
<td>Symptoms such as cough, fever, weight loss</td>
</tr>
<tr>
<td>Not infectious</td>
<td>Often infectious before treatment</td>
</tr>
<tr>
<td>Not a case of TB</td>
<td>A case of TB</td>
</tr>
</tbody>
</table>

HIGH RISK for TUBERCULOSIS

Who do we need to see?

PAY ME NOW OR PAY ME LATER

EVERY TB CASE WE NOW HAVE WAS ONCE LTBI
REFUGEES and IMMIGRANTS
- Yellow sheets CDC 75.17 - version 2
- Classifications
  - Class A
  - Class B1
  - Class B2
  - Class B3

Others at High Risk?
- Recent Convertors
- Congregate living
- Substance Abuse
- Illegal Immigrants
- Persons in US on Visa
- Contacts
- TNFa drugs
- College/University applicants

Identifying Risk Factors
That Lead to Development of TB Disease
Persons at Risk for Developing TB Disease

Persons at high risk for developing TB disease fall into 2 categories

- Those who have been recently infected
- Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

Recently Infected

- Close contacts to person with infectious TB
- Skin test converters (within past 2 years)
- Recent immigrants from TB-endemic regions of the world (within 5 years of arrival to the U.S.)

Recent Infection as a Risk Factor

- Children ≤ 5 years with a positive TST
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include

- Immuno-suppressed persons (HIV, TNFa, high doses of steroids)
- Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph

Increased Risk for Progression to TB Disease

- Underweight or malnourished persons
- Injection drug users
- Those receiving TNF-α antagonists for treatment of rheumatoid arthritis or Crohn’s disease

Increased Risk for Progression to TB Disease

- Persons with certain medical conditions such as
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoilial bypass
TB SKIN TESTING = TST

- SCREENING
- PLANTING (ADMINISTRATION)
- MEASUREMENT
- INTERPRETATION
- FOLLOW-UP

WHY SCREEN?

- ASSESS FOR SYMPTOMS
- ASSESS RISK FOR ACQUIRING LTBI
- ASSESS RISK FACTORS FOR DEVELOPING TB DISEASE
- NEED TO KNOW RISK TO DETERMINE THE RESULTS

SCREENING

- SCREENING IS A MUST BEFORE ADMINISTERING THE TST
Purpose of TB Screening

- Identify individuals with TB infection and TB
- Provide appropriate treatment

Overall goals
- Reduce morbidity in community
- Reduce transmission

Diagnosis of TB Infection:
Mantoux TB Skin Test (TST)

- Is the preferred type of skin test
- Determines if a person has TB infection
- Is useful in:
  - Screening people for TB infection (contacts and targeted testing)
  - Examining a person who has symptoms of TB disease

Mantoux Tuberculin Skin Test

- Multiple puncture test (e.g. Tine Test) are inaccurate and not recommended

- Emergency Box

- QuantiFERON Gold
INTERFERON GAMMA RELEASE ASSAYS (IGRAs)

- Measures interferon-gamma (IFN-γ) released from a patient’s T cells after stimulation with specific TB antigens
- QuantiFERON - TB Gold (QFT-G)  2005
- QuantiFERON - TB Gold InTube  10/2007
- T-SPOT.TB Test approved 2009

IN VIRGINIA, only prescribers (MD, NP & PA) RN’s and LPN’s (working under the direct supervision of an RN) can legally possess and administer tuberculin which is regulated as a class VI substance.

- Code 54.1-3408 (G)

TST. WHO CAN ADMINISTER?

- IN VIRGINIA, only prescribers (MD, NP & PA) RN’s and LPN’s (working under the direct supervision of an RN) can legally possess and administer tuberculin which is regulated as a class VI substance.
- Code 54.1-3408 (G)

Administering and Reading the Mantoux TST

- Inject intradermally 0.1 ml of 5 tuberculin units of liquid tuberculin using a 27 gauge needle
- Use the forearm whenever possible volar surface
- Produce a wheal 6 to 10 mm in diameter
- Examine the patient’s arm 48-72 hours after the tuberculin is injected
  - Assess the injection site for erythema (redness) and induration (swelling that can be felt)
  - Measure across the forearm the diameter of the indurated area only in millimeters
  - Do not measure the erythema
Reading the TST

- Educate clients regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours
Persons Positive at ≥ 5 mm

- People with HIV infection
- Close contacts of people with infectious TB
- Persons with chest x-ray findings suggestive of previous TB disease
- Persons on TNF-a drugs (Humaria, Remicaide)
- Persons on high doses of steroids

Persons Positive at ≥ 10 mm

- Persons born/lived in areas of the world with high TB prevalence
- Injection drug users
- Persons who work or reside in high-risk congregate settings
- People with medical conditions that increase the risk for TB (those listed on risk screen)
- Children younger than 4 years old
- Locally identified groups at higher risk for exposure
Persons Positive at ≥ 15 mm

- Persons who have no risk factors for TB
- Certain individuals may require TST for employment or school attendance

TST Result: False Positive

Possible causes
- Nontuberculous mycobacteria
- BCG vaccination
  - Routinely administered to children in countries where TB is prevalent
  - Not a contraindication for the administration of the TB skin test
  - Wanes over time; if TST is + likely due to TB infection if risk factors present

TST Result: False-Negative

Causes include
- Anergy
- Recent TB infection (within past 10 weeks)
- Very young age (younger than 6 months old)
- Incorrect administration and storage of test solution
- Live-virus vaccination
- Overwhelming TB Disease
- Poor TST administration technique
Other Issues in Skin Testing

- Booster phenomena
  - Ability to react to tuberculin may wane with time
- Two-step testing 1 to 3 weeks apart
  - Use with groups who will have repeated TSTs as part of infection control programs
  - Use to validate test results

Diagnosis of Active TB

- Evaluate all patients with symptoms of TB for TB disease, regardless of the patient’s skin test reaction
- 1/4 to 1/3 of all active MTB cases have negative TST at onset of treatment

Diagnosis of TB Disease: Chest X-Ray

- Check for lung abnormalities suggestive of TB disease
- Typical findings may include cavities, infiltrates, effusions
- Does not confirm TB disease
- May not disprove active TB in immune compromised individuals
Diagnosis of TB Disease: Bacteriologic Examinations

- Sputum collection
  - Spontaneous or induced
  - All symptomatic individuals
  - Abnormal CXR
- *M. tb* can be cultured from any body fluid or tissue
  - Specimen collected depends on the site of potential disease

Yield of smear and culture from repeated sputum induction for the diagnosis of pulmonary tuberculosis.

Induced sputum (% yield)

<table>
<thead>
<tr>
<th>specimen</th>
<th>one</th>
<th>two</th>
<th>three</th>
<th>four</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB smear</td>
<td>64</td>
<td>81</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>AFB culture</td>
<td>70</td>
<td>91</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>


Bacteriologic Examination (Cont.)

- Microscopy
  - “Smear results”
  - Presence acid-fast bacilli (AFB)
  - AFB are bacteria that remain stained even after they have been washed in an acid solution
  - Tubercle bacilli are only one kind of AFB
  - Results available usually within one day
**Bacteriologic Examination: AFB Smear Interpretation**

- Classify smear according to the number of AFB seen
- Measure of number of organisms presented (negative to 4+)
- Helps to determine level of potential infectiousness
- If no AFB seen, result is negative
- Does not rule out possibility of TB

---

**NEW TESTING NAAT (nucleic acid amplification testing)**

- MTD NAA testing of RNA for MTb is now done on all positive AFB smears at the state lab results within 48 hours
- PCR
- HAINES
Bacteriologic Examination: Culturing the Specimen

- Grow the mycobacteria on media
  - Several types of media
- All specimens should be cultured, regardless of whether the smear is positive or negative
- Results may take up to 6-8 weeks
- If *M. tuberculosis* present, confirms diagnosis of TB disease

Bacteriologic Examination: Drug Susceptibility Testing

- Critical test for appropriate management of active TB disease
- Test mandated by VA TB Control laws
- Determines which drugs will kill the tubercle bacilli that are causing disease in the individual patient
- Done in initial positive culture for *M. tuberculosis*
- May need to be repeated later in treatment course
- Drug levels

Antituberculosis Drugs Currently in Use in the US

First-line Drugs
- Isoniazid
- Rifampin
- Rifapentine
- Rifabutin
- Ethambutol
- Pyrazinamide

Second-line Drugs
- Cycloserine
- Ethionamide
- Levofloxacin
- Moxifloxacin
- Gatifloxacin
- P-Aminosalicylic acid
- Streptomycin
- Amikacin/kanamycin
- Capreomycin
- Linezolid
Treatment of MTB Case

- Initial Phase – Direct Observed Therapy
  - 7 d/wk for 56 doses or 5d/wk for 40 doses
  - INH
  - Rifampin
  - Ethambutol
  - PZA

Treatment of MTB Case

- CONTINUATION PHASE by DOT
  - Either 4 or 7 months
  - Daily 126 doses (INH and RIF)
  - 5X/wk 90 doses (INH and RIF)
  - 2X/wk 36 doses (INH and RIF)
  - 1X/wk 18 doses (INH and RPT)

The 4 month continuation phase will be used on most clients.

Continuation Phase for 7 months

- Cavitory pulmonary TB caused by drug-susceptible organisms and whose sputum culture obtained at completion of 2 month initial phase is positive
- No PZA in initial phase
- INH and Rifapentine 1X/wk whose sputum culture is + at end of initial phase
Children with MTB
- CXRs reveal different findings; see MMWR 6-20-03 pg 55 section 8.2
- Drug dosages are different
- Child = less than 40kg by weight or less than 15 years old
- Not usually given ETH unless drug resistance suspected or adult type cavitation on CXR (visual acuity)
- Younger than 4 start Tx ASAP

DRUG RESISTANCE
- MONO-RESISTANT resistant to one drug only
- POLY-RESISTANT resistant to more than one drug, but not the combination of INH and RIF

DRUG RESISTANCE
- MDR (Multiple Drug Resistance) INH AND Rifampin
- XDR (Extreme Drug Resistance) INH and Rifampin plus any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin or capreomycin)
Definitions

- **Primary drug resistance:**
  - Infected with TB which is already drug resistant
- **Secondary (acquired) drug resistance:**
  - Drug resistance develops during treatment

WHAT CAUSES SECONDARY DRUG RESISTANCE??

TREATMENT FAILURE

WHO IS AT HIGHER RISK OF MDR-TB???

- History of previous TB Tx especially if recent
- Foreign-born patients from countries or ethnicities with high prevalence of MDR
- Poor response to standard 4 drug regimen
- Known exposure to MDR-TB case
- HIV+
### Step 1

Use any available

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

PLUS

One of these

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

### Step 2

Pick one or more of these

**Oral second line drugs**
- Cycloserine
- Ethionamide
- PAS

### Step 3

Consider use of these

**Third line drugs**
- Imipenem
- Linezolid
- Macrolides
- Amoxicillin/Clavulanate

**In consult with:**
- MDRTB experts
Criteria for Reporting TB Cases

- All TB cases and suspects are required to be reported in Virginia (EPI 1)
  - Positive smear
  - Positive culture
  - Clinical findings and/or treatment started
- All children under age 4 found to have latent TB infection are required to be reported (EPI 1)

COUNTING CASES

- Culture confirmed MTB
- Clinical TB Case
  - Keep on medicines for two months and if there is clinical and radiographic improvement and meets other CDC guidelines, can be classified as a clinical case
- Suspects
LTBI Treatment Regimens

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

As tuberculosis (TB) disease rates in the United States (U.S.) decrease, finding and treating persons at high risk for latent TB infection (LTBI) has become a priority.

Before Initiating Treatment

- Rule out TB disease (i.e., wait for culture result if specimen obtained)
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy
**Isoniazid Regimens**

- 9-month regimen of Isoniazid 300mg qd (INH) is the preferred regimen (270 doses in 12 months)
- 6-month regimen is less effective but may be used if unable to complete 9 months (180 doses)
- May be given daily or intermittently (twice weekly)
  - Dosage different 900mg twice weekly
  - 76 doses in 12 months or 52 doses in 9 months
  - Use directly observed therapy (DOT) for intermittent regimen
- Private sector/HD does not do intermittent INH

**Rifampin Regimens (1)**

- Rifampin 600mg (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
  - 120 doses in 6 months
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

**Regimens ...Suspects**

- RIF daily for 4 months  
  *(120 doses within 6 months)*
- RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events
Completion of Therapy

Completion of therapy is based on the total number of doses administered, not on duration alone.

TB in SELECTED RISK FACTORS 2009

- HEALTH CARE WORKERS 11
- EXPIRED from TB 13
- LTC 3
- CORRECTIONS 4
- HIV 18
- PEDIATRIC (0-14) 22
- DIABETIC 37
- DRUG RESISTANCE 30 (3MDR)

WHAT ARE WE TRYING TO PREVENT?