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Advanced Concepts in Pediatric Tuberculosis: Mycobacteriology, Pathogenesis and Epidemiology

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Objectives

At the end of this session, participants will be able to:

- Recognize the epidemiology of Tuberculosis in the U.S and in the world
- Identify typical microbiologic characteristics of Mycobacterium tuberculosis
- Describe the pathogenesis of tuberculosis
- Recognize the risk factors for tuberculosis infection and disease

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Case

Case – History

- A 6-year-old Bosnian male presented to ED with one-week history of fever and occasional vomiting. No cough, difficulty breathing or weight loss.
- Social History
  - Patient lived with both parents and a younger sibling. They all immigrated to U.S. from Bosnia about six months before.
  - At that time, they all had TST/PPD placed. Both parents tested positive with negative CXR, but elected not to take meds. Both children tested negative (less than 10 mm).

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Case – Physical Examination

- T: 103.2°
- P: 154
- R: 24
- BP: 111/70.
- O2 Sat. on RA: 96–97%.
- Patient was awake, alert, in no apparent distress.
- Chest: markedly decreased BS in the right lung field.
- Rest of exam was within normal limits.

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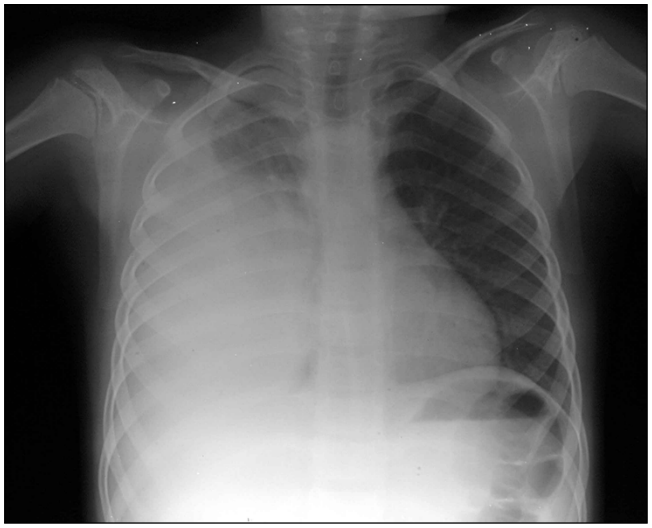

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Case

- He was admitted to the hospital and started on IV antibiotics: ceftriaxone first, then vancomycin was added.
- After 3 days, he continued having daily fever spikes, without changes in his respiratory status.
- Peds ID was consulted.
  - What is your differential diagnosis?
  - Would you do any further evaluation?
  - Repeat TST?
  - What is the best sample for cultures?
  - Other tests?

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Epidemiology

TB Epidemiology Global

- Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent.
- It is estimated that there are 1.7 Billion persons infected with TB worldwide: 1/3 of the world's population.
- In 2012, there were 8.6 million cases of TB and 1.3 million died from TB.
- Over 95% of TB deaths occur in low- and middle-income countries.
  - About 80% of reported TB cases occur in 22 countries.

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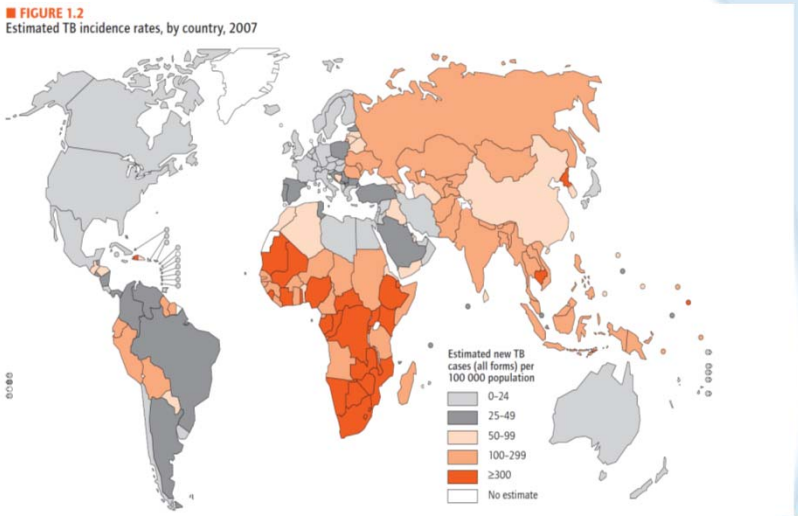
Estimated Tuberculosis Incidence WHO



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TB Epidemiology Global

- TB is a leading killer of people living with HIV causing one fifth of all deaths.
- At least 1/3 of people living with HIV worldwide in 2012 were infected with TB.
  - People with co-infection are 30 times more likely to develop active TB disease than people without HIV.
- HIV and TB form a lethal combination, each speeding the other's progress.
  - In 2012 about 320,000 people died of HIV-associated TB.
  - Approximately 20% of deaths among people with HIV are due to TB.

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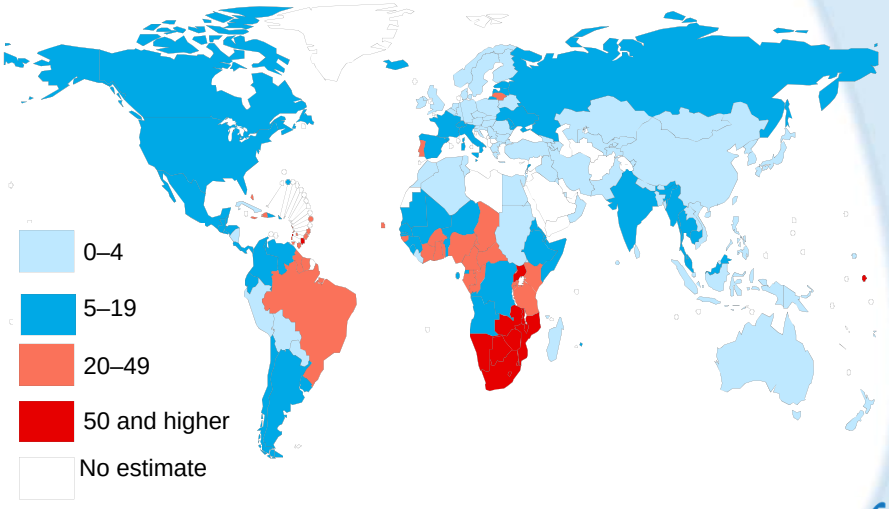
Estimated prevalence of HIV co-Infection among New TB cases



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TB Epidemiology Global

- Multi-drug resistant TB (MDR-TB) is present in virtually all countries surveyed.
  - 450,000 cases of MDR-TB in the world in 2012.
  - >50% in India, China and the Russian Federation.
  - About 10% of MDR-TB cases had XDR-TB.
- The estimated number of cases of TB each year is declining, although very slowly.
- The TB death rate dropped 45% between 1990 and 2012.
- An estimated 22 million lives saved through use of DOTS and the Stop TB Strategy recommended by WHO.

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TB in Children Global

- In 2012, WHO estimated there were 530,000 TB cases in children.
  - 74,000 HIV-negative children died of TB that year.
- According to a recent study, the number of cases calculated using a mathematical model is 25% higher than the WHO estimate.*
  - Confirmation of TB in children is challenging
  - Under-reporting is common

*Dodd PJ et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Glob Health 2014;2:453-59

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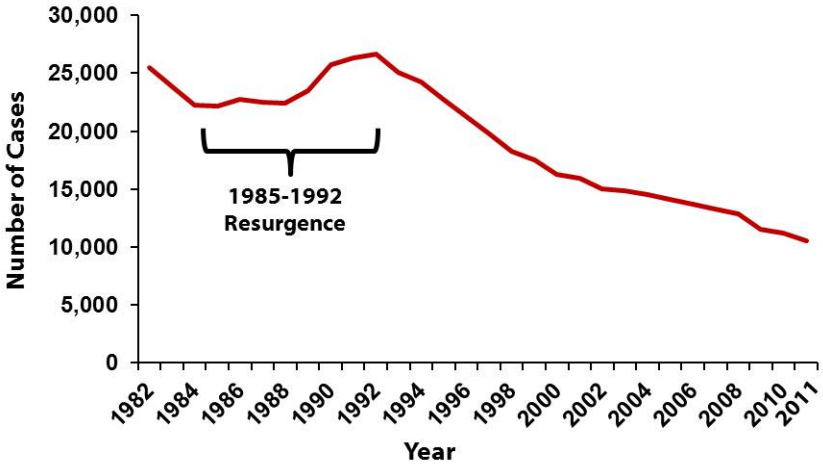
Reported TB Cases United States, 1982–2011*



*Updated as of June 25, 2012.

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Factors Contributing to the Increase in TB Morbidity: 1985–1992

- Emerging HIV/AIDS epidemic
- Immigration from countries where TB was common
- Transmission of TB in congregate settings
- Development of multidrug-resistant (MDR) TB
- Funding cuts for TB control programs

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Factors Contributing to the Decrease in TB Morbidity Since 1993

Success attributed to increased efforts to:

- Promptly identify persons with TB
- Initiate appropriate treatment
- Ensure completion of therapy

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TB Elimination Barriers in the US

- U.S. TB cases occur largely in high-risk populations
  - In these populations, TB is difficult to detect, diagnose, and treat
- Global TB epidemic persists
- Current TB control measures are limited
  - New tests, vaccines, drugs needed

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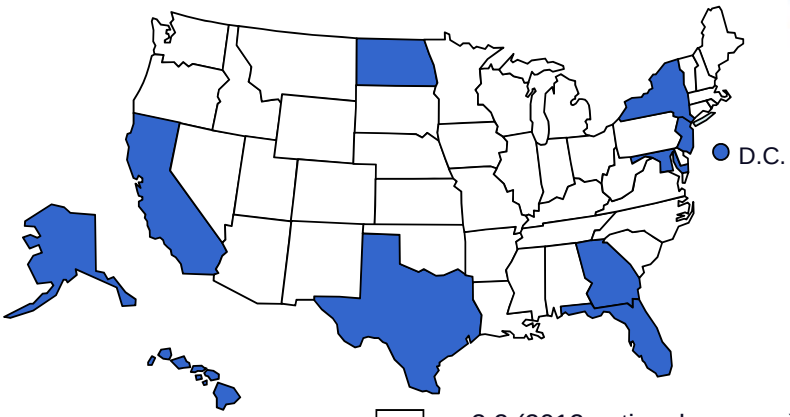
TB Case Rates,* United States, 2012



≤ 3.2 (2012 national average)

>3.2

*Cases per 100,000.

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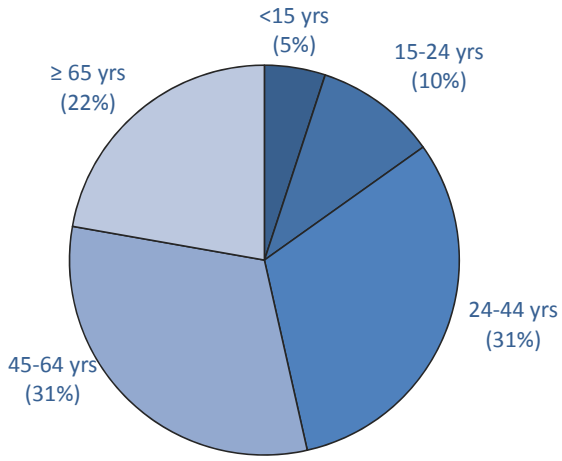
Reported TB Cases by Age Group, United States, 2012



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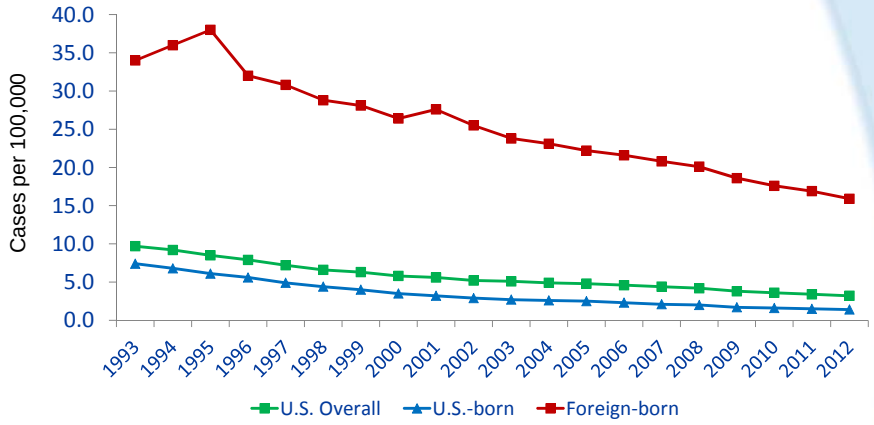
TB Case Rates in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2012*



*Updated as of June 10, 2013.

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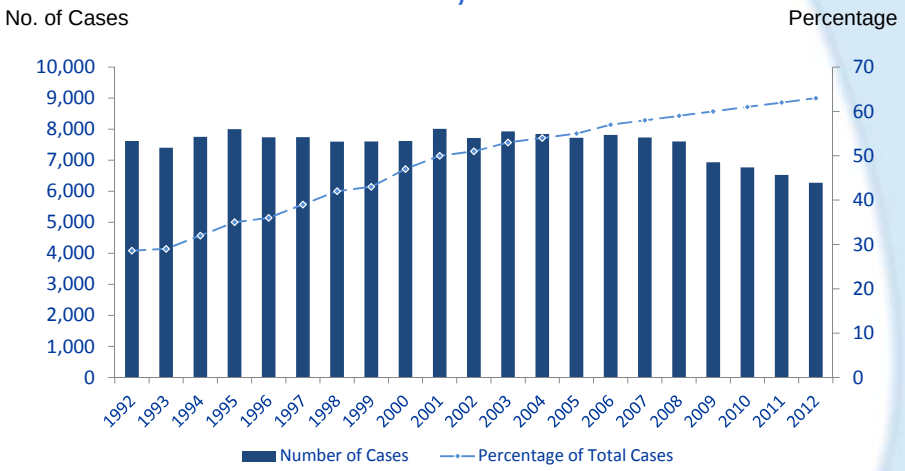
Trends in TB Cases in Foreign-born Persons, United States, 1992 – 2012*



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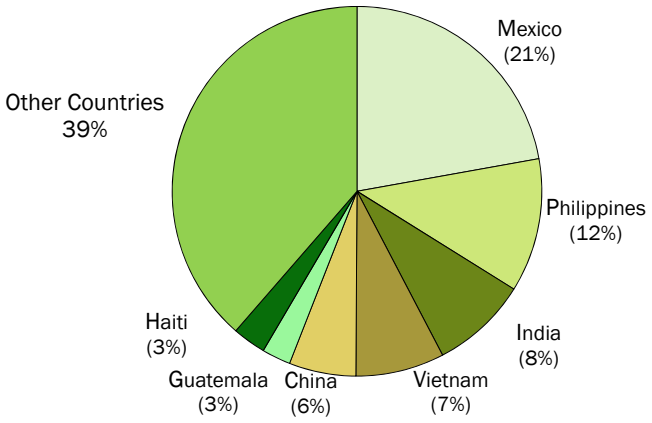
Countries of Birth of Foreign-born Persons Reported with TB, United States, 2012



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Pediatric TB
How cases are discovered

- Active
  - Contact investigation
  - Screening of high risk groups
- Passive
  - Symptomatic children

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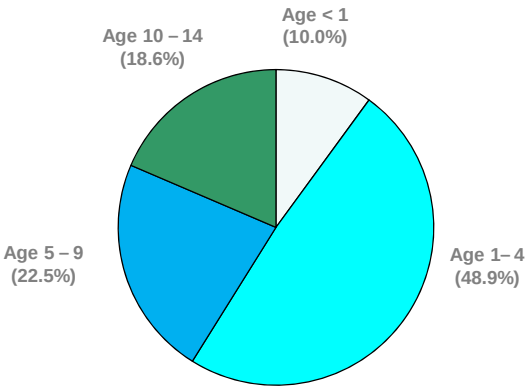
Percent of Pediatric TB Cases by Age Group, 1993–2012 USA



Pediatric & Adolescent TB in USA 2008-2010*

- Study included patients 0 to <18 y/o, and data on parent/legal guardian country of origin and h/o having lived internationally.
- 2660 cases.
  - At least 1/3 were symptomatic.
- 75% had International connection: FB, FB-parents or residence outside of USA.
- 31% FB
  - 52% of FB were teens who had lived in the USA 3.5 y before dx.
- Among US-born, 66% had at least 1 FB parent and 13% had lived outside USA for >2 months.

*Winston CA, Menzies HJ. Pediatrics 2012;130;e1425

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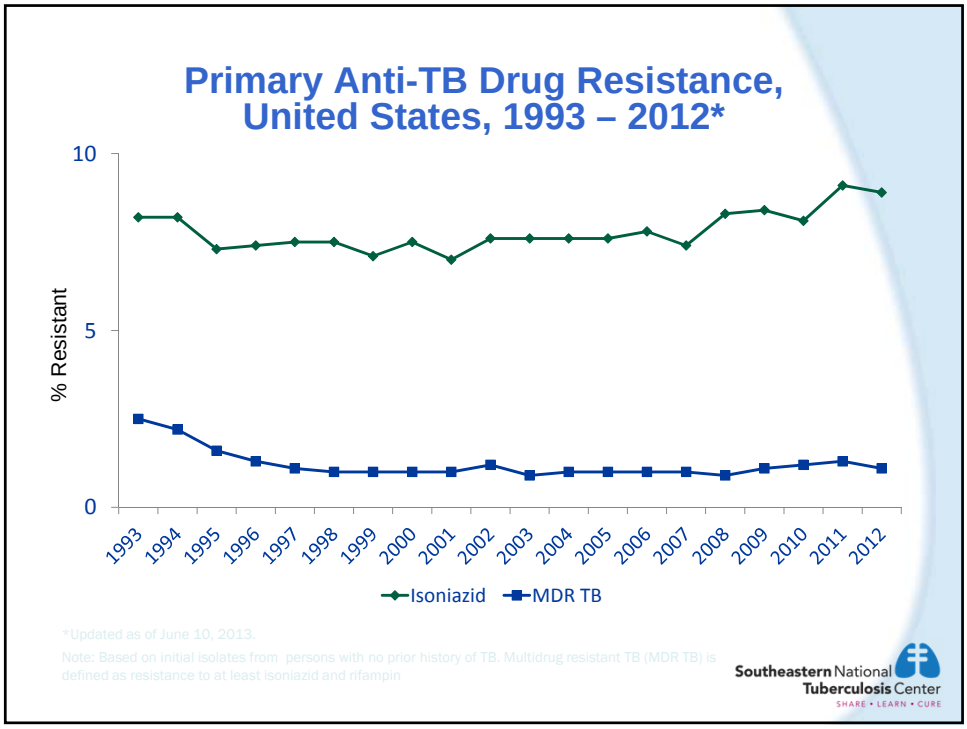
Primary Anti-TB Drug Resistance, United States, 1993 – 2012*
% Resistant
10
5
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Isoniazid
MDR TB
*Updated as of June 10, 2013.
Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin
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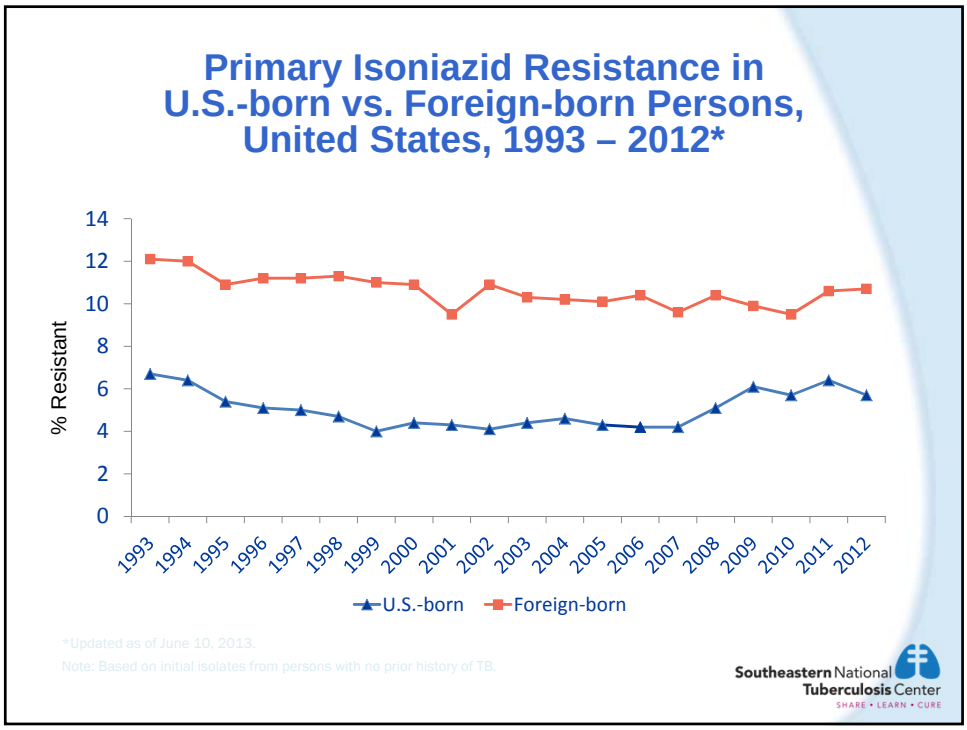
Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2012*
% Resistant
14
12
10
8
6
4
2
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
U.S.-born
Foreign-born
*Updated as of June 10, 2013.
Note: Based on initial isolates from persons with no prior history of TB.
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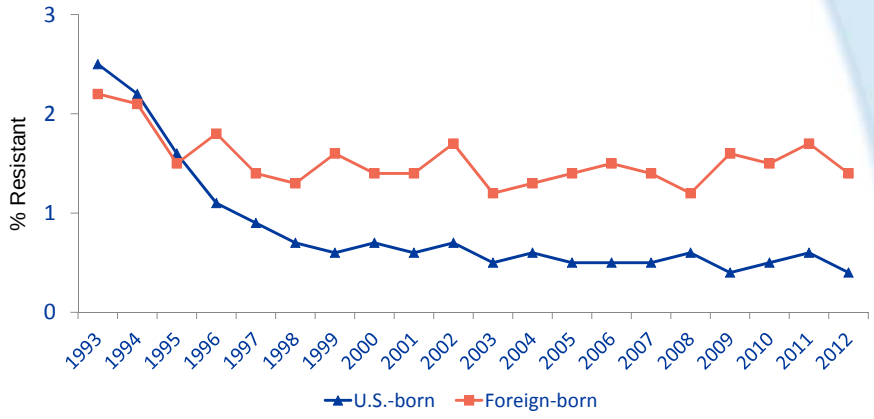
Primary MDR TB in U.S.-born vs. Foreign-born Persons United States, 1993 – 2012*



*Updated as of June 10, 2013.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

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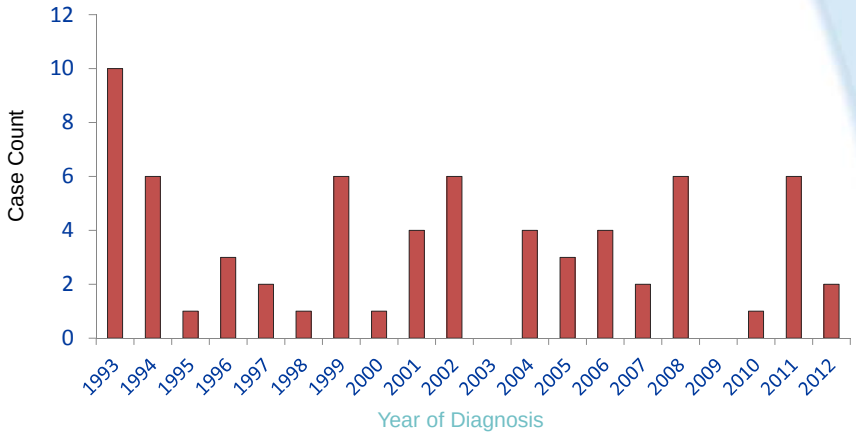
XDR TB Case Count Defined on Initial DST* by Year, 1993 – 2012**



* Drug susceptibility test

** Updated as of June 10, 2013.

Note: Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs

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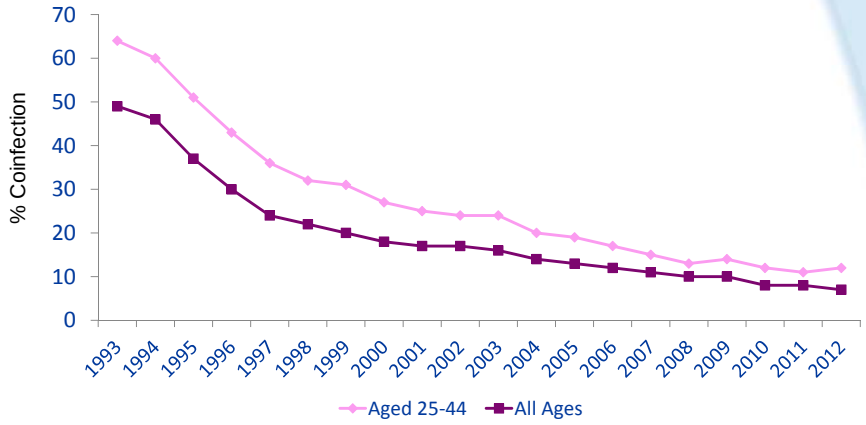
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 – 2012*



*Updated as of June 10, 2013

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

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Microbiology

Microbiology

- Mycobacterium tuberculosis complex
  - M. tuberculosis – most common
  - M. bovis
  - M. africanum
- Belongs to the order Actinomycetales and family Mycobacteriaceae
- Gram stain: weakly Gram positive or not at all ("ghosts").
- Acid-fast bacteria
  - Resistant to decolorization by acids during staining procedures

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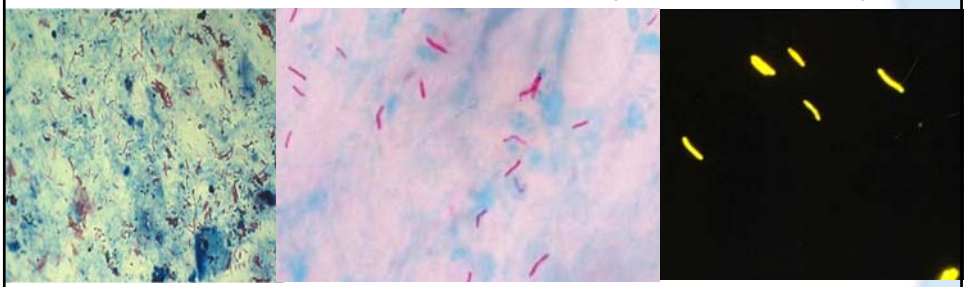
AFB Staining

Ziehl-Neelsen stain
Kinyoun method
Auramine-rhodamine stain (fluorochrome)



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Microbiology

- Fairly large nonmotile rod-shaped bacteria
- Obligate aerobe
- Facultative intra-cellular (macrophages)
- In vitro only grows in special media:
  - Solid
    - Lowenstein-Jensen medium: egg-based
    - Middlebrook's medium: agar based
  - Liquid
    - Automated radiometric (e.g. BACTEC)
- Takes 6-10 weeks to grow in solid media and 1-6 weeks in liquid media.

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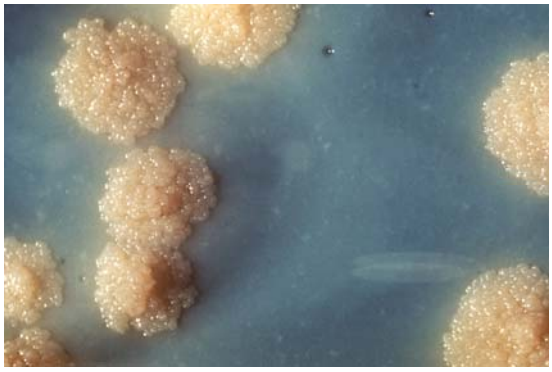
- **Colonies of *M. tuberculosis* Growing on Media: small and buff colored**



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Pathogenesis

Persons at Higher Risk for Exposure to or Infection with TB

- Close contacts of person known or suspected to have active TB
- Foreign-born persons from areas where TB is common
- Persons who visit TB-prevalent countries
- Residents and employees of high-risk congregate settings

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Persons at Higher Risk for Exposure to or Infection with TB

- Medically underserved, homeless, users of illicit drugs
- Health care workers (HCWs) who serve high-risk clients
- Children and adolescents frequently exposed to adults at increased risk for infection or disease

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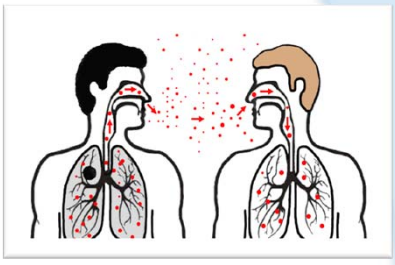
Transmission of *M. tuberculosis*

- *M. tb* spread via airborne particles called droplet nuclei
- Expelled when person with infectious TB coughs, sneezes, shouts, or sings



- Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi

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Probability TB Will Be Transmitted

- Susceptibility of the exposed person
- Infectiousness of person with TB (i.e., number of bacilli TB patient expels into the air)
- Environmental factors that affect the concentration of *M. tb* organisms
- Proximity, frequency, and duration of exposure (e.g., close contacts)
- Can be transmitted from children, though less likely

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Pathogenesis

	Droplet nuclei measure 5 µm and may contain 1-10 bacilli. The size allows them to remain suspended in the air for long periods of time. 5-200 bacilli are usually necessary for infection. They are inhaled, enter the lungs, and travel to the alveoli. M. bovis is transmitted most often by ingestion of unpasteurized dairy products.
	In the alveoli, some tubercle bacilli are killed, but a few multiply.

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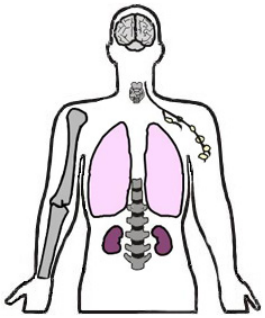
Pathogenesis



A small number of tubercle bacilli enter the bloodstream and spread throughout the body.
The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the upper portions of the lungs, the brain, larynx, lymph node, bone, or kidney).

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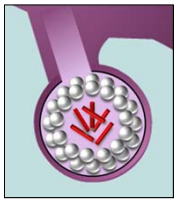
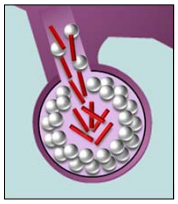
Pathogenesis



Within 2 to 10 weeks, macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI).



If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.

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Latent TB Infection (LTBI)

- Granulomas may persist (LTBI), or may break down to produce TB disease
- 2 to 10 weeks after infection, LTBI can be detected via TST or interferon-gamma release assay (IGRA)
- The immune system is usually able to stop the multiplication of bacilli
- At this time, the CXR is normal
- Persons with LTBI are not infectious and do not spread organisms to others

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TB Disease

- In some, the granulomas break down, bacilli escape and multiply, resulting in TB disease
- Can occur soon after infection, or years later
- Persons with TB disease are usually infectious and can spread bacteria to others.

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Sites of Disease

- Lungs (pulmonary)
  - Most common site; usually infectious
- Miliary
  - Occurs when bacilli spread to all parts of the body; rare, but fatal if untreated

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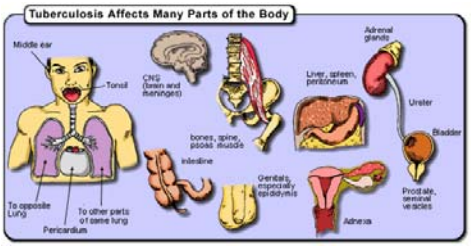
Sites of Disease

- Chronic or subacute lymphadenitis
- Meningitis
- Chronic otitis media/Mastoiditis
- Osteomyelitis
- Gastrointestinal
- Renal
- Anywhere!



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Sites of Disease

Extrapulmonary

- Usually not infectious, unless person has
  - Concomitant pulmonary disease,
  - Extrapulmonary disease in the oral cavity or larynx, or
  - Extrapulmonary disease with open site, especially with aerosolized fluid.

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Risk of Developing Disease Normal Immune System

- Untreated
  - 5% of infected persons with normal immunity develop TB in first 1–2 years post infection
  - another 5% later in life
- Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

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Risk of Developing Disease
Weak Immune System

- **Persons with weak immunity at increased risk of progressing to TB disease**
  - Untreated HIV infection highest risk factor
    - Risk is 7%–10% *each year*
  - Immunosuppressive therapy: post-transplant tx, prolonged or high dose corticosteroids, chemotherapy, TNF-alpha antagonists

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Risk of Developing Disease

- Recent infection with M. tuberculosis
  - Infants <4years of age and post-pubertal adolescents are at increased risk compared to other children
- Substance abuse (especially drug injection)
- Certain medical conditions: Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure/hemodialysis, silicosis, low body weight (10% or more below the ideal)

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Drug-Resistant TB

- Caused by organisms resistant to one or more TB drugs
- Transmitted same way as drug-susceptible TB, and no more infectious
- Delay in detecting drug resistance may prolong period of infectiousness because of delay in starting correct treatment

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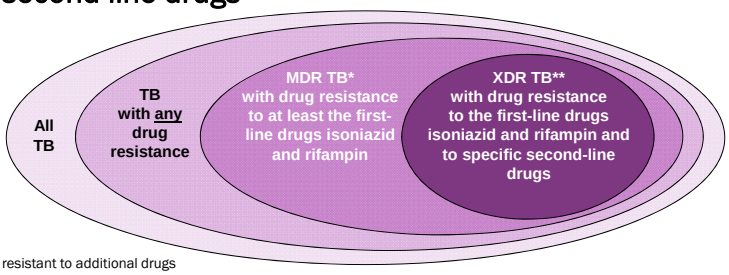
Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) TB

- MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin
- XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs



*Often resistant to additional drugs
**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin

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Types of Drug Resistance

Drug resistance develops in two ways:

- Primary resistance develops in persons initially infected with resistant organisms
- Secondary (acquired) resistance develops during TB therapy

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Circumstances Increasing the Risk of Drug-Resistant TB

Risk of drug-resistant TB is increased with exposure to a person who

- Has confirmed drug-resistant TB
- Had prior unsuccessful treatment for TB, and drug susceptibility results not known
- Originated in a drug-resistant TB prevalent country
- Has positive smear and culture 2 months after treatment start

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Back to our Case

- A 6-year-old Bosnian male, who presented to ER with one-week history of fever and occasional vomiting. No cough, difficulty breathing or weight loss.
- Social History
  - Patient lives with both parents and a younger sibling. They all immigrated to U.S. from Bosnia about six months before.
  - He had a negative PPD at that time.

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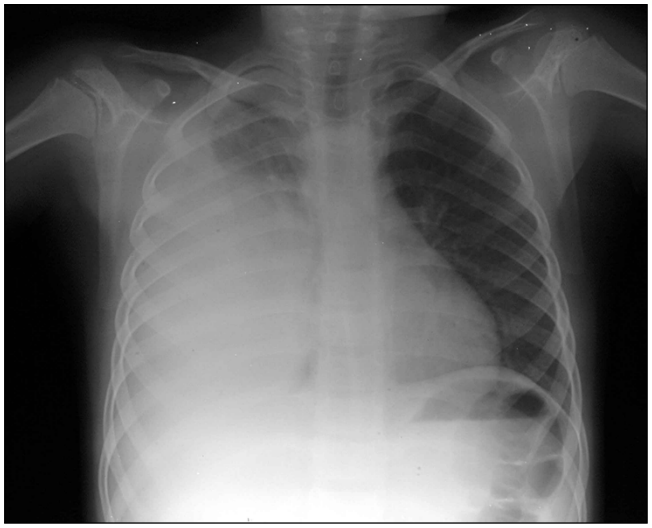

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Case

- He was admitted to the hospital and started on IV antibiotics: ceftriaxone first, then vancomycin was added.
- After 3 days, he continued having daily fever spikes, without changes in his respiratory status.
- Peds ID was consulted.
  - What is your differential diagnosis?
  - Would you do any further evaluation?
  - Repeat TST?
  - What is the best sample for cultures?
  - Other tests?

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Case – Hospital Course

- Chest US showed a loculated, organized pleural effusion.
- Surgery was consulted and they performed a video-assisted thoracotomy and decortication.
  - Pleural biopsy, AFB cultures and PCR, as well as bacterial cultures, were sent.
- TST was placed and read in 48 hours as 22 mm of induration.
- Induced sputum x1/early morning gastric aspirates x3 were obtained.
- HIV antibody: negative

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Case – Hospital Course

- Patient was started on INH, Rif, PZA and Ethambutol.
- He improved with resolution of fever in three days.
- He was discharged home to continue meds under Directly Observed Therapy (DOT).

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Case – Final Results

- Gastric aspirates X 3
  - AFB smear and cultures were negative
- Induced sputum AFB smear was negative
- Pleural Biopsy
  - Multiple caseating granulomas
- Pleural fluid/biopsy
  - AFB smear and PCR for *M.Tb* were negative
- Induced sputum and pleural cultures grew *M. tuberculosis*, resistant to INH

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Case – Teaching Points

- Epidemiology/Risk factors/Clinical manifestations:
  - TB should be considered in a child with pneumonia, not responding to appropriate antibiotics, especially if the patient is foreign-born.
- Pathogenesis
  - TST may take up to 10 weeks from exposure to convert.

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Case – Teaching Points

- Work up:
  - It is important to obtain cultures for TB in children, especially when the source case is unknown.
  - Induced sputum samples may have better yield than gastric aspirates. Consider in children older than five years.
- Treatment:
  - Suspect drug resistance in foreign-born patients with TB
  - Use a fourth drug (EMB) until susceptibilities are available.

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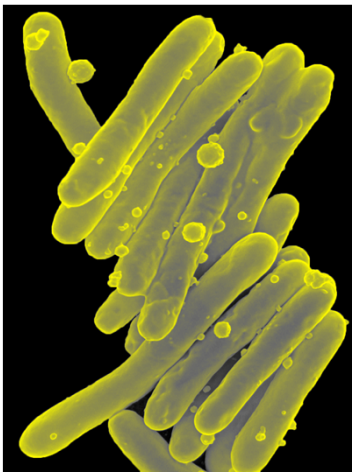
Questions?



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ADVANCED CONCEPTS IN PEDIATRIC TUBERCULOSIS

WEBINAR SERIES

In this 8-part series of modules, the Pediatric ID Board Certifying Examination Content related to TB is presented by expert speakers via case-based, interactive live webinars. The series goes beyond basic TB concepts while following the pediatric ID guidelines and is intended for a diverse audience, including pediatric ID fellows and faculty as well as other clinicians who diagnose and treat TB in children.

Advanced Concepts in Pediatric Tuberculosis series topics include:

- Introduction, Mycobacteriology, Pathogenesis and Epidemiology with Ana Alvarez - August 14, 2014
- Latent TB Infection with Nizar Maraqa - September 11, 2014
- Diagnosis: Old and New Diagnostic Tools & Challenges with Entesar Husain - October 23, 2014
- Clinical Manifestations and Work Up with Amina Ahmed - November 13, 2014
- TB and HIV with Ayesha Mirza - January 8, 2015
- Treatment of TB, including MDR with Jeffrey Starke - February 12, 2015
- Pharmacotherapeutics of TB Drugs with Charles Peloquin - March 12, 2015
- Infection Control, Source Case and Contact Investigation with Ana Alvarez - April 9, 2015

OBJECTIVES

Participants who complete this series will be able to recognize, evaluate and manage Mycobacterium tuberculosis infections in children.

REGISTRATION & COURSE DETAILS

- Register online for each live event: http://sntc.medicine.ufl.edu/Training.aspx
- Completion of a post-test evaluation is required to receive continuing education credit
- These webinars will be recorded and available on our website in the future.

QUESTIONS?

Contact the Southeastern National Tuberculosis Center (SNTC) by email at **sntc@medicine.ufl.edu** or call **352-273-7682** (toll free at **888-265-7682**).

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