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## The Future of Latent TB Infection Treatment

### Keeping With the Pace 2011

**Michael Lauzardo, MD MSc**  
 Division of Mycobacteriology  
 Southeastern National Tuberculosis Center  
 University of Florida

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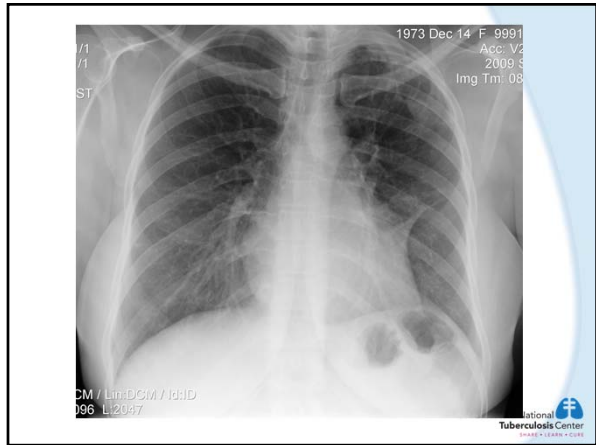
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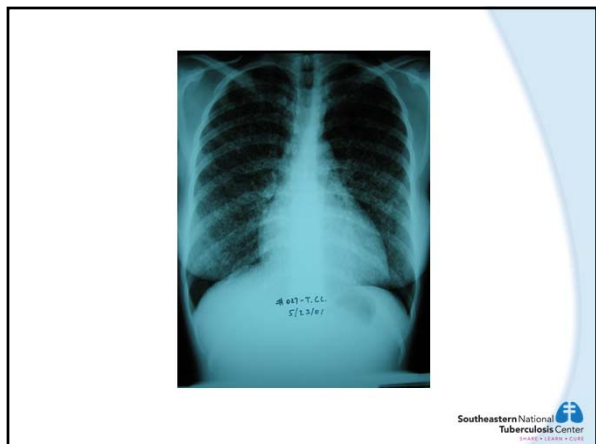
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## A Silent Global Epidemic

- One-third of the world's population infected
- Eight million new cases of active disease per year
- Two to three million deaths per year
- One person is newly infected every second and one person dies every 10 seconds
- Rising incidence of drug-resistant disease
- Billions of dollars in lost productivity

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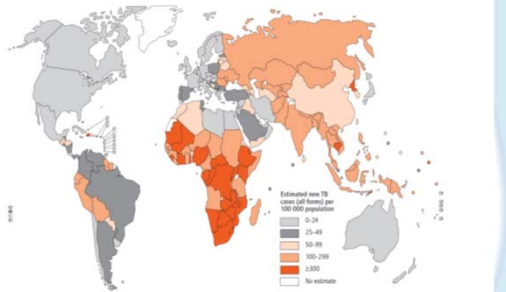
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## Estimated Tuberculosis Incidence WHO

FIGURE 1.2  
Estimated TB incidence rates, by country, 2007



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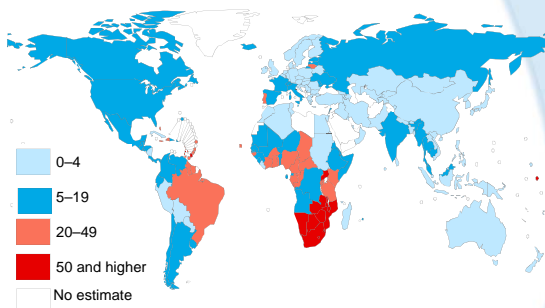
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## Estimated prevalence of HIV co-infection among New TB cases



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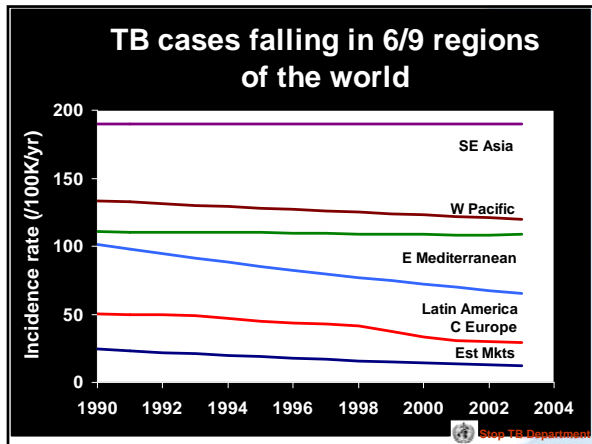
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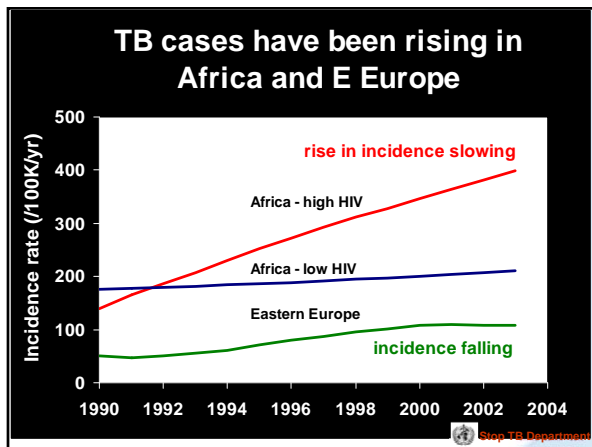
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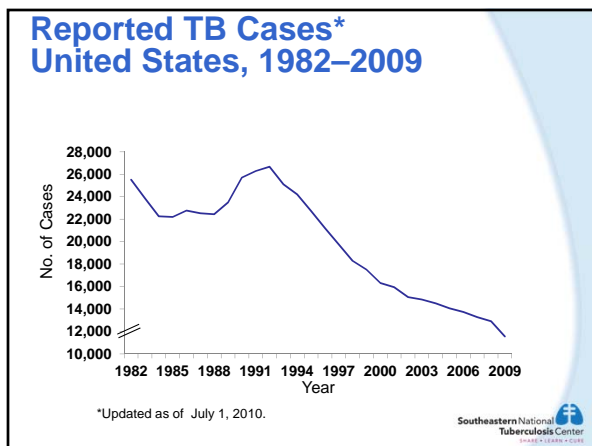
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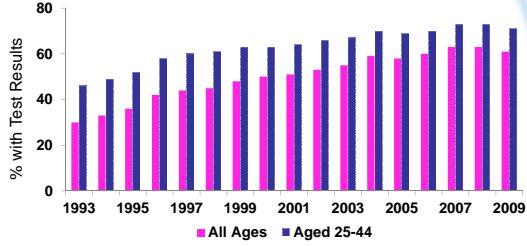
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### Reporting of HIV Test Results in Persons with TB by Age Group United States, 1993–2009\*



\*Updated as of July 1, 2010.

Note: Includes TB patients with positive, negative, or indeterminate HIV test results. Persons from California reported with AIDS only through 2004. (HIV test results are not reported from California)




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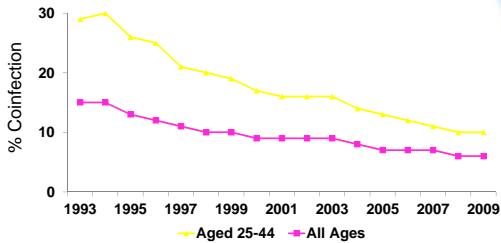
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### Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2009\*



\*Updated as of July 1, 2010.

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




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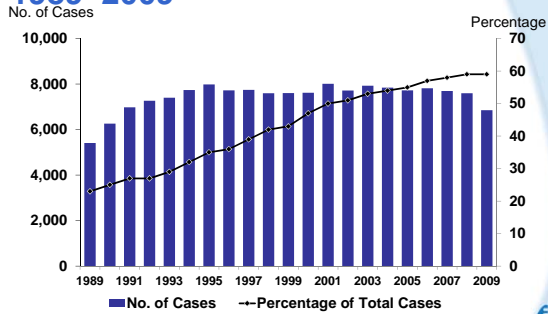
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### Trends in TB Cases in Foreign-born Persons, United States, 1989–2009\*



\*Updated as of July 1, 2010.




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**Diagnosis of Latent TB  
Infection  
(LTBI)**

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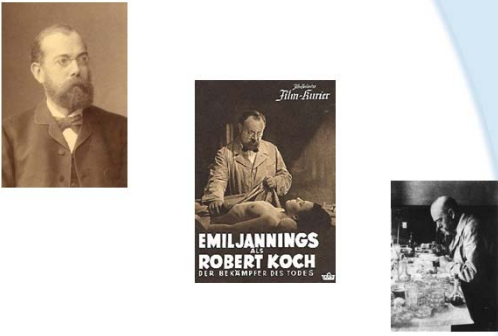
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**LTBI Diagnostic Tests Developed  
in the 20<sup>th</sup> Century**

- There were NO new diagnostic tests for LTBI throughout the entire 20<sup>th</sup> century!

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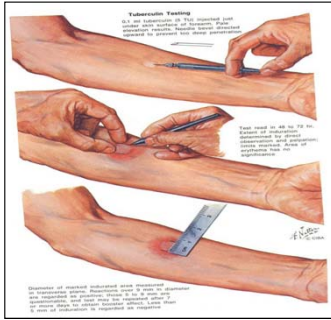
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## Diagnosis of TB Infection Tuberculin Test –(PPD)



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## Mantoux Tuberculin Skin Test Interpreting the Reaction

Interpretation of TST reaction depends on size of induration and person's risk factors for TB



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## Mantoux Tuberculin Skin Test Interpreting the Reaction

- Induration of  $\geq 5$  mm is considered positive for:
  - People living with HIV
  - Recent close contacts of people with infectious TB
  - People with chest x-ray findings suggestive of previous TB disease
  - People with organ transplants
  - Other immunosuppressed patients

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## Mantoux Tuberculin Skin Test Interpreting the Reaction

- Induration of  $\geq 10$  mm is considered a positive reaction for:
  - People who have recently come to U.S. from areas where TB is common
  - People who inject drugs
  - People who live or work in high-risk congregate settings
  - Mycobacteriology laboratory workers



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## Mantoux Tuberculin Skin Test Interpreting the Reaction

- Induration of  $\geq 10$  mm is considered a positive reaction for:
  - People with certain medical conditions that increase risk for TB
  - Children younger than 4 years old
  - Infants, children, or adolescents exposed to adults in high-risk categories



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## Mantoux Tuberculin Skin Test Interpreting the Reaction

- Induration of  $\geq 15$  mm is considered a positive reaction for people who have no known risk factors for TB



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## Sensitivity and Specificity of the Tuberculin Skin Test (TST)

- Depending on prevalence of disease in population you are testing and geographical area
  - Up to 20% of positive reactions might be false positives
    - Infected with Mycobacteria other than TB (e.g. MAC)
    - BCG vaccine
  - Up to 20% of individuals with active TB may be false negative
    - Critically ill TB patient
    - Immunosuppressed person
    - Recently vaccinated with live virus
    - Recent TB infection



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## Mantoux Tuberculin Skin Test False-Positive Reaction

- Factors that can cause people to have a positive reaction even if they do not have TB infection:
  - Infection with nontuberculous mycobacteria
  - BCG vaccination
  - Administration of incorrect antigen
  - Incorrect measuring or interpretation of TST reaction



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## Mantoux Tuberculin Skin Test BCG Vaccine

- People who have been vaccinated with BCG may have a false-positive TST reaction
  - However, there is no reliable way to distinguish between reaction caused by TB infection or by BCG vaccine
- Individuals should always be further evaluated if they have a positive TST reaction



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## Mantoux Tuberculin Skin Test False-Negative Reaction

- Factors that can cause false-negative reactions:
  - Anergy
  - Recent TB infection (within past 8 – 10 weeks)
    - It can take 2 – 8 weeks after TB infection for body's immune system to react to tuberculin
  - Younger than 6 months of age
  - Recent live-virus (e.g., measles or smallpox) vaccination
  - Incorrect method of giving the TST
  - Incorrect measuring or interpretation of TST reaction



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## Mantoux Tuberculin Skin Test

Any patient with symptoms of TB disease should be evaluated for TB disease, regardless of his or her skin test reaction.



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## Mantoux Tuberculin Skin Test Anergy

- Inability to react to skin tests due to weakened immune system
- Anergy testing is no longer routinely recommended



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## Baye's Theorem

The accuracy of a test is dependent upon the prevalence of the disease in the population



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## Cases

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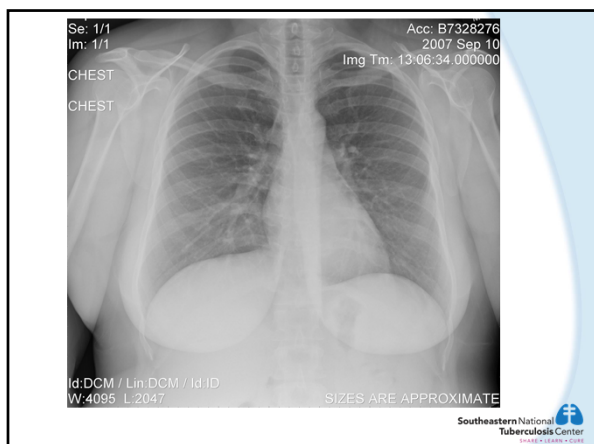
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## IGRA

- Interferon-Gamma Release Assays (IGRAs) are whole-blood tests that can aid in diagnosing *Mycobacterium tuberculosis* infection, including both latent tuberculosis infection (LTBI) and tuberculosis (TB) disease.
- Three IGRAs that have been approved by the U.S. Food and Drug Administration (FDA) are commercially available in the U.S.:
  - QuantiFERON®-TB Gold test (QFT-G);
  - QuantiFERON®-TB Gold In-Tube test (QFT-GIT);
  - T-SPOT®.TB test (T-Spot)

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## IGRA General Points

- IGRAs are highly specific
  - Both commercially available tests (QFT and T-SPOT TB) are substantially more specific than the PPD since they are not impacted by BCG
- IGRAs have a moderate to high sensitivity compared to PPD
  - QFT being as sensitive as PPD (70-80%) in immunocompetent
  - T-SPOT TB is more sensitive than QFT and PPD in the immunocompromised



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## IGRA: Advantages

- Requires a single patient visit to conduct the test.
- Results can be available within 24 hours.
- Does not boost responses measured by subsequent tests.
- Prior BCG (bacille Calmette-Guérin) vaccination does not cause a false-positive IGRA test result.



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## IGRA: Disadvantages

- Blood samples must be processed within 8-16 hours after collection while white blood cells are still viable.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs.
- Limited data on the use of IGRAs to predict who will progress to TB disease in the future.
- Limited data on the use of IGRAs for:
  - Children younger than 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons; and
  - Serial testing.
- Tests may be expensive.



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### What test should be used to diagnose LTBI in HIV infected patients?

- TB is the most frequent opportunistic infection and a leading cause of death in people living with HIV.
- IPT has been shown to reduce the risk of TB and is now universally recommended in HIV-infected individuals with LTBI or at high risk of having LTBI.
- However, the optimal test for identifying HIV-infected individuals who would benefit most from IPT remains uncertain.
- Consequently, the most recent national and international guidelines differ in their recommended LTBI screening strategies.



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### What test to use: TST vs IGRA?

- Pai and colleagues conducted a systematic review that addressed two questions relevant for determining whether IGRAs should replace TST as a screening test for LTBI in people living with HIV:
  - 1) are IGRAs better than TST at predicting which HIV-infected individuals are at highest risk of progression to active TB; and
  - (2) are IGRAs more sensitive than TST for diagnosis of MTB infection, particularly in HIV-infected individuals with advanced immunosuppression?

JAIDS: Volume 56(3), 1 March 2011, pp 230-238



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### Results of Meta Analysis

JAIDS: Volume 56(3), 1 March 2011, pp 230-238

- 37 studies that included 5736 HIV-infected individuals.
- In three longitudinal studies, the risk of active TB was higher in HIV + individuals with (+) versus (-) IGRA results.
- However, the risk difference was not statistically significant in the two studies that reported IGRA results according to manufacturer-recommended criteria.
- In persons with active tuberculosis (a surrogate reference standard for latent tuberculosis infection), pooled sensitivity estimates were heterogeneous but higher for TSPOT (72%; 95% confidence interval [CI], 62-81%) than for QFT-GIT (61%; 95% CI, 47-75%)



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## Treatment of LTBI

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### Animal Studies and INH Dosing

- Before clinical trials in humans, the effective dose of isoniazid was established in guinea pigs
- Varying doses of INH was given to guinea pigs after challenge with virulent TB bacilli
- Those challenged with at least 5mg/kg were protected
- This formed the basis of using 5mg/kg for humans



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### Clinical Trials in HIV Negative Persons

- In the 1950's and 1960's large trials looking at INH for treatment of LTBI
- Conducted in both industrialized and developing nations
- Included over 100,000 participants and were placebo controlled
- The effectiveness of treatment was between 25% to 92% but when only those thought to be compliant were analyzed the effectiveness was about 90% overall.
- *No cases of hepatitis reported or recognized.*

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## Rifampin daily for Four Months

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### 6 Months Rifampin Mono-Therapy (For contacts of INH resistant cases) *(Polesky et al., AJRCCM; 1996: 155: 1735-38)*

- 204 Homeless persons in Boston,
- Documented TST conversions
- 71 no therapy – 8.6% active TB
- 38 given INH – 7.9% active TB (INH Resistant)
- 49 RIF only - no active TB, no increased LFT's

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**4 months Rifampin vs 9 months INH**  
**A retrospective review (non-randomized)**  
**Patient characteristics**  
*(Page et al, Archives Int Med; 2006; 166: 1863-1870)*

	9 INH	4 RIF	(Pvalue)
Patients starting therapy	770	1379	
Age	30.1	34.2	(.001)
Sex (% females)	59%	54%	(.03)
HIV positive	1.8%	0.7%	(.01)
Abnormal baseline LFT's	5.7%	4.3%	(NS)
<b>Percent completing</b>	<b>53%</b>	<b>72%</b>	<b>(.001)</b>

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**Treatment of LTBI:**  
**Current Recommendations**

Drug	Dose	Duration
INH	300 MG Daily	9 Months
RIF	600 MG Daily	4 Months
RIF/PZA	600MG/ 45-30 MG/KG Daily	2 Months - No Longer Recommended
RBN	300 MG Daily	4 Months

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**Adherence to LTBI Therapy**

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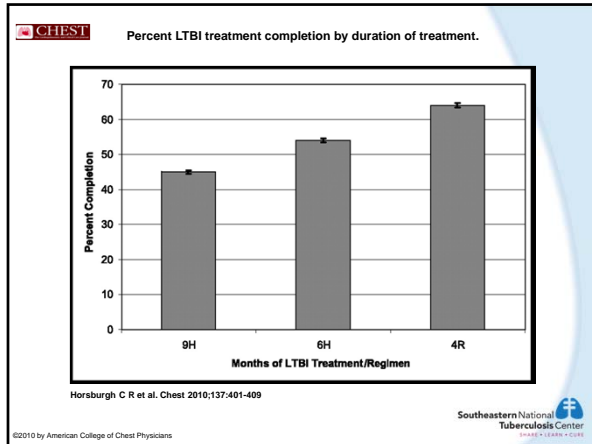
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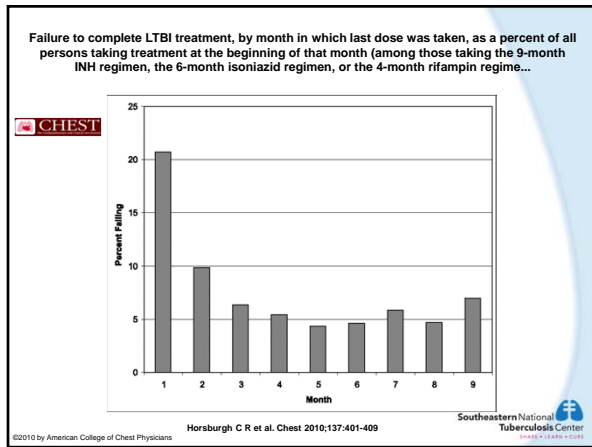
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## The Future of LTBI Therapy

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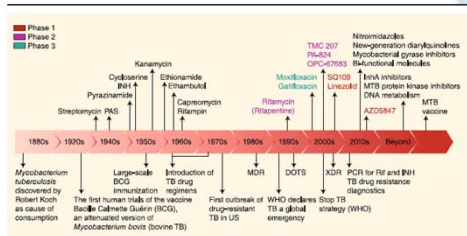
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## TB Drug Development Timeline



Laloo et al, Curr HIV/AIDS Rep 2010




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## Need TB Resources?

SNTC's website:

<http://sntc.medicine.ufl.edu/>

Consultation Hotline:

800-4TB-INFO




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