



# Tuberculosis



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**WRAIR- GEIS 'Operational Clinical Infectious Disease' Course**



UNCLASSIFIED

OCID course 2015





# Acknowledgments

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Cincinnati Historical Society





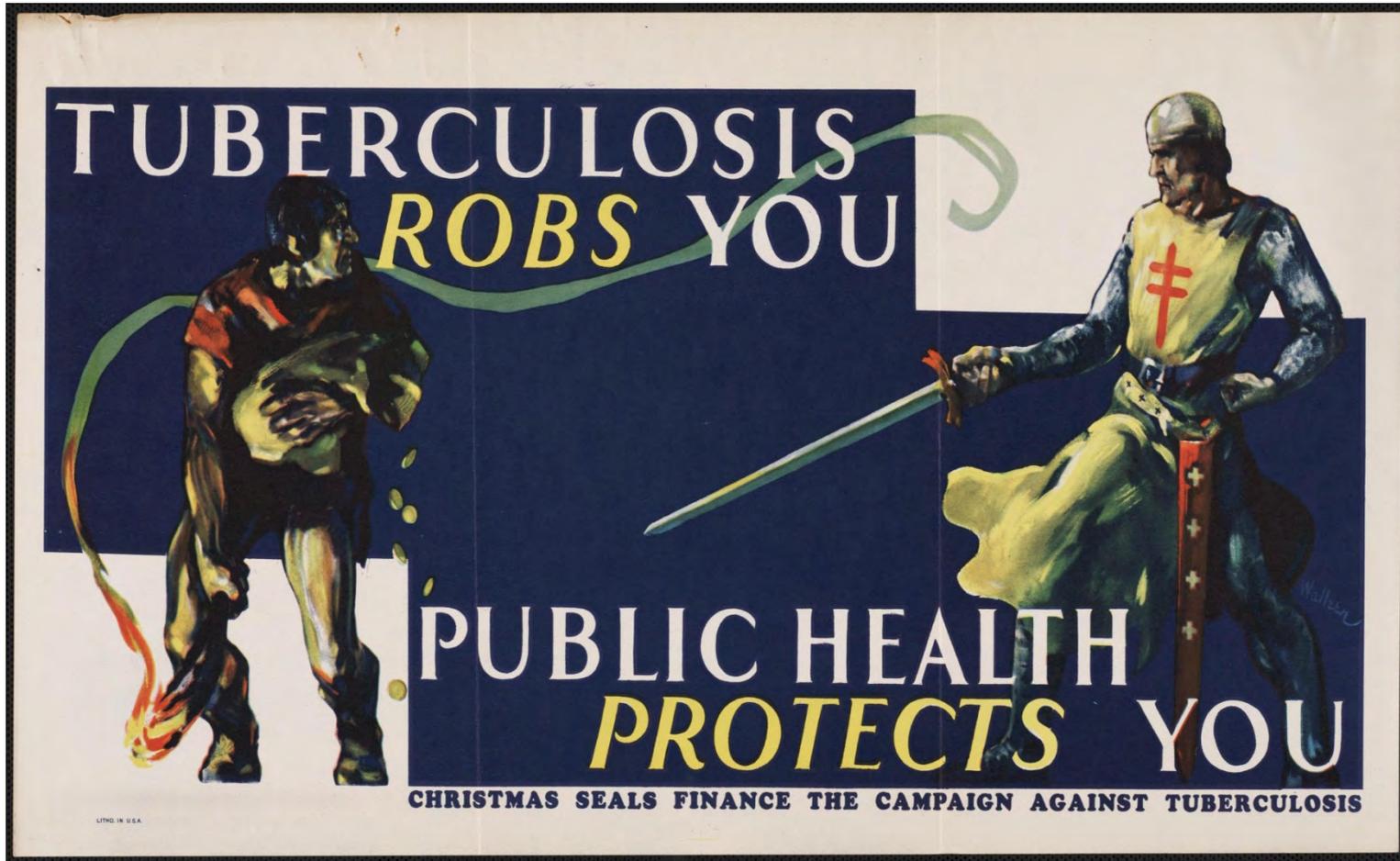
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# Tuberculosis





# Outline

- Global Burden of Tuberculosis
- Active vs. Latent TB Infection
- Diagnosis and Treatment of Active TB
- Diagnosis and Treatment of Latent TB
- Military screening policies
- Managing Exposure in a Deployed Environment
- Other issues





# Global Burden of Tuberculosis

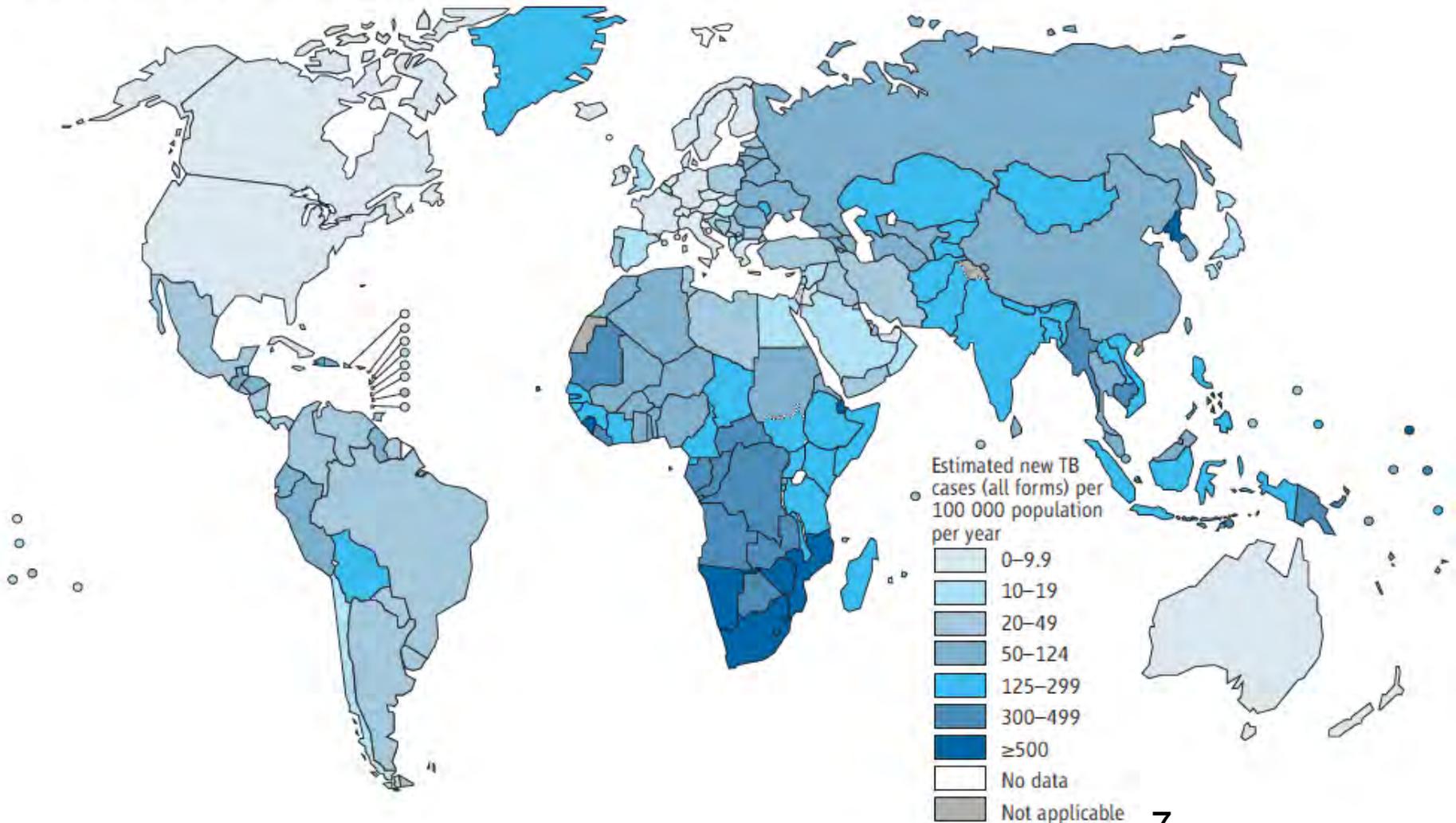
- 9.2 million cases and 1.7 million deaths yearly
- Associated with co-pandemic of HIV
- Drug-resistance increasingly common
- One third of the world's population is infected with LTBI
  - Focus is on identification and treatment of active TB (DOTS)
  - Screening for LTBI is not routinely done in most countries
  - Increasing efforts to extend LTBI treatment to HIV populations





# Global Burden of Tuberculosis

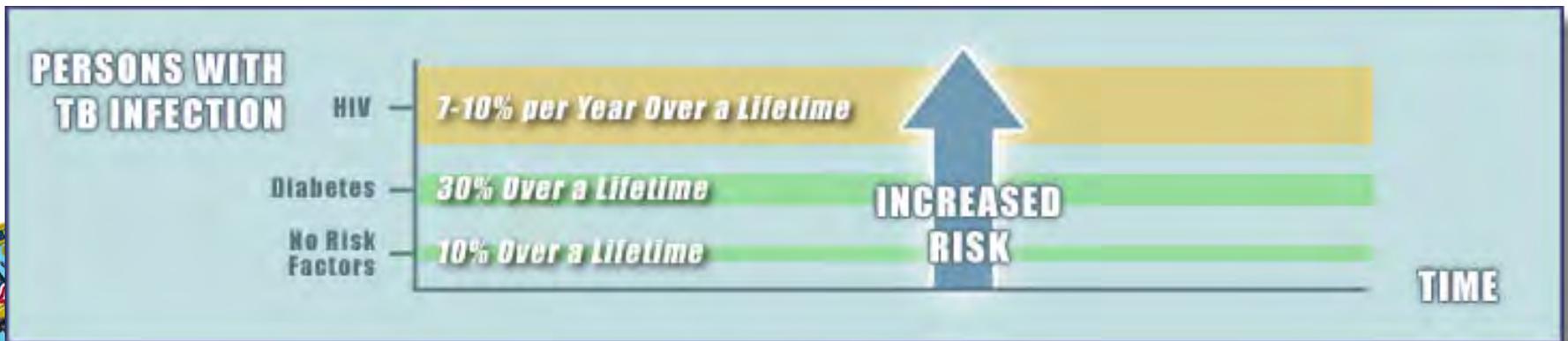
Estimated TB incidence rates, 2012





# TB Pathophysiology

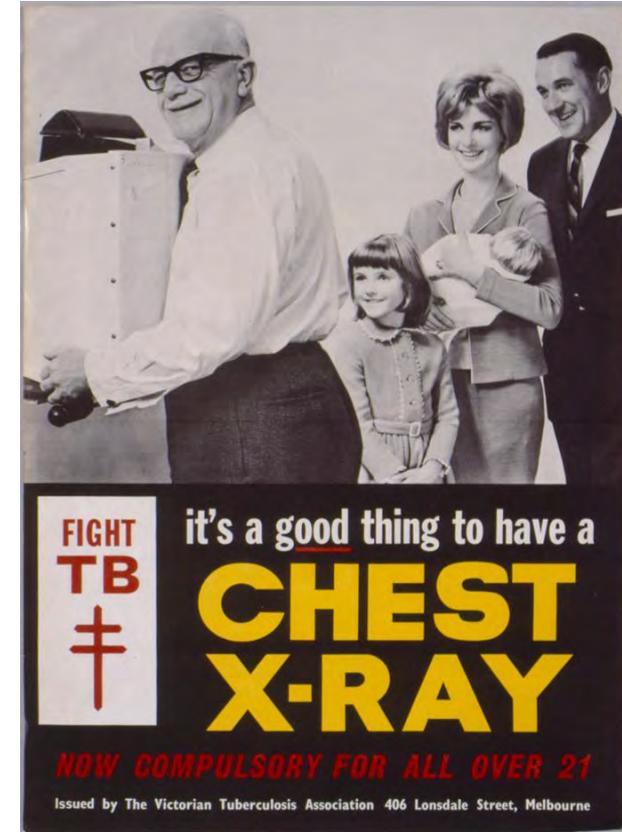
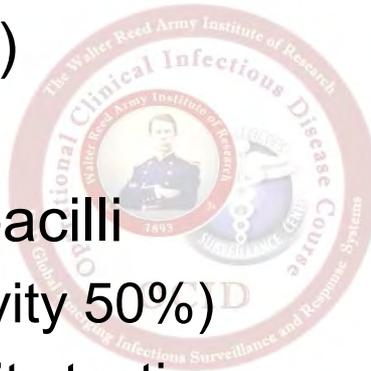
- Spread person-to-person through the air
- Droplet nuclei may remain in the air
- Primary infection
  - Inhale tubercle bacilli
  - Reach alveoli, engulfed by macrophages
  - Some multiply intracellularly and released
  - Immune system (cell-mediated) prevents progression
- Activation
  - Tubercle bacilli overcome immune system
  - “5% risk in 2 years, 10% lifetime” (may be lower – Am J Respir Crit Care Med 2014 NOV 1; 190: 1044)





# Diagnosis of TB

- Clinical symptoms and signs
- CXR (not confirmatory)
- Detection of tubercle bacilli
  - AFB Smear (sensitivity 50%)
  - Culture and sensitivity testing
  - Nucleic Acid Amplification Tests



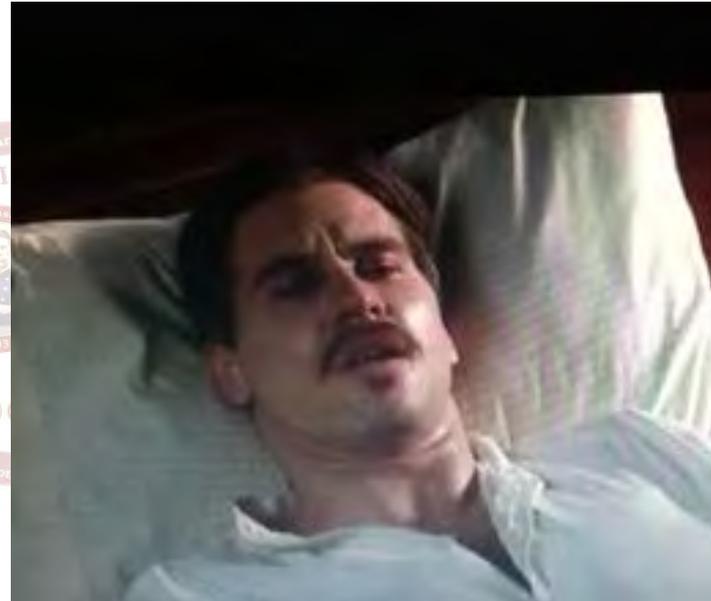
[museumvictoria.com.au](http://museumvictoria.com.au)





# Symptoms of Active TB

- Fever
- Chronic cough
- Night sweats
- Hemoptysis
- Weight loss
- Fatigue





# Active TB

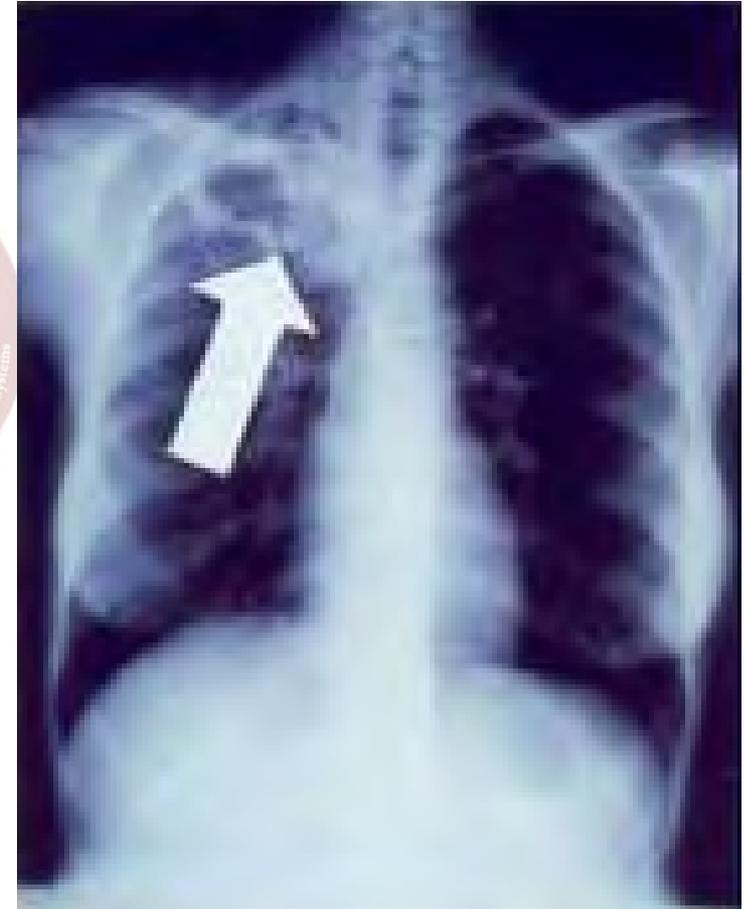
- Chronic infection with *Mycobacterium tuberculosis*.
- Pulmonary most common (80%)
  - Pulmonary and laryngeal TB are contagious
- Extrapulmonary (20%)
  - Lymphadenitis (scrofula)
  - Skeletal
  - Renal
  - Meningeal





# CXR

- Patchy or nodular infiltrate
- Apical- or subapical-posterior areas of the upper lobes or the superior segment of a lower lobe
- Especially if bilateral or associated with cavity formation





# AFB Smear

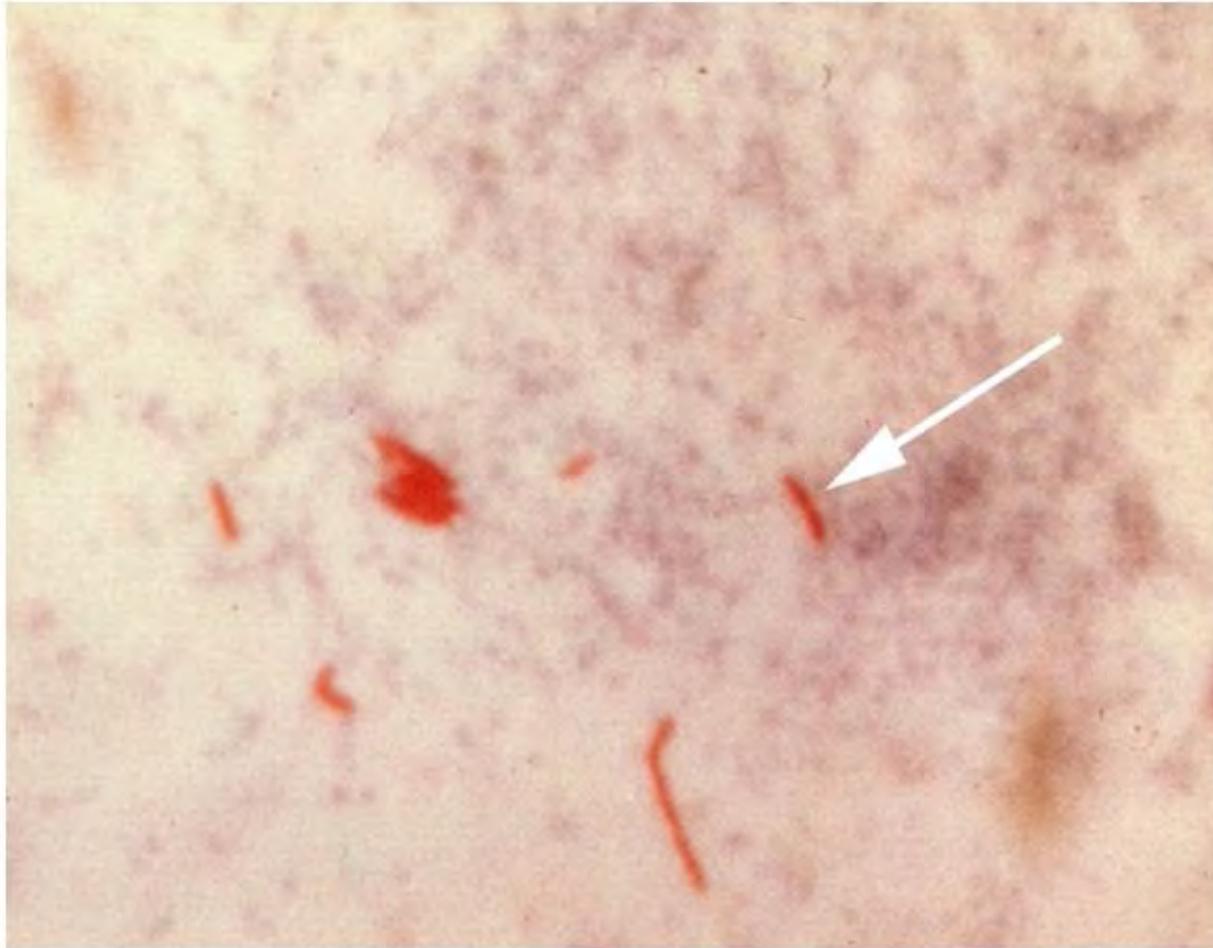


Figure 9. Sputum specimen demonstrating acid fast bacilli (AFB) (arrow). Source CDC.





# Treatment of ACTIVE TB

- “4 for 2 and 2 for 4”
  - INH, RIF, PYR, ETH X 2 months, **then**
  - INH, RIF X 4 months
- Modify regimen if necessary after antibiotic susceptibility results are available
- Check bacteriologic response monthly
- HIV test
- **“Never add a single drug to a failing regimen”**

INH = isoniazid  
PYR = pyrimethamine

RIF = rifampin  
ETH = ethambutol





# Treatment of ACTIVE TB

- 4 Month Moxifloxacin based regimens for Drug-Sensitive TB
  - 1931 patients randomized into 1 of 3 treatment groups (1:1:1)
    - Control group (standard RIPE therapy) – 6 months
    - “INH” arm (Moxi, INH, RIF for 4 months to include 2 months PZA)
    - “ETH” arm (Moxi, RIF for 4 months to include 2 months PZA and ETH)
  - No significant safety differences
  - The regimens with 4 months of moxifloxacin did **NOT** meet criteria for noninferiority compared to the standard of care
    - Moxi groups had a more rapid decline in bacterial load compared to standard
    - Moxi groups had more likelihood of relapse at the end of therapy





# When are they non-infectious?

- On adequate therapy
- Clinical response
- **Three consecutive negative sputum smears from sputum collected on different days**





# Infection Control

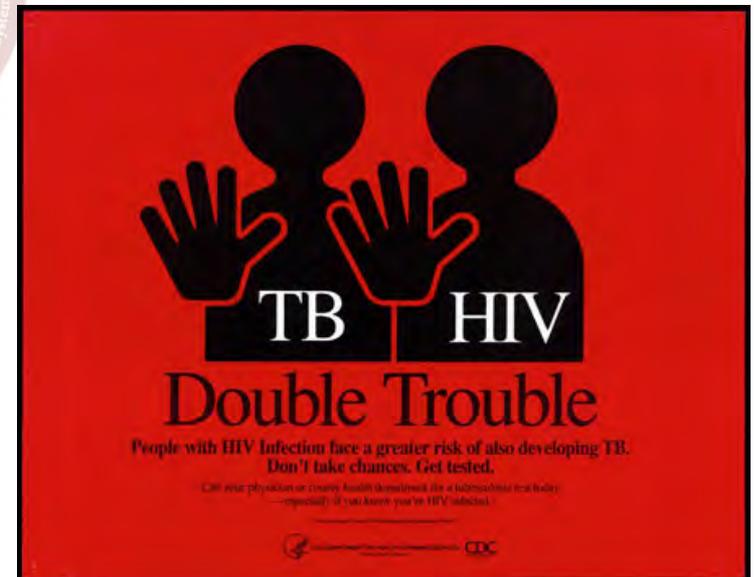
- Administrative controls
  - Primary strategy for infection control! \*\*\*\*\*
  - “Develop policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB”
- Engineering controls (ventilation)
  - Isolation
  - Negative pressure rooms
- Personal respiratory protection (N95)





# HIV and TB

- 10% risk of progression per year
- Atypical presentations, anergy
- Leading cause of death in HIV patients
- MDR and XDR TB
- Drug interactions
- Reconstitution syndrome



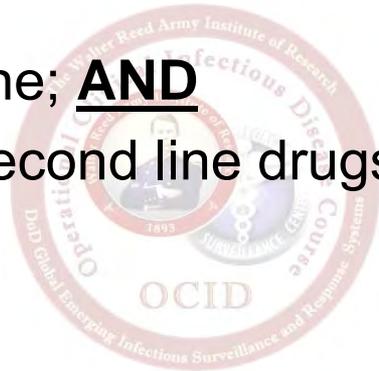
MDR = multi-drug resistant

XDR = extremely drug resistant



# MDR and XDR

- MDR=INH and RIF resistance
- XDR=MDR+
  - Any fluoroquinolone; **AND**
  - 1 of 3 injectable second line drugs
    - Capreomycin
    - Kanamycin
    - Amikacin



MDR = multi-drug resistant

XDR = extremely drug resistant

INH = isoniazid

RIF = rifampin

# LTBI vs. Pulmonary TB Disease

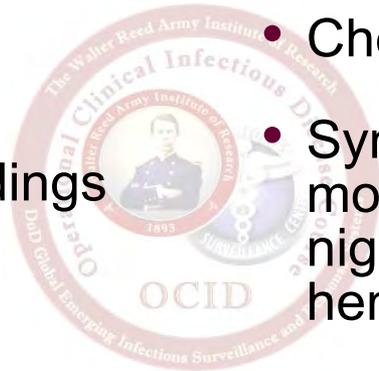


## LTBI

- TST\* or IGRA† positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease

## Active Pulmonary TB

- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens *may* be smear or culture positive

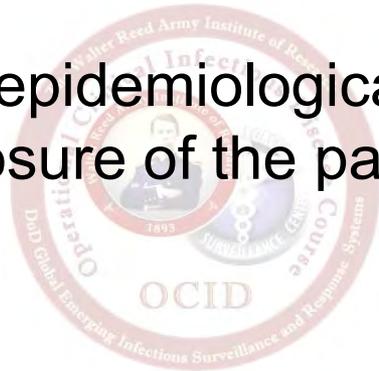


\* Tuberculin Skin Test (TST)  
† Interferon Gamma Release Assay (IGRA)



# What defines a positive TB test?

- a) 5 mm
- b) 10 mm
- c) 15 mm
- d) It depends on the epidemiological characteristics and degree of TB exposure of the patient





**Table 7. Criteria for tuberculin positivity, by risk group**

Reaction $\geq 5$ mm of induration	Reaction $\geq 10$ mm of induration	Reaction $\geq 15$ mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees <sup>†</sup> of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of $\geq 15$ mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of $\geq 10\%$ of ideal body weight, gastrectomy, and jejunioileal bypass Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

Includes patients taking TNF- $\alpha$  antagonists

\* Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

<sup>†</sup> For persons who are otherwise at low risk and are tested at the start of employment, a reaction of  $\geq 15$  mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19-34.





# CDC Guidelines Call for Targeted Testing Only

- Targeted testing:
  - “...targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk.” (MMWR 2000)
  - All military services conduct testing at accession
- CDC clearly considers high-risk:
  - Hospitals and health care settings
  - Prisons
  - HIV-infected
  - Homeless
  - Contacts of active case

**NOT Military**





# Testing for *M. tuberculosis* Infection

## Mantoux tuberculin skin test (TST)

Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

## Interferon Gamma Release Assays (IGRAs)

Blood tests that measure and compare amount of interferon-gamma (IFN- $\gamma$ ) released by blood cells in response to *M. tuberculosis* antigens.

These include:

1. Quantiferon® Gold-in-tube (QFT-GIT)
2. T-SPOT®.TB



Harnessing the power of T cell measurement





# The Tuberculin Skin Test

- Cell-free purified protein fraction extracts obtained from a human strain of *M. tuberculosis*
- In use for over a century
- Problems with TST
  - ***Positive predictive value is low if prevalence of infection is low***
  - Errors and variability in administration
  - False negatives and false positives
- Pseudoepidemics of TST reactions reported in hospitals, prisons, reservations, military populations





# Administering the TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produces a wheal 6 to 10 mm in diameter



CDC. *MMWR* (Appendix F) 2005;54(RR-17):138-9.





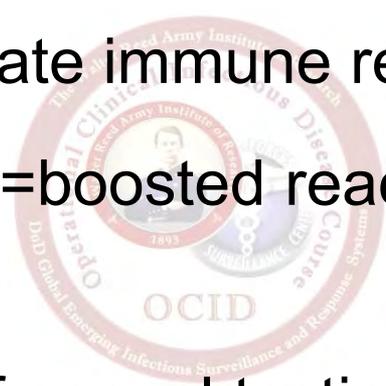
# Reading the TST

- Measure reaction in 48 to 72 hours
- Measure induration, **not erythema**
- Record reaction in millimeters, not “negative” or “positive”
- Ensure trained health care professional measures and interprets the TST





# Boosting and Two-Step Testing



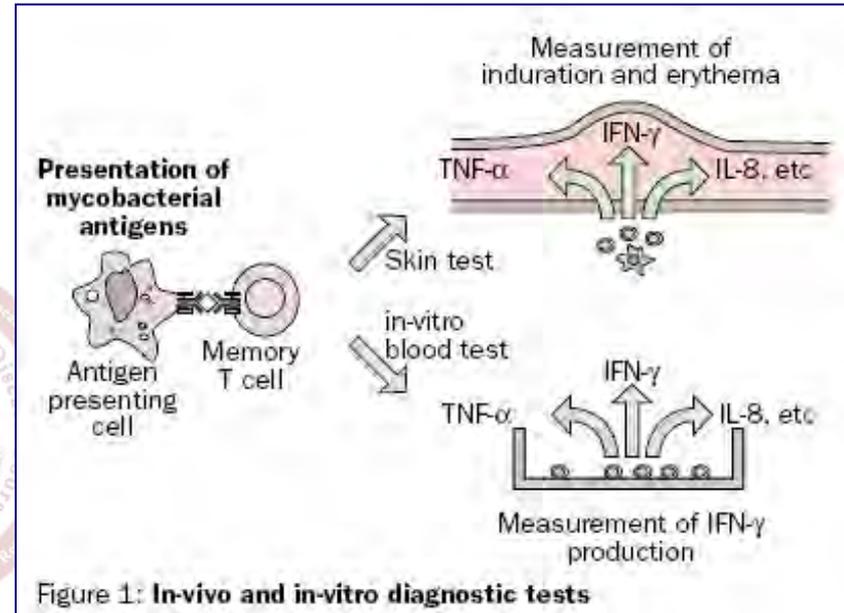
- Boosting
  - May have an initially negative test due to waning responsiveness
  - First test may stimulate immune response for second test
  - Second test positive=boosted reaction
- Two-step testing
  - Done on initial test if annual testing is planned
  - Prevents interpreting a subsequent annual TST as a new seroconversion
  - A negative first test with a positive second test should be evaluated for LTBI.





# Interferon Gamma Release Assays (IGRA)

- Measures interferon- $\gamma$  released from lymphocytes incubated with antigens to MTB
  - *Unknown rate of progression to active TB*
  - *Lack of “gold standard” for LTBI prevents defining the sensitivity and specificity of the test*



Andersen P et al. *Lancet* 2000;356:1099.





# When should I use the IGRA?

- Depends who you talk to
  - CDC guidelines: may be used to replace TST, but don't do both
  - UK, many other European countries: use IGRA as confirmatory test
  - Military policies conform with CDC, but Navy Great Lakes was using it as a confirmatory test
- Evolving issue, not resolved yet
  - More data
  - Evolving technology
- IGRA preferred among BCG vaccinated





## Other LTBI Testing Issues

- Must maintain good quality testing program, whether TST or IGRA
  - Both are difficult in the field
  - **Should only be performed for contact investigations**
  - Useful QA/QC guidelines for TST quality control in Appendix F of: CDC. *MMWR* 2005;54(RR-17):138-9
- **Tubersol® is the only TST that should be used**
  - False positives with Aplisol®
  - HA Policy 08-012 (29 Sept 08)





# Decision to treat

- **“A decision to test is a decision to treat”**
  - Don't ignore a positive test
  - But be skeptical in low-risk populations (don't test)
- **Must rule out active TB first**
  - Symptoms of active TB
  - Compatible chest x-ray findings
  - **If symptoms→3 sputum smear, culture, at least 1 NAAT test**
- Look at criteria to determine cutoff
- **Assess risks & benefits for each individual patient**
  - Medical history (esp. liver disease, alcohol abuse)
  - How recent was TB exposure?
  - Pregnancy
  - Allergies





# Decision to treat

- LTBI Treatment options:
  - Isoniazid x 9 months 5 mg/kg daily (max 300 mg daily)
  - Isoniazid x 9 months 15 mg/kg twice weekly (max 900 mg daily)
    - Don't use the 6 month option if your patient can tolerate the longer option
  - Isoniazid 15 mg/kg (max 900 mg) + Rifapentine once weekly for x 3 months given once weekly
    - 10.0–14.0 kg 300 mg
    - 14.1–25.0 kg 450 mg
    - 25.1–32.0 kg 600 mg
    - 32.1–49.9 kg 750 mg
    - $\geq 50.0$  kg 900 mg maximum
  - Rifampin 10 mg/kg (max 600 mg) x 4 months

When dosing, round up to the nearest 50-100 mg

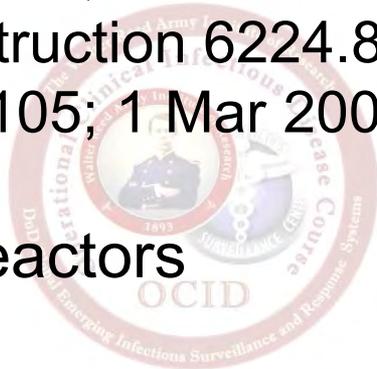
**TREATMENT DOSE NOT ELIMINATE  
THE RISK OF ACTIVE DISEASE\***



# Screening for LTBI in the US Military



- Over 250,000 tests per year among recruits
- Accessions: all services do universal screening
  - Army (DA PAM 40-11; 20 Oct 2008)
  - Navy (BUMED Instruction 6224.8A; 12 Feb 2009)
  - Air Force (AFI 48-105; 1 Mar 2005)
- Prevalence of TST reactors
  - Navy: 5%
  - Army: 3%
  - Air Force: 1.5%
  - ***Depends on proportion of foreign-born***
- **Deployment-related screening**



# What about guidelines for travelers?



- US Guidelines (CDC Yellow Book): both pre- and post-travel testing for those with “prolonged exposure to tuberculosis...e.g. [routine contact with] hospital, prison, and homeless shelter populations”
- IDSA Guidelines: TST “should be performed for those with anticipated exposure to TB or long-term stays in developing areas or when requested by the traveler because of concern about exposure”
- TRAVAX: “travelers to countries with high risk (i.e., > 100 cases per 100,000) should have pre-departure testing if staying for > 1 month; travelers to countries with moderate risk (approximately 25-100 cases per 100,000) should have pre-departure testing if they plan on staying for > 3 months”
- Canadian Guidelines: a single, post-travel test based on duration of travel as well as TB incidence in the country visited.

1. MF Iademarco. Tuberculosis. In: Health Information for International Travel 2008. Atlanta, GA: CDC, 2008.
2. Hill et al. *CID* 2006;43:1514.
3. Shoreland. Tuberculosis. Available at [www.travax.com](http://www.travax.com) ; Accessed 6 June 2009.
4. W Wobeser et al. Surveillance and screening in tuberculosis control. In: Canadian tuberculosis standards: Public Health Agency of Canada, 2007.





# What does the US military do for deployers?

- Air Force
  - Targeted testing after deployment since '05 (AFI 48-105)
- Navy
  - Used to test operational units yearly with TST
  - Now targets testing during PHA with questionnaire (BUMEDINST 6224.8A, 12 Feb 2009)
- Army
  - Used to test before deployment, after deployment, and then again 3-6 months after deployment (3 tests per deployment)
  - In 2008, moved to targeted testing after deployment using DD 2796 (OTSG Memo, 25 Sept 2008)
  - Testing **SHOULD NOT** be routinely performed during deployment

• See <http://www.pdhealth.mil/tuberculosis.asp>





# Recent Deployment TB Epidemiology

- Outbreaks on Navy ships—common in the 1960s
  - USS Wasp (1998): 21 infected from failure to diagnose index case
  - USS Ronald Reagan (2003): 1 reactivation despite prior INH Rx
- Active TB: **lower rate of disease than in the US population**
- TST reactors during deployment
  - Prevalence of TST conversion: 1-2% without specific exposure history (similar to prevalence in recruits)
  - Numerous false positives and pseudo-outbreaks reported



Lamar. *Mil Med* 2003; 168(7):523-7.

CDC. *MMWR*. 2007;55:1381-2.

Camarca MM and Krauss MR. *Mil Med* 2001;166(5):452-6

Mancuso J. *AJRCCM* 2008;177:1285-9.





# Managing TB Exposure in a Deployed Setting

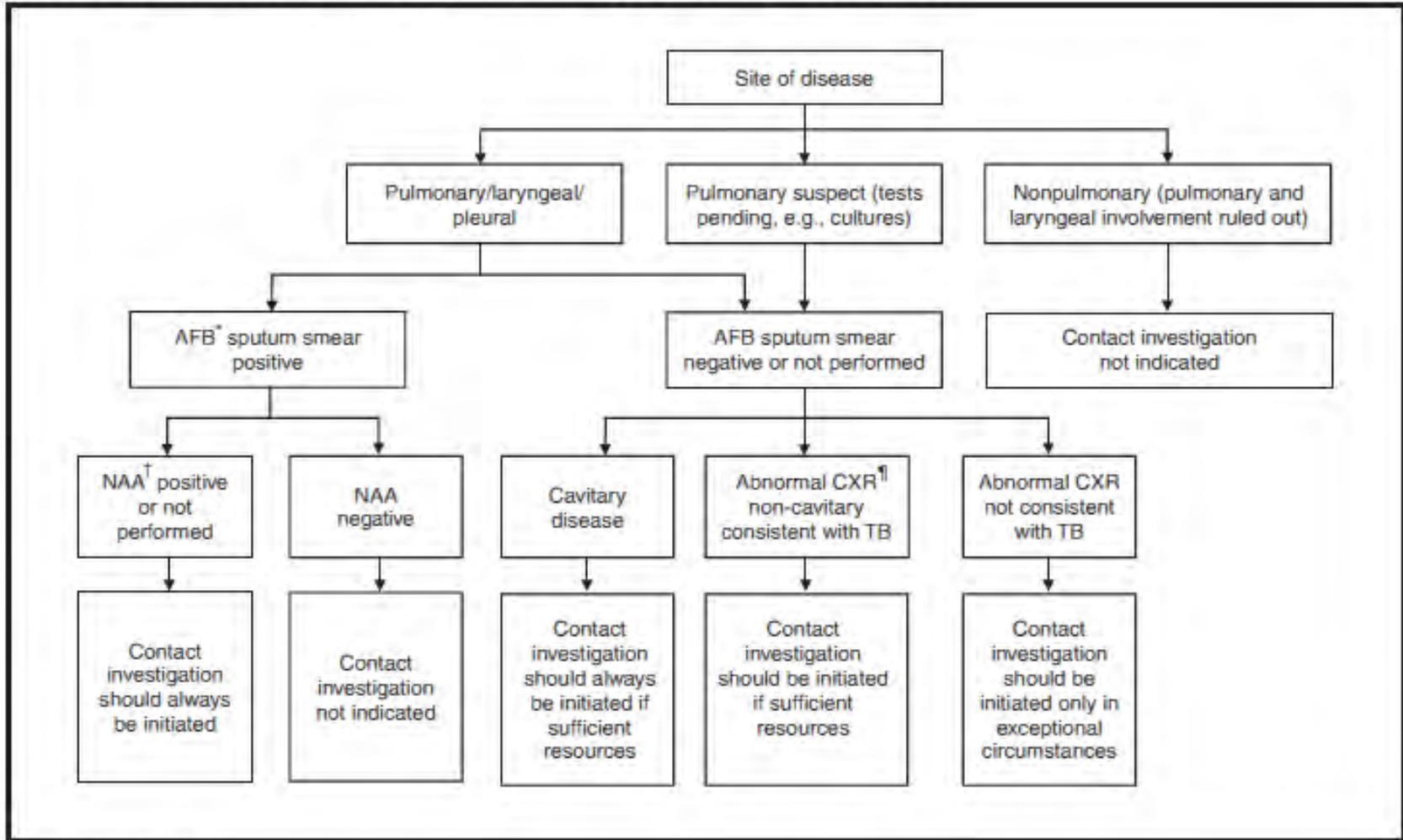
- Refer to Preventive Medicine





# Managing TB Exposure in a Deployed Setting

FIGURE 1. Decision to initiate a tuberculosis (TB) contact investigation



\* Acid-fast bacilli.

† Nucleic acid assay.

‡ According to CDC guidelines.

¶ Chest radiograph.



# Managing TB Exposure in a Deployed Setting



- Document TB symptoms (or the lack thereof)
- High or medium priority contacts should receive TST at initial encounter
- All contacts should have a TST at 8-10 weeks post-exposure
- A diameter  $>5$  mm is positive for any contact
- Any contact with TB symptoms should be managed immediately regardless of skin test results

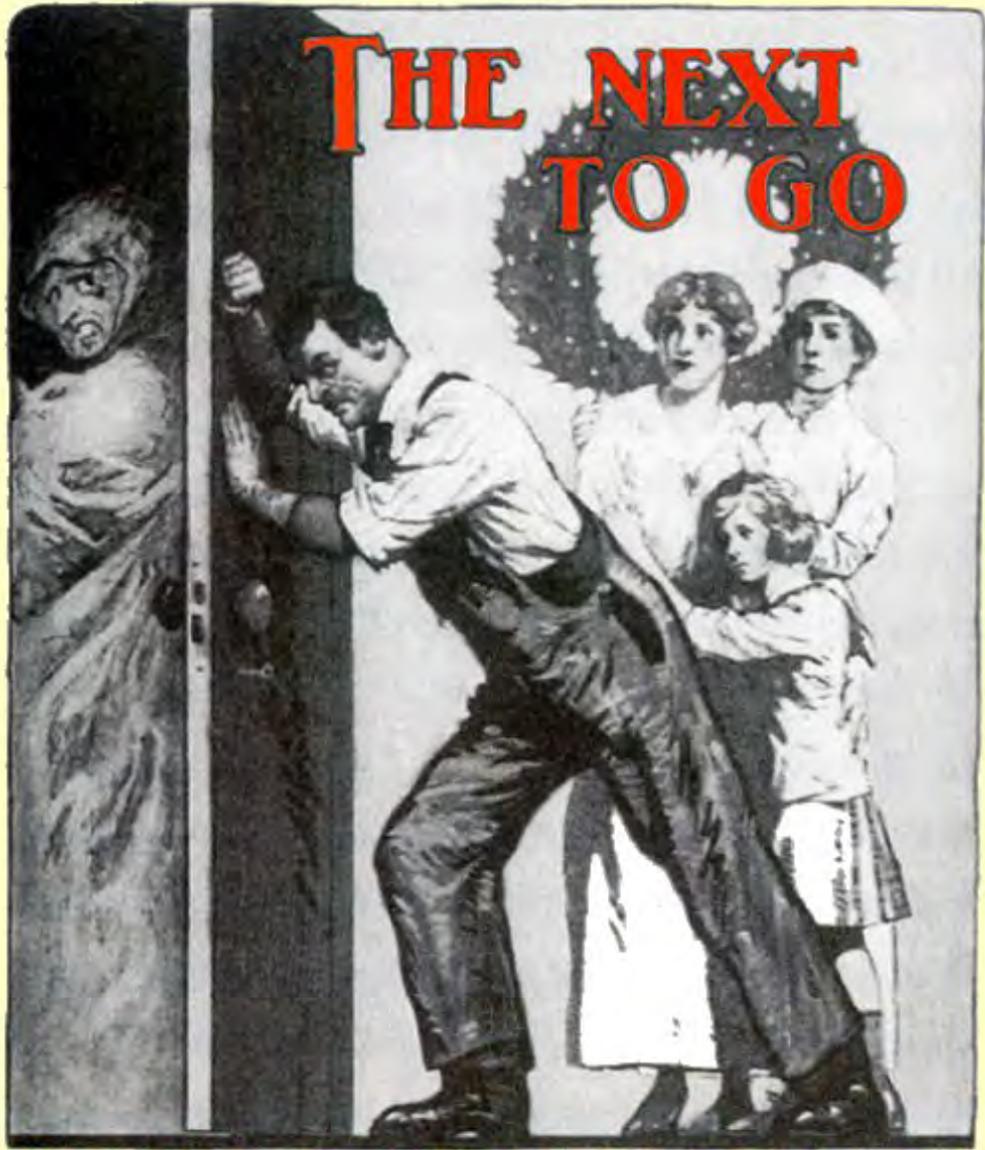


# Other important management issues



- Directly observed therapy (DOT)
  - Standard of care for **Active** TB
  - May be used for LTBI, but uncommon
  - **Refer to Preventive Medicine**
- Disease reporting
  - **Active TB is a reportable disease**, LTBI is not
  - Positive TST or IGRA must be documented in an electronic registry (ALTHA, MEDPROS, etc)
  - Reportable diseases are reported to Preventive Medicine both in garrison and on deployment





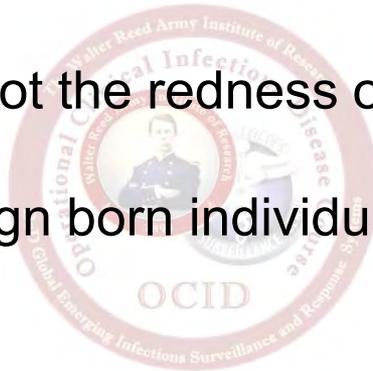
**FIGHT TUBERCULOSIS!**  
Red Cross Christmas Seal Campaign



# Summary

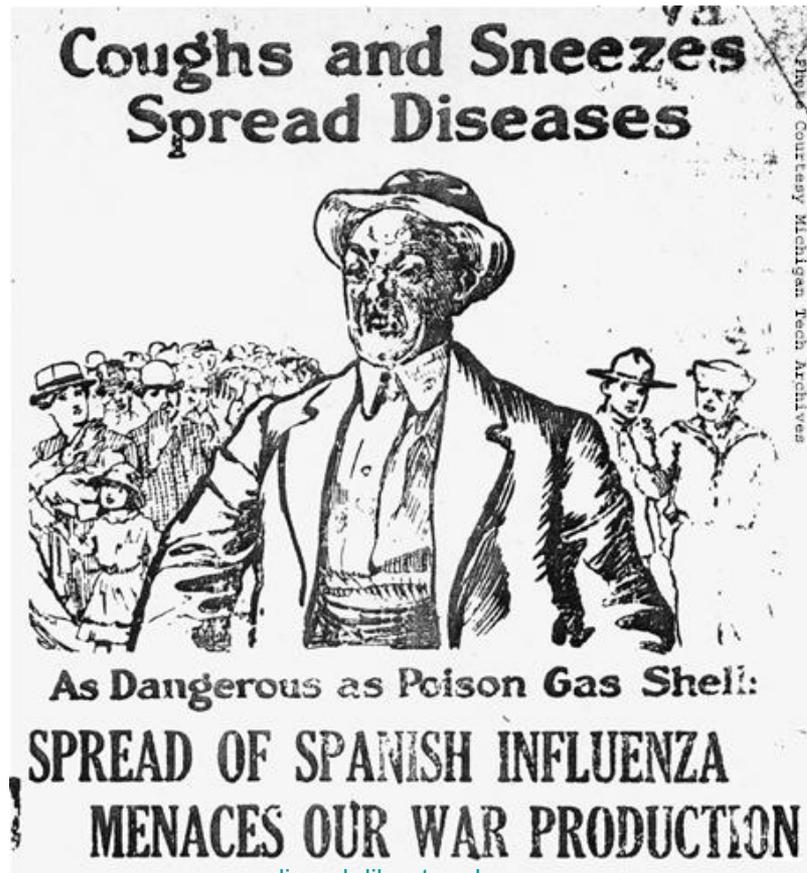


- Remember for TB testing, a decision to test is a decision to treat
- LTBI is not symptomatic and has normal Chest X-ray
- Targeted testing for TB with skin test or IGRA (“TB blood test”)
- Measure the swelling, not the redness on a TB skin test
- Consider IGRA for foreign born individual who may have received BCG as child
- Always rule out active TB before treating for LTBI
- Active TB requires airborne isolation when possible
- Report active TB cases to preventive medicine
- Directly observed minimum 4 drug therapy for active TB





# Thank You Questions?



[digarch.lib.mtu.edu](http://digarch.lib.mtu.edu)

