



TUBERCULOSIS 101

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Epidemiology of TB: World

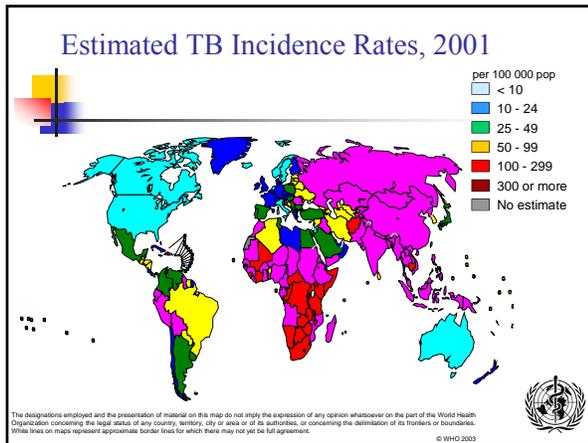
- One third of the world's population is infected with TB
- 9 million new cases of TB per year
 - 2 million deaths a year can be attributed to TB disease
 - 2009 in US just under 11,540 TB cases
 - 2009 in US estimated approx 10 million with LTBI

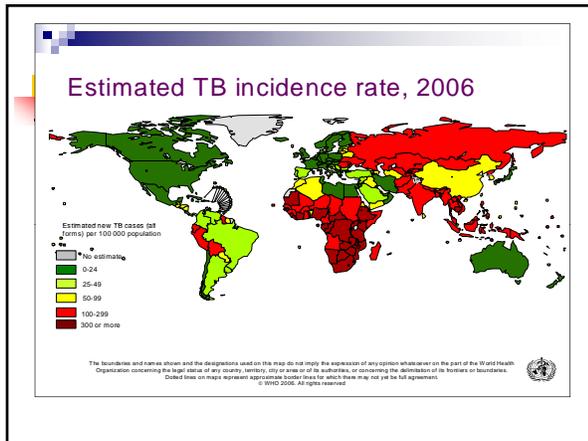
Have germs, will travel... Migrating populations in the 1990s



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

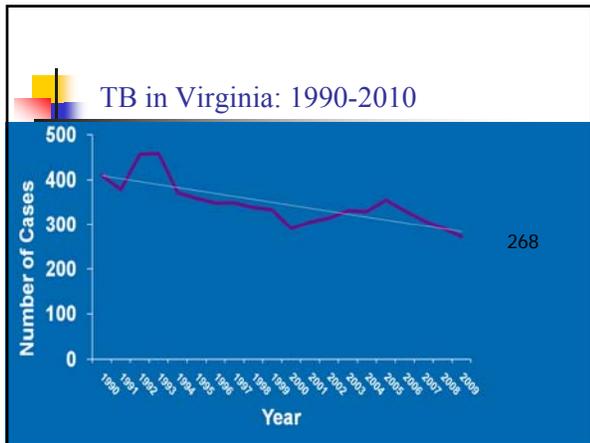
Source: Population Action International 1994

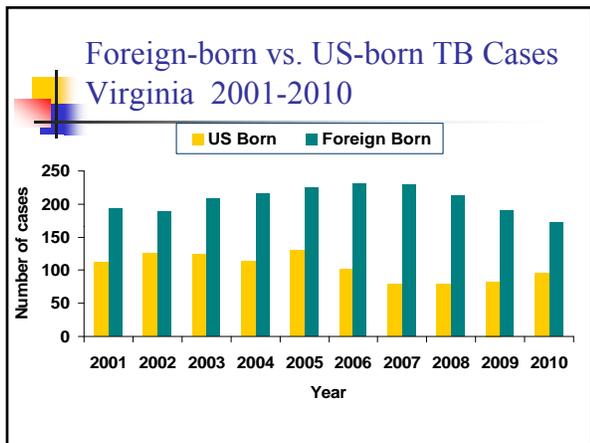


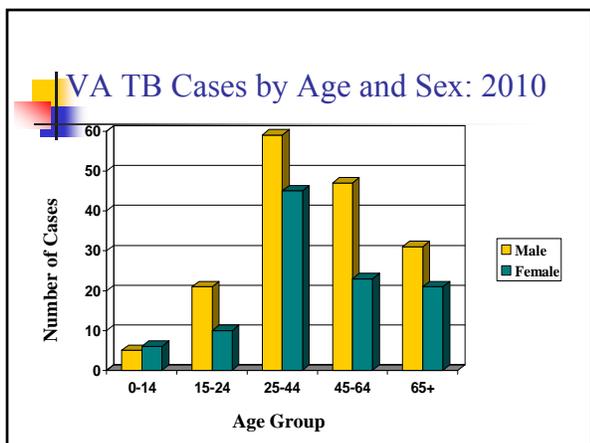


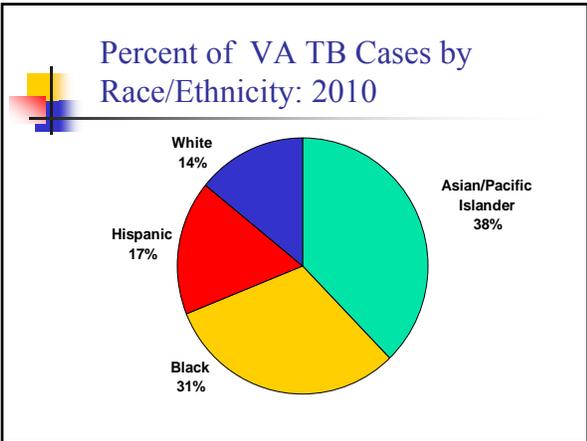
Epidemiology of TB: National

- Decline of TB cases from the 1950s to 1984
 - Availability and effectiveness of TB medications
- Increase in TB cases from 1985 to 1993
 - HIV, increased immigration, decrease in funding, apathy
- US TB rates have been declining since 1993









- ### TB Control in Virginia
- Code of Virginia
 - Reportable Diseases
 - EPI 1
 - Virginia TB Law book
 - Discharge Plan
 - Health Department Eligibility Guidelines
 - VDH Nursing Directives
 - CDC MMWR guidelines
 - Laboratories

HEALTH DEPARTMENT IS RESPONSIBLE FOR TB CONTROL

- TO ENSURE THAT ALL PERSONS WHO ARE SUSPECTED OF HAVING TUBERCULOSIS ARE IDENTIFIED AND EVALUATED PROMPTLY AND THAT AN APPROPRIATE COURSE OF TREATMENT IS PRESCRIBED AND COMPLETED SUCCESSFULLY



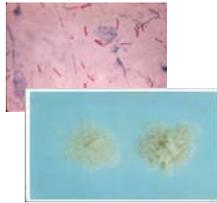
VDH TB Prevention and Control Policies and Procedures

- Based on USPHS/CDC, ATS, IDSA and Pediatric "Red Book" guidelines
- Adapted to address uniquely Virginia issues
- <http://www.cdc.gov/tb/publications/reportsarticles/mmwr/default.htm>
- MMWRs on TB topics





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. pinnipedii*)

M. leprae



Probability of TB Transmission

- Transmission dependent on three factors
 - Infectiousness of the person with TB
 - Environment in which the transmission occurs
 - Duration of the exposure to TB bacteria



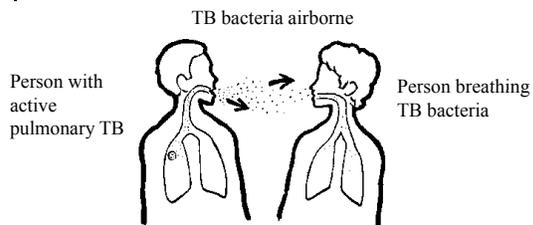
Transmission of TB

- Spread person to person through the air



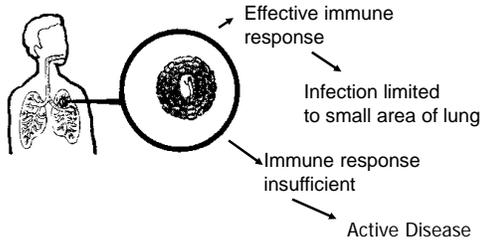


TB: Airborne Transmission





TB Invades/Infects the Lung

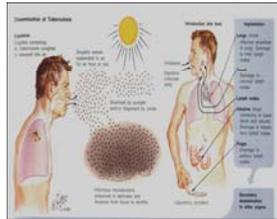




Transmission of Tuberculosis

■ **THREE STEP PROCESS**

- Transmission of bacteria,
- Establishment of infection, and
- Progression to disease.





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 surround 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



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
- Younger than 4 start Tx ASAP
- ETHAMBUTOL 4 drugs resistance suspected or adult type cavitation on CXR (visual acuity)



Latent Infection vs. Active Disease

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



Identifying Risk Factors That Lead To Development of TB DISEASE

- A TB Risk Assessment is recommended
 - TST or IGRA
 - To be done by health care professional

- 1/3 of all full blown TB Cases will have neg TST
 - Neg TST or IGRA does not r/o active MTB



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



Recent Infection as a Risk Factor

Persons more likely to have been recently infected include:

- 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 (2)

- 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:

- HIV-infected persons
- Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph



Increased Risk for Progression to TB Disease (2)

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



Increased Risk for Progression to TB Disease (3)

- 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 jejunioileal bypass



Diagnosis of TB Infection: Risk Screen, TB Skin Test (TST)/IGRAs

- 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



TB Skin Testing

- Tubersol/Aplisol
- Storage/Handling
- Who can Administer
- BCG



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.
- VIRGINIA CODE 54.1-3408 G



Mantoux Tuberculin Skin Test

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



INTERFERON GAMMA RELEASE ASSAY IGRAs (BAMT)

- QuantiFERON Gold Intube QFT-GIT 2005
- T-Spot 2008



IMMUNE GAMMA RELEASES ASSAYS-IGRAs

- CDC GUIDELINES MMWR June 25, 2010
 - RECOMMENDED FOR THOSE WITH HX BCG
 - **NOT** RECOMMENDED FOR CHILDREN LESS THAN 5 YEARS OF AGE
 - FALSE POSITIVES CAUSED BY
 - M KANSASI
 - M SZALGAI
 - M.MARINUM



Publications Comparing IGRAs

Lee et al., *European Respiratory Journal* (2006)



	TST (≥10mm)	Gold	T-SPOT.TB Test
Overall Sensitivity Culture-Confirmed TB	66.7%	70.1%	96.6% p<0.05
Immunocompetent	82.8% (48/58)	74.1% (43/58)	94.8% (55/58)
Immunosuppressed	34.5% (10/29)	62.1% (18/29)	100% (29/29)
Indeterminates	-	9.2% (8/87)	0.0% (0/87)

* Immunocompromised subjects were defined as: those on immunosuppressive drugs (post-transplantation, anti-cancer chemotherapy, receiving > 15 mg/day prednisone for > 1 month), undergoing hemodialysis, who had a hematologic malignancy (leukemia, lymphoma) or diabetes mellitus



When to Use What Test?

- Hx of BCG IGRA
- Children less than 5 TST
- Looking for old infection? TST
- Looking for new infection? IGRA?
- HIV IGRA
- Newly hired HCW?
- Post exposure can use either TST or IGRA
 - Baseline and 10 to 12 weeks for either



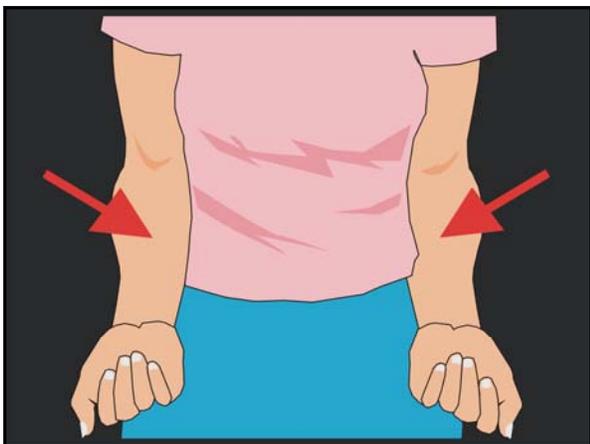
Administering and Reading the Mantoux TST

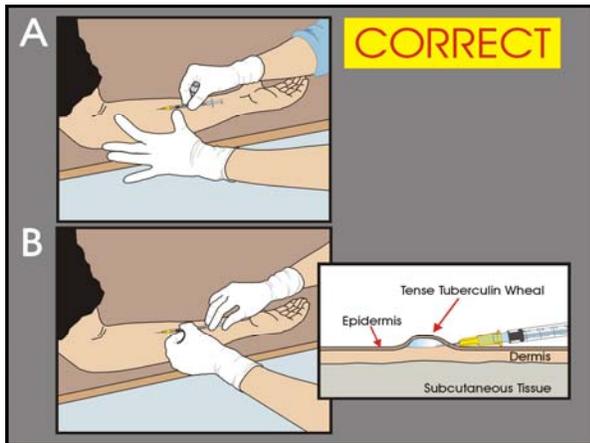
- Inject intradermally 0.1 ml of 5 tuberculin units of liquid tuberculin using a 27 gauge needle
 - Use the forearm whenever possible volar surface
 - Produce a wheal 6 to 10 mm in diameter
- Examine the patient's arm 48-72 hours after the tuberculin is injected
 - Assess the injection site for erythema (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

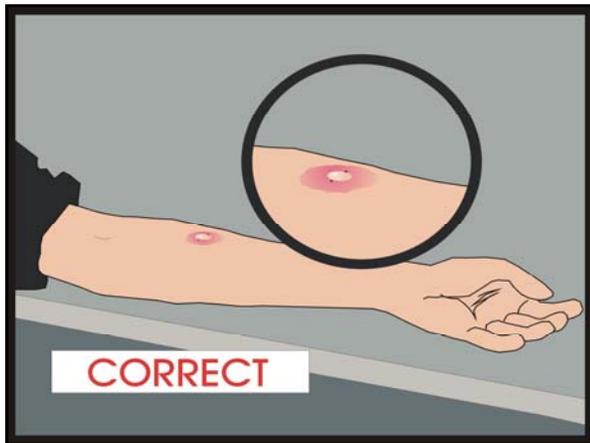


Reading the TST

- Educate client and family regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days per CDC
 - Virginia TB Control as long as + reading
- 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- α drugs or high doses of steroids
- 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 TB

Induced sputum (% yield)

specimen	one	two	three	four
AFB smear	64	81	91	98
AFB culture	70	91	99	100

Int J Tuberc Lung Dis. 2001 Sep;5(9):855-60. Al Zahrani K, et al.



Bacteriologic Examination

- 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 (10-09)
- 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

- | | |
|---|--|
| <ul style="list-style-type: none"> ■ First-line Drugs <ul style="list-style-type: none"> ■ Isoniazid ■ Rifampin ■ Rifapentine ■ Rifabutin ■ Ethambutol ■ Pyrazinamide | <ul style="list-style-type: none"> ■ Second-line Drugs <ul style="list-style-type: none"> ■ 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

See page 5 of Treatment statement



Treatment of MTB Case - 2

- 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

- Cavitary 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



Complex Case Management Issues

- Poor adherence
 - DOT failure
 - Slow sputum conversion/delayed clinical improvement
 - Poor acceptance of TB diagnosis
 - Clinical deterioration
 - Appointment failure
 - Documentation of interventions/counseling and response – build the case



Complex Case Management Issues - 2

- Other medical issues requiring close case management
 - Dialysis
 - Drug-drug interactions
 - Adverse reactions to TB treatment
 - Substance abuse
 - HIV infection
 - Diabetes



Clinical/Bacteriologic Improvement

- If there is **NO** improvement
 - Notify physician and health director
 - Appropriate steps should be take to determine why
 - Drug resistance
 - Repeat susceptibilities
 - Request assistance for PCR based susceptibilities
 - Malabsorption
 - Serum level testing
 - Maintaining appropriate isolation is critical



What Causes MDR TB?

- TREATMENT FAILURE
- POOR COMPLIANCE

“Almost all drug resistant TB results from treatment failure and poor compliance.”

Dr. Michael Iseman
NATIONAL JEWISH



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**



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 - 2

- MDR (Multiple Drug Resistance)
INH AND Rifampin

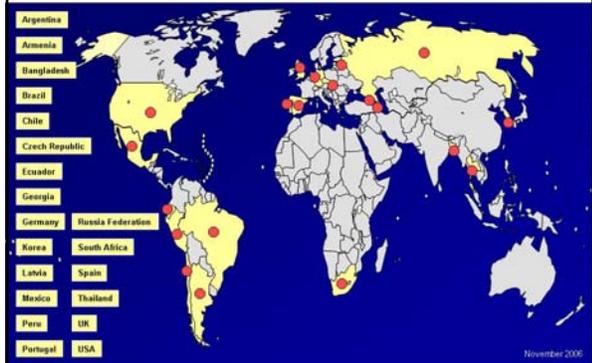
- XDR (Extreme Drug Resistance)
INH and Rifampin plus any fluoroquinolone and
at least one of the three injectable second-line
drugs (amikacin, kanamycin or capreomycin)



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+

Countries with XDR-TB Confirmed cases to date



Step 1

Use any available **PLUS** One of these **PLUS** One of these

Begin with any First line agents to which the isolate is Susceptible

First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide Ethambutol	Levofloxacin Moxifloxacin	Amikacin Capreomycin Streptomycin Kanamycin

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

BS

Step 1

Use any available **PLUS** One of these **PLUS** One of these

Begin with any First line agents to which the isolate is Susceptible

First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide Ethambutol	Levofloxacin Moxifloxacin	Amikacin Capreomycin Streptomycin Kanamycin

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

Step 2

Pick one or more of these

Oral second line drugs
Cycloserine Ethionamide PAS



CONTACT INVESTIGATION

- HOW DO WE DECIDE WHO TO TEST?
- INITIATED WITH THREE DAYS
- VISIT / ACCESS WORKPLACE



LTBI: Targeted Tuberculin Testing and Treatment of Latent TB 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 (INH 300mg) is the preferred regimen (270 doses)
- 6-month regimen is less effective but may be used if unable to complete 9 months (180)
- May be given daily or intermittently (twice weekly)
 - Intermittently not for children
 - 76 doses within 12 months dose is 900mg
 - 52 doses within 9 months dose 900mg
 - Use directly observed therapy (DOT) for intermittent regimen



Rifampin Regimens

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



Rifampin Regimens - 2

- 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

6



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	11
■ LTC	3
■ CORRECTIONS	4
■ HOMELESS	9
■ HIV	18
■ PEDIATRIC (0-14)	22 (1/2 < 4)



Who To Call

VDH, Division of Disease Prevention
TB Control Program

Jane Moore: 804-864-79210
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