

# Tuberculosis Infection in the US Military



Edward Munch.  
*The Sick Child.* (1885)

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Courtesy of : Paul B. Keiser, Feb 2014  
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# Outline

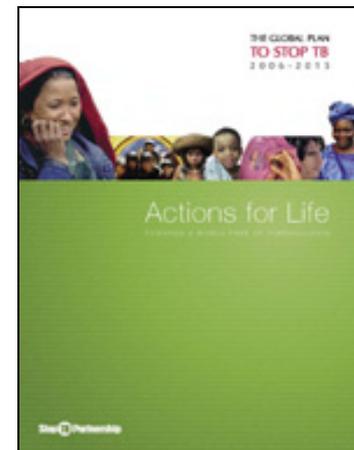
- Global Burden of Tuberculosis
- Active vs. Latent TB Infection
- Diagnosis and Treatment of Active TB.
- Diagnosis and Treatment of Latent TB
- Military screening policies
- Managing Exposure in a Deployed Environment
- Other issues

# Outline

- **Global Burden of Tuberculosis**
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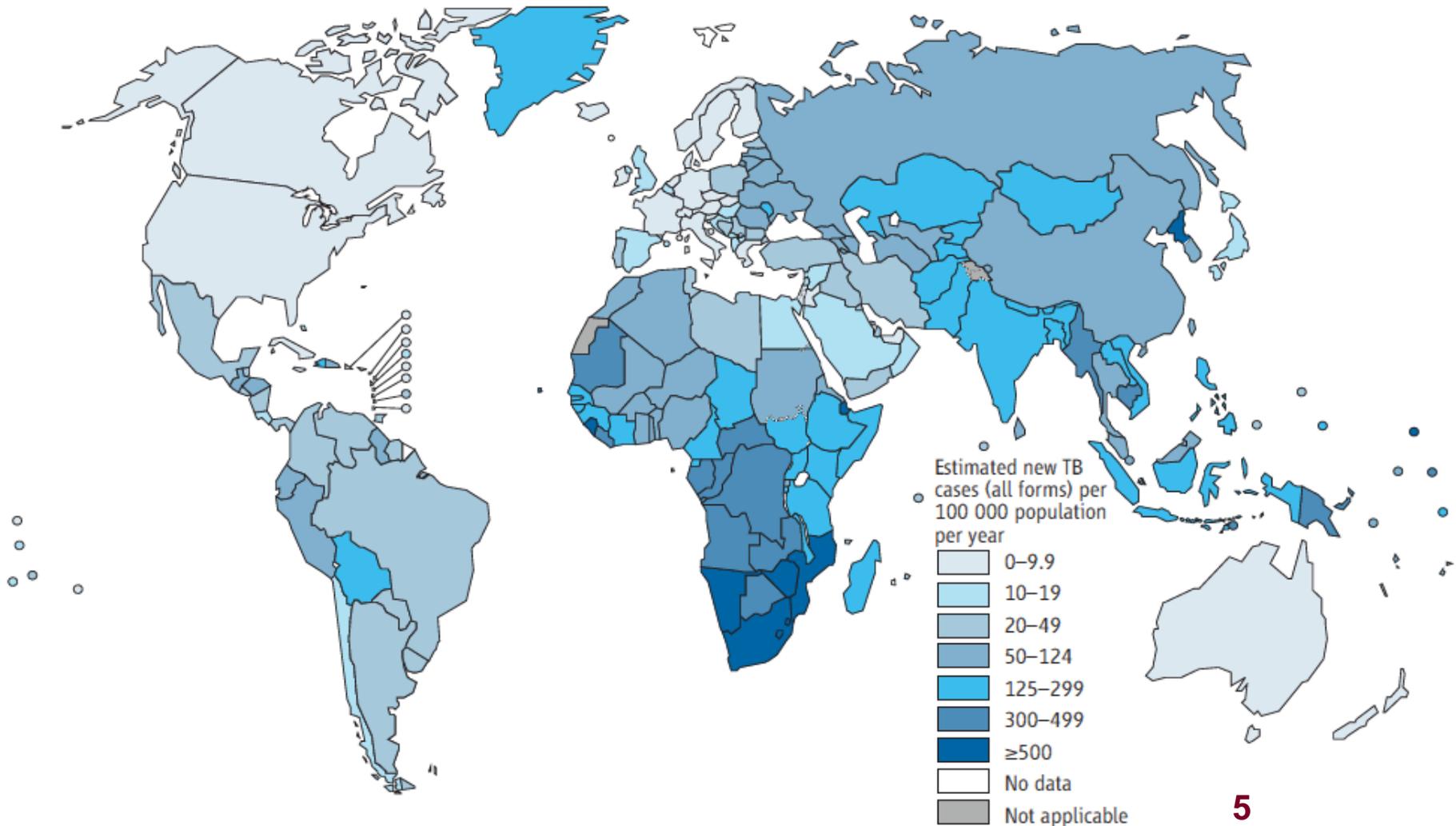
# Global Burden of Tuberculosis

- 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



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# 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”



# Active TB

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

# 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

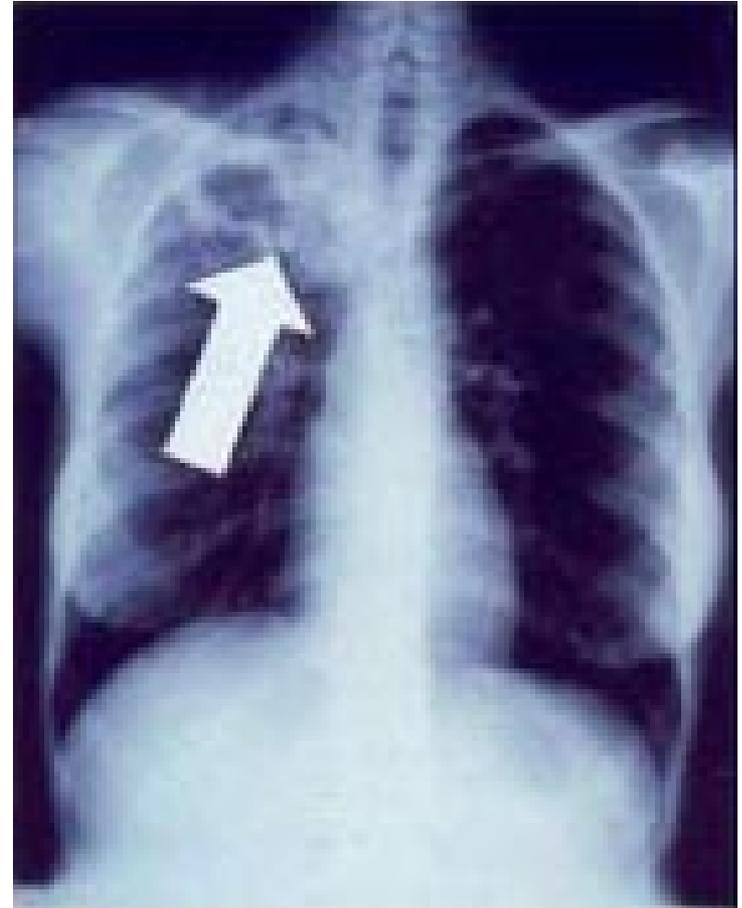
# Symptoms of Active TB

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



# 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

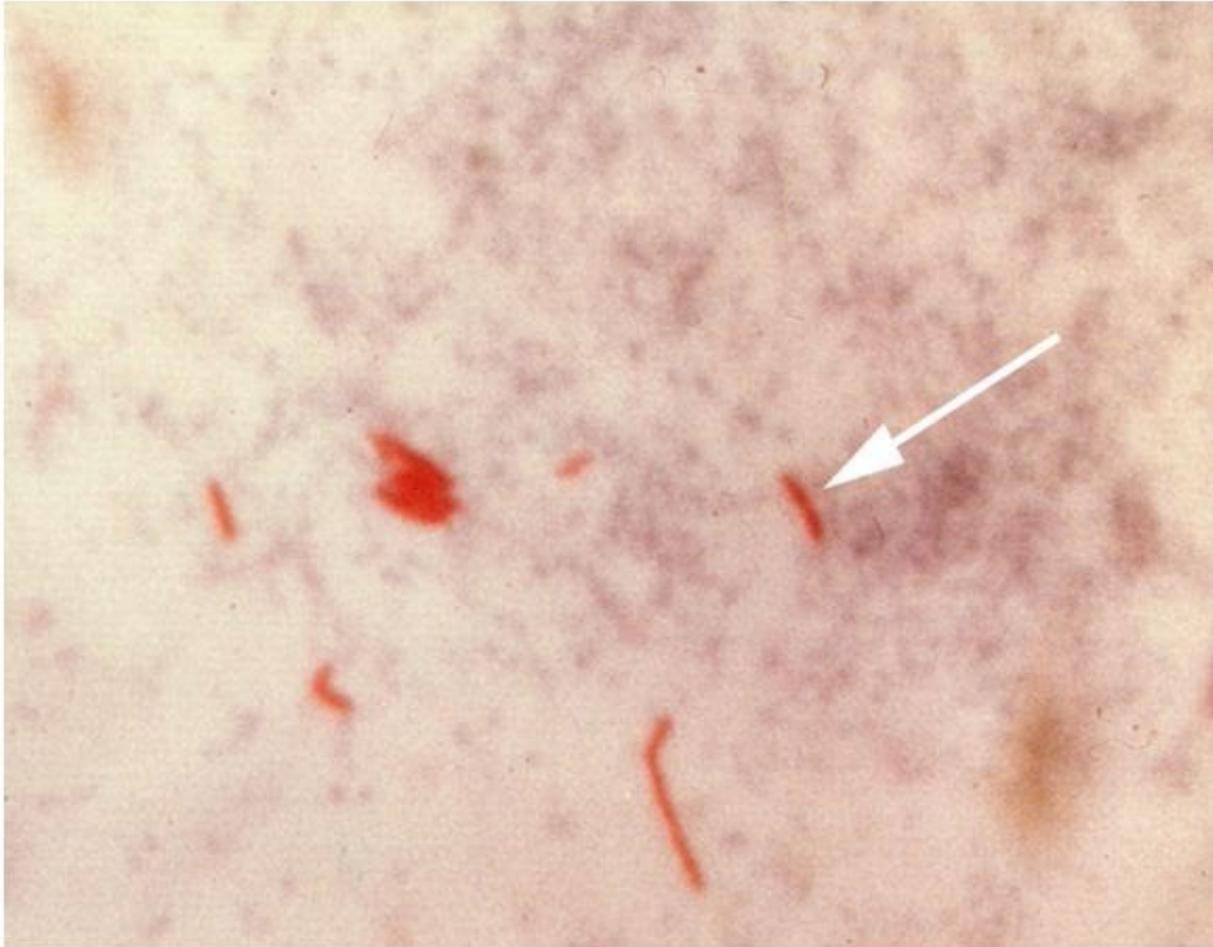


Figure 9. Sputum specimen demonstrating acid fast bacilli (AFB) (arrow). Source CDC.

# Treatment

- “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”

# 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 and XDR

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

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# 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



# 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

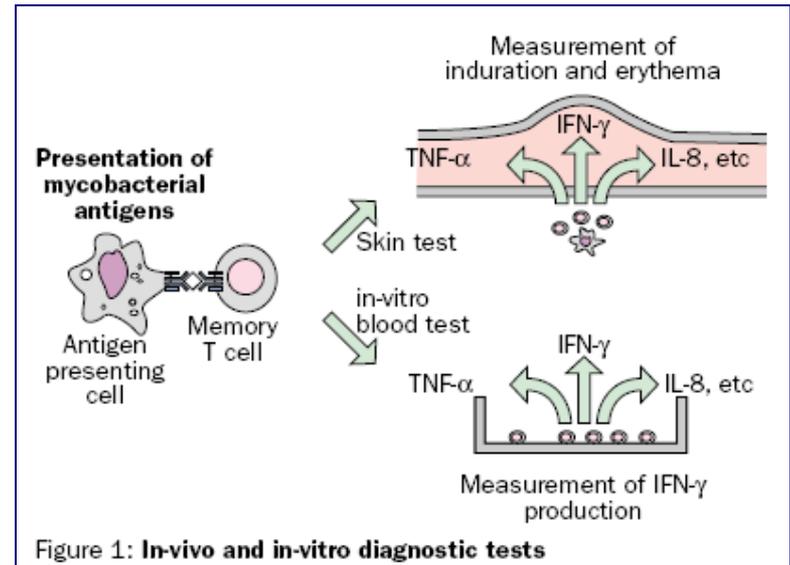


# Boosting and two-step testing

- 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 is 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

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# 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)
- 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.

# Pseudoepidemics of TST conversions in the US Army and their attributed causes, 1983-2005

Year	Population	Location	Pre-investigation estimate of % conversions	Post-investigation estimate of % conversions	% of conversions with negative repeat test	Active TB cases identified	Primary attributed cause(s) of outbreak
2005	1st Infantry Division	Germany	1.7%	5.0%	56%	19	<p>Test administration and reading; use of <b>Aplisol</b>; prior positives not documented; foreign birth</p> <p>Test administration and reading; use of <b>Aplisol</b></p> <p>68% (13 of 19) were prior reactors; conversion rate was not elevated</p> <p>Conversion rate not elevated</p> <p>Use of <b>Aplisol</b></p>
2006	Health care workers	Baltimore, Maryland	2.5%	10.0%	50%	5	<p>3% (25 of 75) were prior reactors; foreign birth</p> <p>Increased surveillance, variability in test administration and reading; ethnic group and region of birth</p> <p>100% (3 of 5) had dominant reactions to PPD-B, indicating cross-reactions with non-tuberculous mycobacteria (NTM)</p>

**Army studying 1st Infantry Division's unusually high rates of TB exposure**

Up to 5 percent of troops returning from Iraq have tested positive

By Steve Liewer  
Stars and Stripes  
Published: July 12, 2005

WÜRZBURG, Germany — Army medical officials are investigating why an unusually high percentage of 1st Infantry Division troops have tested positive for exposure to the lung disease tuberculosis after returning this spring from Iraq.

**Increase in tuberculin skin test converters among health care workers after a change from Tubersol to Aplisol**

Kari A. Gillenwater, MD, MPH,<sup>a</sup> Sandra C. Sapp, RN, BSN, CIC,<sup>b</sup> Kim Pearce, RN, BSN,<sup>b</sup> and George K. Siberry, MD, MPH<sup>a</sup>

AJIC Gillenwater et al December 2006

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# Managing TB Exposure in a Deployed Setting

MILITARY MEDICINE, 173, 7:684, 2008

## Suspected Pulmonary Tuberculosis Exposure at a Remote U.S. Army Camp in Northeastern Afghanistan, 2007

*CPT Remington L. Nevin, USA\**; *CPT John W. Silvestri, USA†*; *Zheng Hu\**; *LTC Steven K. Tobler, USA\**; *COL Richard F. Trotta, USA‡*

**TABLE II.** Case Histories and Clinical Information from Four PPD Skin Test-Positive Personnel

Case	Work Duties	Age (years)	PPD Skin Test Result (mm)	Date of Last PPD	Prior PPD Skin Test Records	Prior No. of Deployments	Deployment Length at Time of PPD Skin Test (days)	Close Contact with TB Suspect?
A	Medic	25	15 <sup>a</sup>	January 2006	2	0	>365	Yes
B	Gate guard	22	5 <sup>b</sup>	October 2005	1	1	<180	Yes
C	Infantry	21	10 <sup>c</sup>	January 2006	2	0	>365	No
D	Infantry	23	5 <sup>d</sup>	January 2006	2	1	>365	No

<sup>a</sup>At 48 hours with Aplisol. Tubersol was 10 mm at 48 hours.

<sup>b</sup>At 48 hours with Aplisol. Tubersol was negative.

<sup>c</sup>At 48 hours with Aplisol. Tubersol was negative.

<sup>d</sup>At 48 hours with Aplisol. Tubersol was 8 mm at 48 hours. Reports history of "borderline" PPD skin test.

# Managing TB Exposure in a Deployed Setting

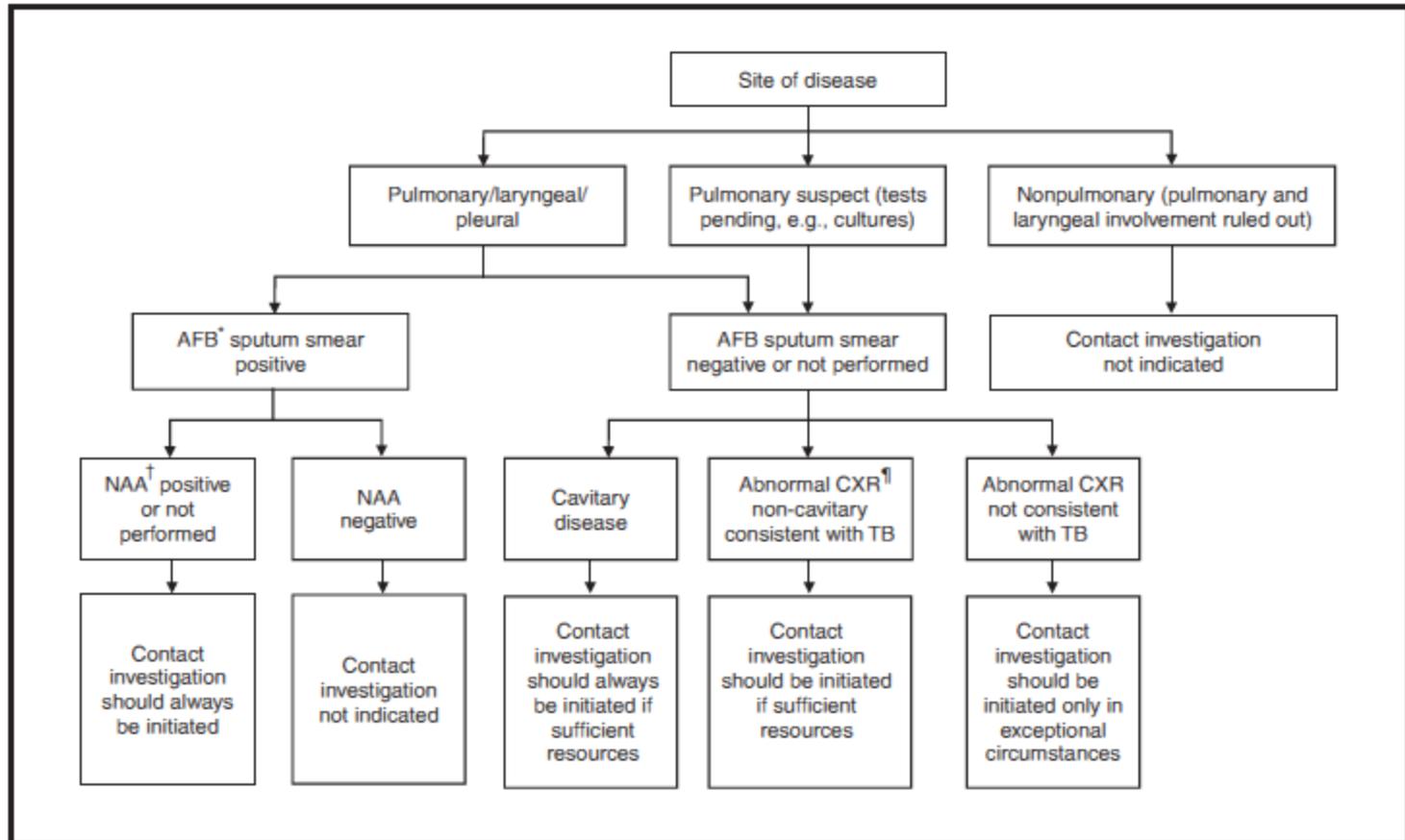
- Refer to Preventive Medicine



**Guidelines for the Investigation of Contacts  
of Persons with Infectious Tuberculosis  
Recommendations from the National Tuberculosis  
Controllers Association and CDC**

# Managing TB Exposure in a Deployed Setting

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

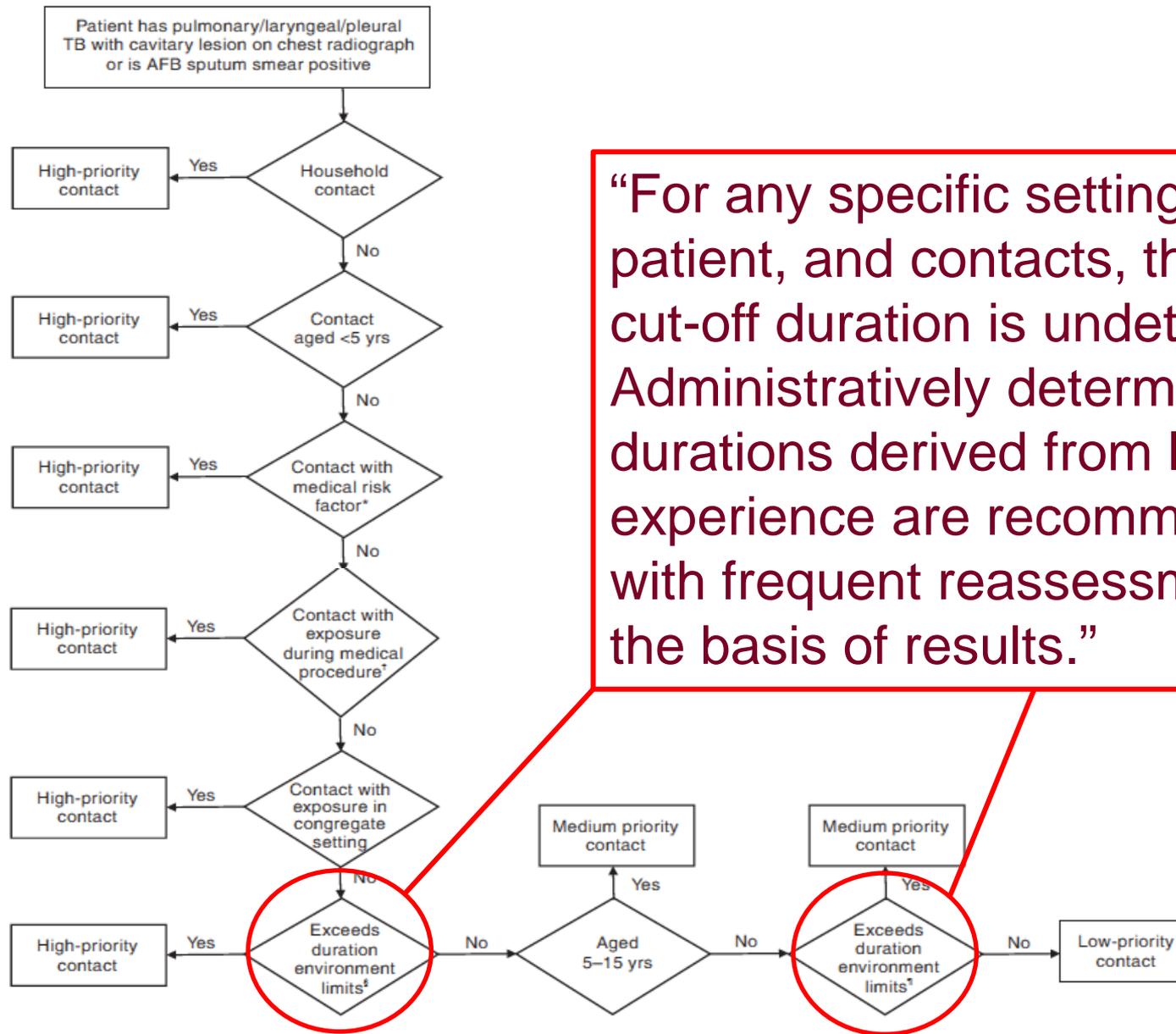


\* Acid-fast bacilli.

† Nucleic acid assay.

§ According to CDC guidelines.

¶ Chest radiograph.



“For any specific setting, index patient, and contacts, the optimal cut-off duration is undetermined. Administratively determined durations derived from local experience are recommended, with frequent reassessments on the basis of results.”

\* Human immunodeficiency virus or other medical risk factor.

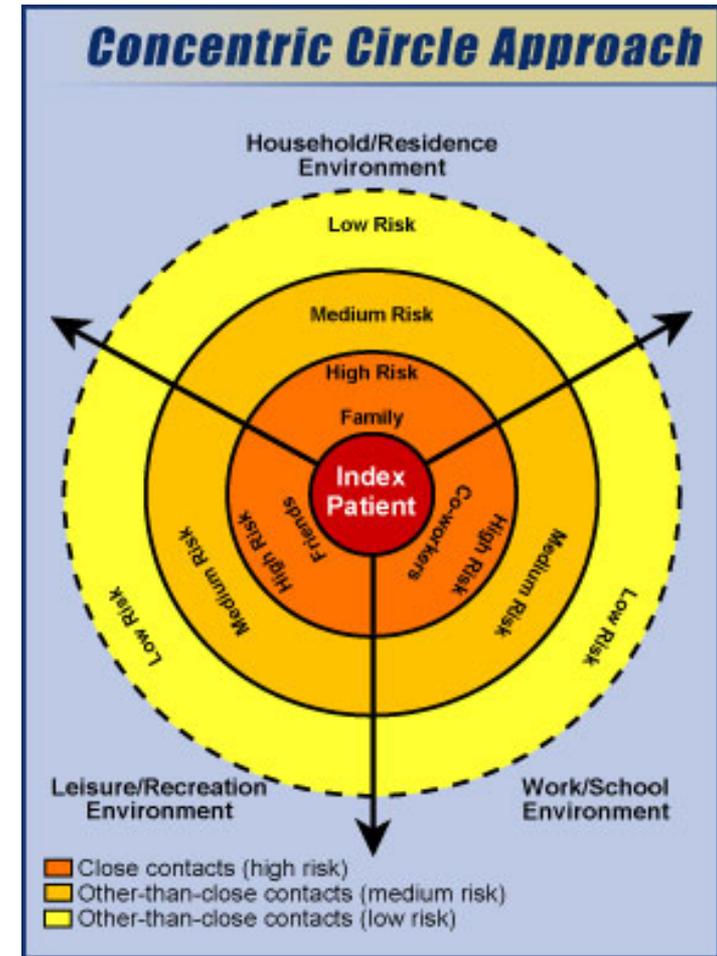
† Bronchoscopy, sputum induction, or autopsy.

‡ Exposure exceeds duration/environment limits per unit time established by the health department for high-priority contacts.

§ Exposure exceeds duration/environment limits per unit time established by the health department for medium-priority contacts.

# 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.

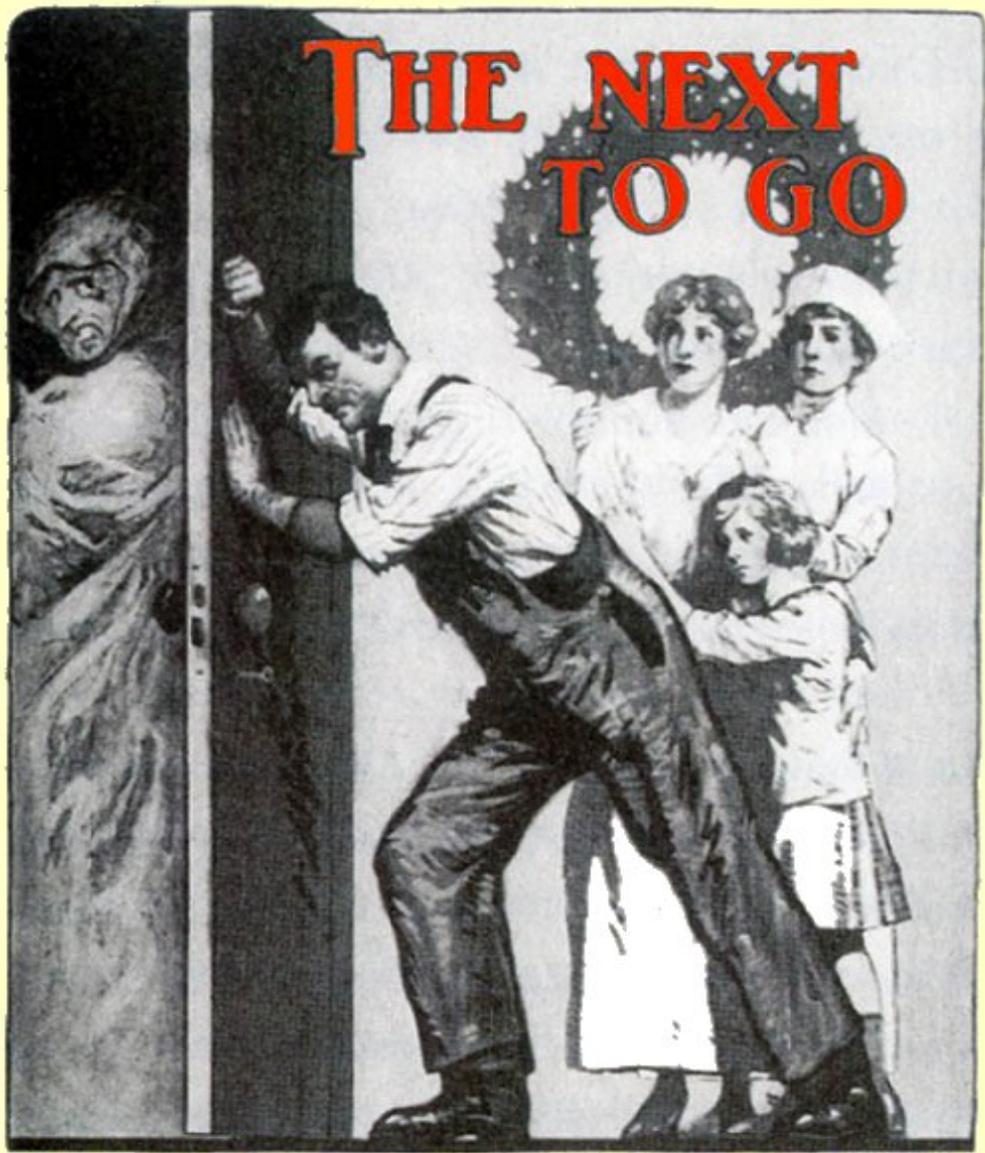


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# Other important management issues

- 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 †