
**Network di Microbiologia e Virologia del Nord Est**

*Incontro di Aggiornamento*

INTERFERON GAMMA RELEASE ASSAYS (IGRAs) NELLA DIAGNOSI E MONITORAGGIO DELLE MALATTIE INFETTIVE

Trento, 19 aprile 2013

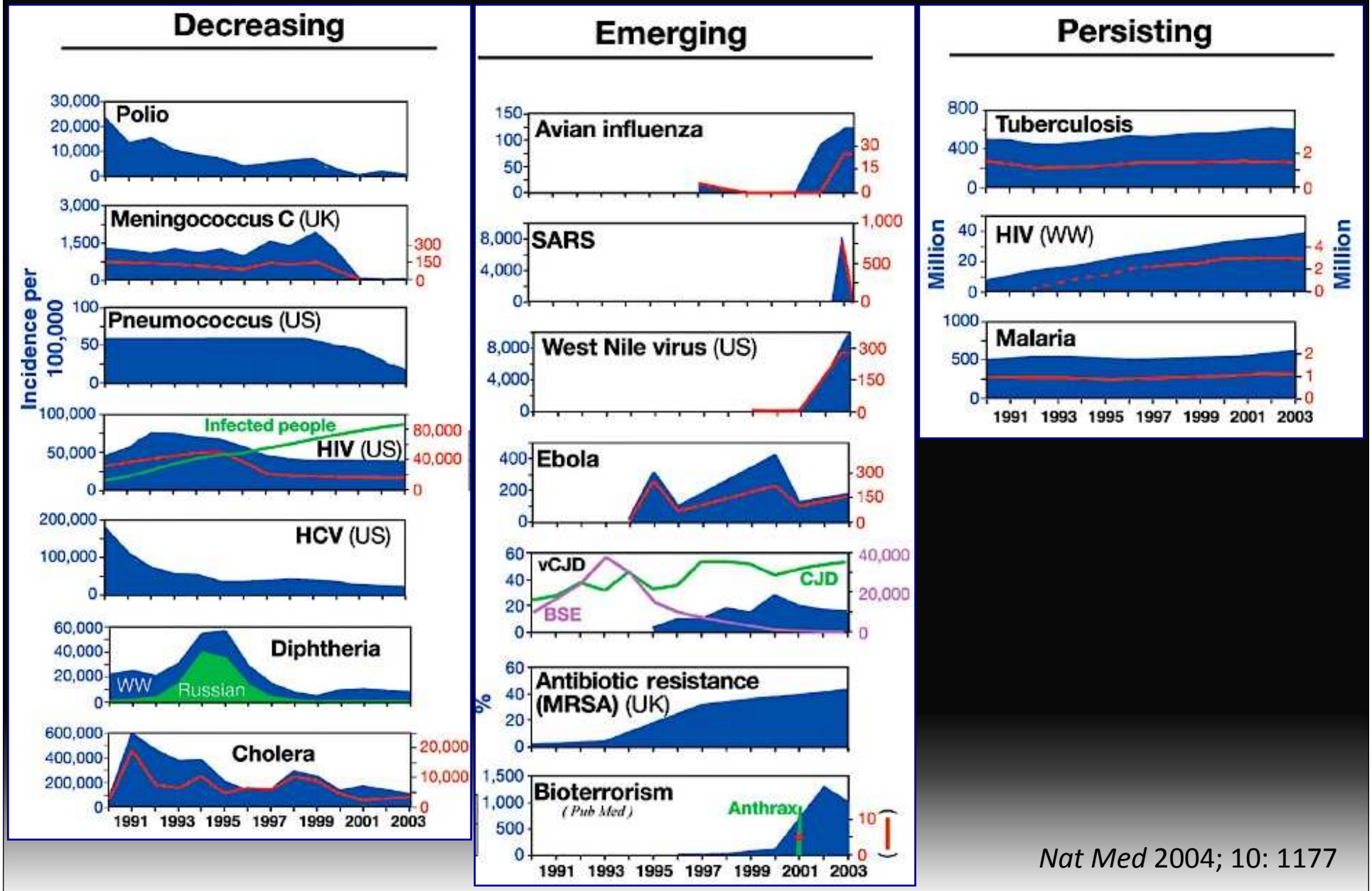
# IGRAs TEST NELLA DIAGNOSI DELL'INFEZIONE TUBERCOLARE

Luca Richeldi

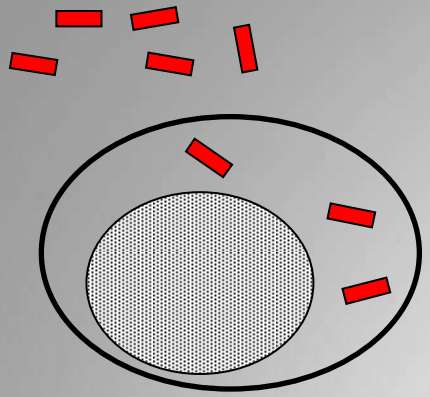
Università di Modena e Reggio Emilia

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

# EPIDEMIOLOGICAL CLASSIFICATION OF INFECTIOUS DISEASES




*Nat Med* 2004; 10: 1177



Alveolar macrophage kill MTB: **no infection**

**Infection**: MTB released in extra-cellular space, recruitment of mononuclear cells

**LATENT INFECTION**

Strong effective cellular response

Containment of MTB proliferation

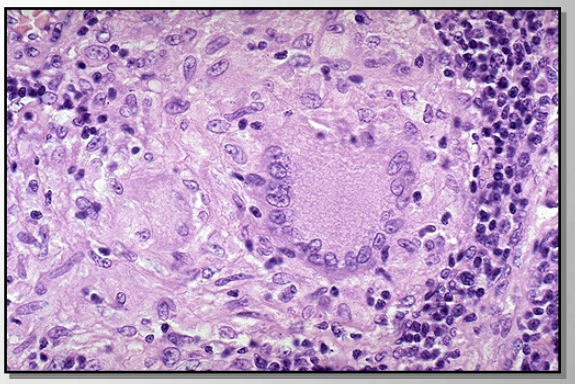
**REACTIVATION**

HIV

Drugs

Senescence

Co-morbidities



Granuloma formation
Spread to lymph nodes, blood and other organs

**ACTIVE DISEASE**

Poor ineffective immune response

Progressive disease

*Nat Med* 2000; 6: 1327-9 modified

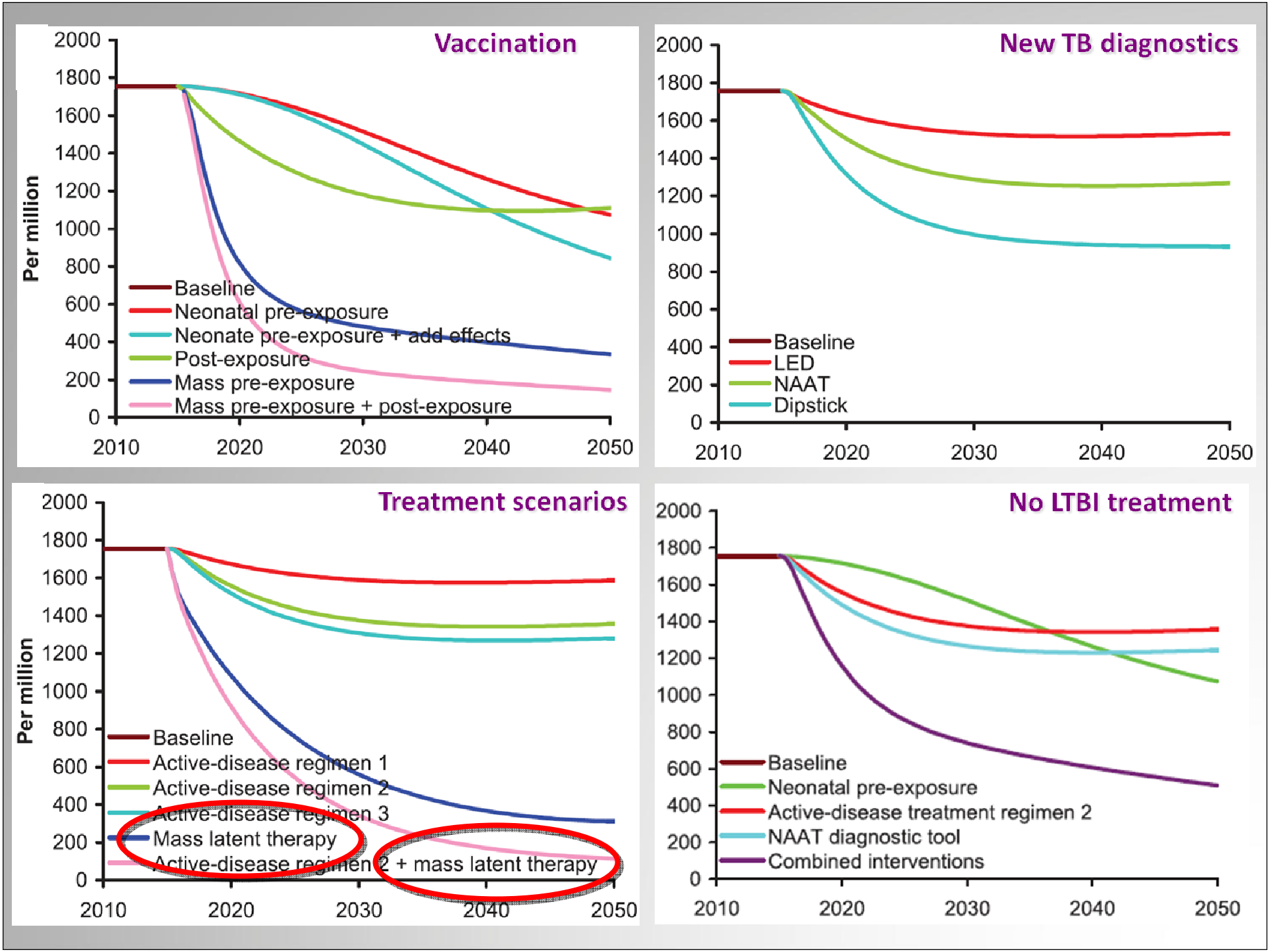
# Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

Laith J. Abu-Raddad[a,1], Lorenzo Sabatelli[a], Jerusha T. Achterberg[a,b,c], Jonathan D. Sugimoto[a,b], Ira M. Longini, Jr.[a,d], Christopher Dye[e], and M. Elizabeth Halloran[a,d,2]

[a]Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; Departments of [b]Epidemiology, [c]Anthropology, and [d]Biostatistics, University of Washington, Seattle, WA 98195; and [e]Office of HIV/AIDS, Tuberculosis, Malaria, and Neglected Tropical Diseases, World Health Organization, CH-1211 Geneva 27, Switzerland

- **Using an age-structured mathematical model of TB, analysis of the potential benefits of novel interventions under development and those not yet in the portfolio.**

*PNAS* 2009; 106: 13980


Vaccination
Per million
2000
1800
1600
1400
1200
1000
800
600
400
200
0
2010
2020
2030
2040
2050
Baseline
Neonatal pre-exposure
Neonate pre-exposure + add effects
Post-exposure
Mass pre-exposure
Mass pre-exposure + post-exposure
New TB diagnostics
Baseline
LED
NAAT
Dipstick
Treatment scenarios
Baseline
Active-disease regimen 1
Active-disease regimen 2
Active-disease regimen 3
Mass latent therapy
Active-disease regimen 2 + mass latent therapy
No LTBI treatment
Baseline
Neonatal pre-exposure
Active-disease treatment regimen 2
NAAT diagnostic tool
Combined interventions

# TREATMENT OF LTBI IS ONE OF THE MOST COST-EFFECTIVE HEALTH INTERVENTIONS


Mount FW, Ferebee SH.
The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis.
*Am Rev Respir Dis* 1962; 85: 821-7.

Ferebee SH, Mount FW, Murray FJ, Livesay VT.
A controlled trial of isoniazid prophylaxis in mental institutions.
*Am Rev Respir Dis* 1963; 88: 161-75.

Comstock GW, Ferebee SH, Hammes LM.
A controlled trial of community-wide isoniazid prophylaxis in Alaska.
*Am Rev Respir Dis* 1967; 95: 935-43.

American Thoracic Society.
Preventive treatment in tuberculosis: a statement by the Committee on Therapy.
*Am Rev Respir Dis* 1965; 91: 297-298.

American Thoracic Society.
Chemoprophylaxis for the prevention of tuberculosis: a statement by an Ad Hoc Committee.
*Am Rev Respir Dis* 1967; 96: 558-562.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

# Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

**3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg)**

***vs***

**9 months of self-administered daily isoniazid (300 mg)**

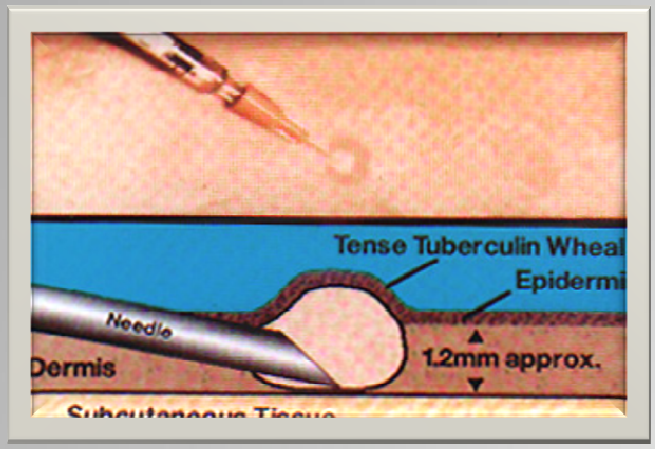
**Active TB in 7 of 3986 (cumulative rate 0.19%)**

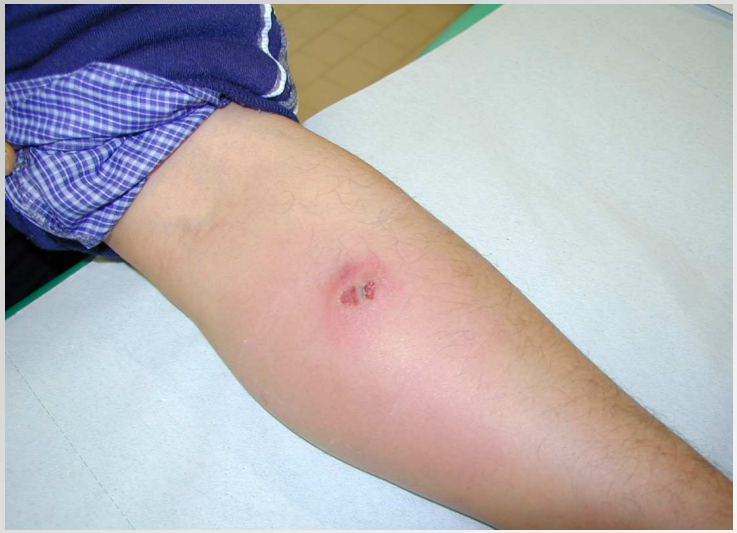
***vs***

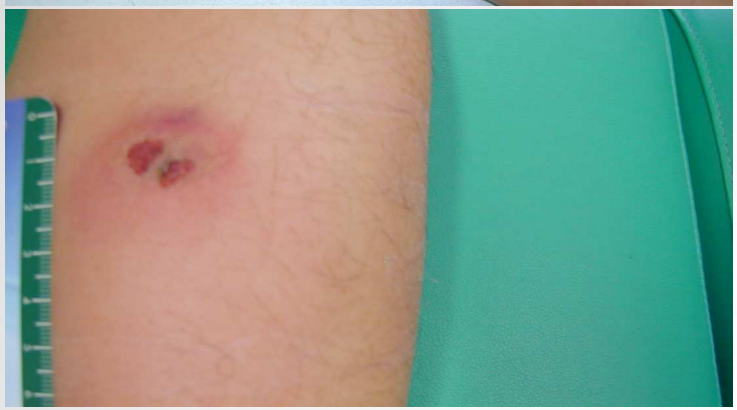
**15 of 3745 subjects (cumulative rate 0.43%)**

*N Engl J Med* 2011; 365: 2155-66

# THE TUBERCULIN SKIN TEST





C. Mantoux. Intradermo-réaction de la tuberculine. Comptes rendus de l'Académie des sciences. Paris, 1908; 147: 355-357.

# THE USE OF CHEMOTHERAPY AS A PROPHYLACTIC MEASURE IN TUBERCULOSIS

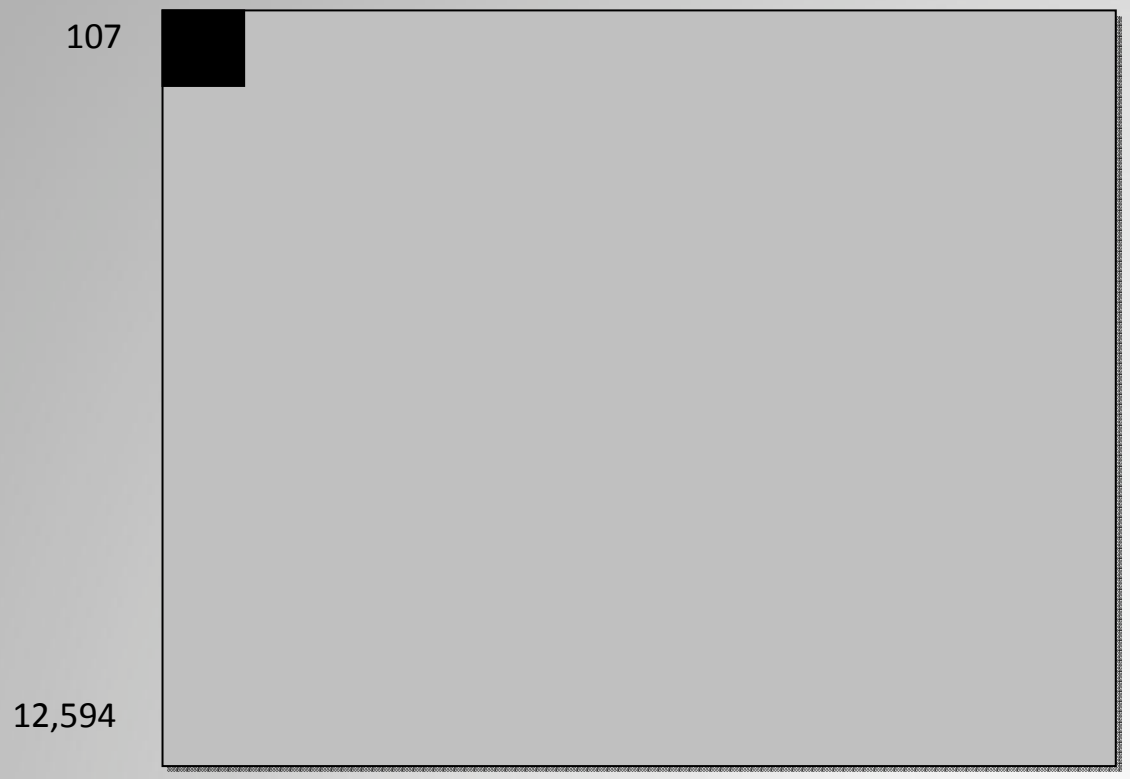
Shirley H. Ferebee, Frank W. Mount, George W. Comstock

*Operational Research Section, Tuberculosis Program, Public Health Service, Department of Health, Education and Welfare, Washington, D.C.*

*Ann NY Acad Sci*, 1963; 106: 151-6

## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

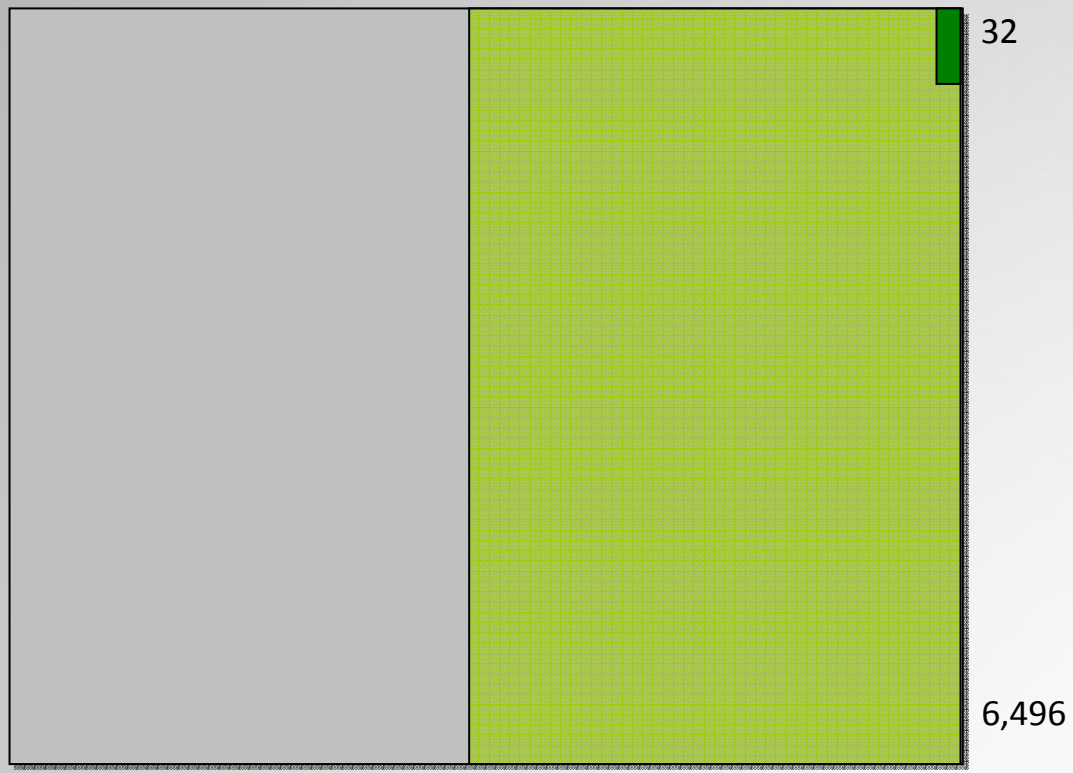
## TOTAL POPULATION RECEIVING PLACEBO




Rate per 1,000: **8.5**

## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

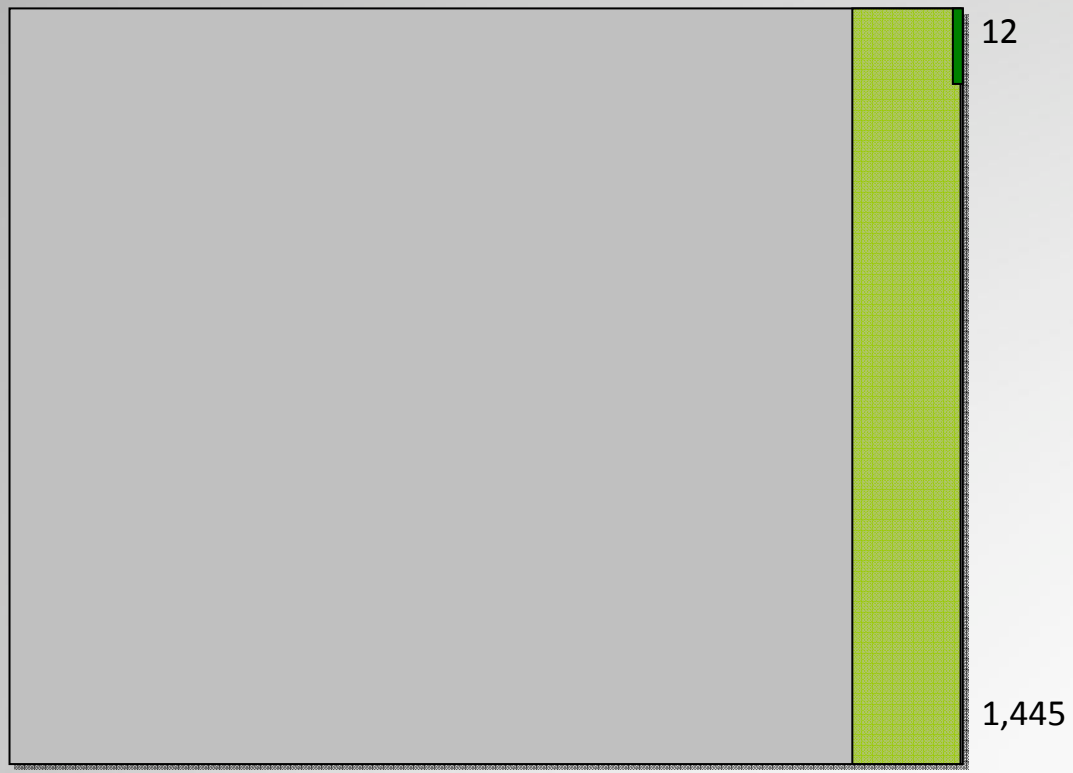
## TST < 5 MM RECEIVING PLACEBO




Rate per 1,000: **4.9**

## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

## TST > 5 < 9 MM RECEIVING PLACEBO




Rate per 1,000: **8.3**

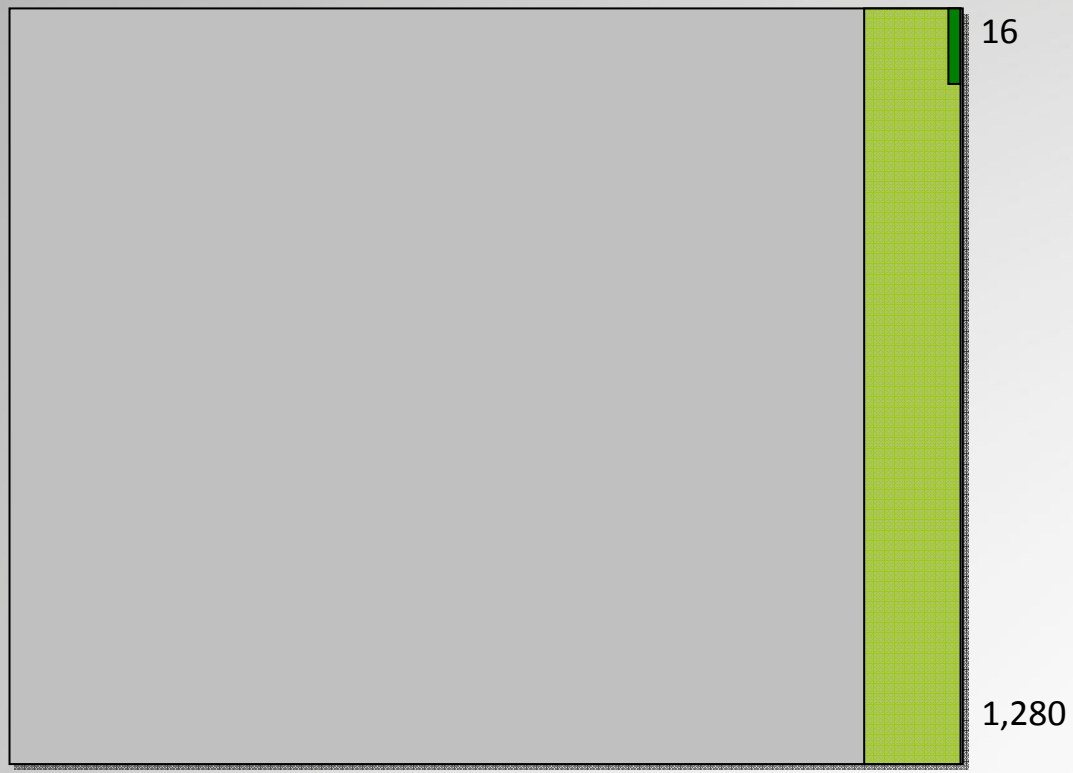
## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

## TST > 10 < 14 MM RECEIVING PLACEBO


Rate per 1,000: **10.3**

## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

## TST > 15 < 19 MM RECEIVING PLACEBO




Rate per 1,000: **12.5**

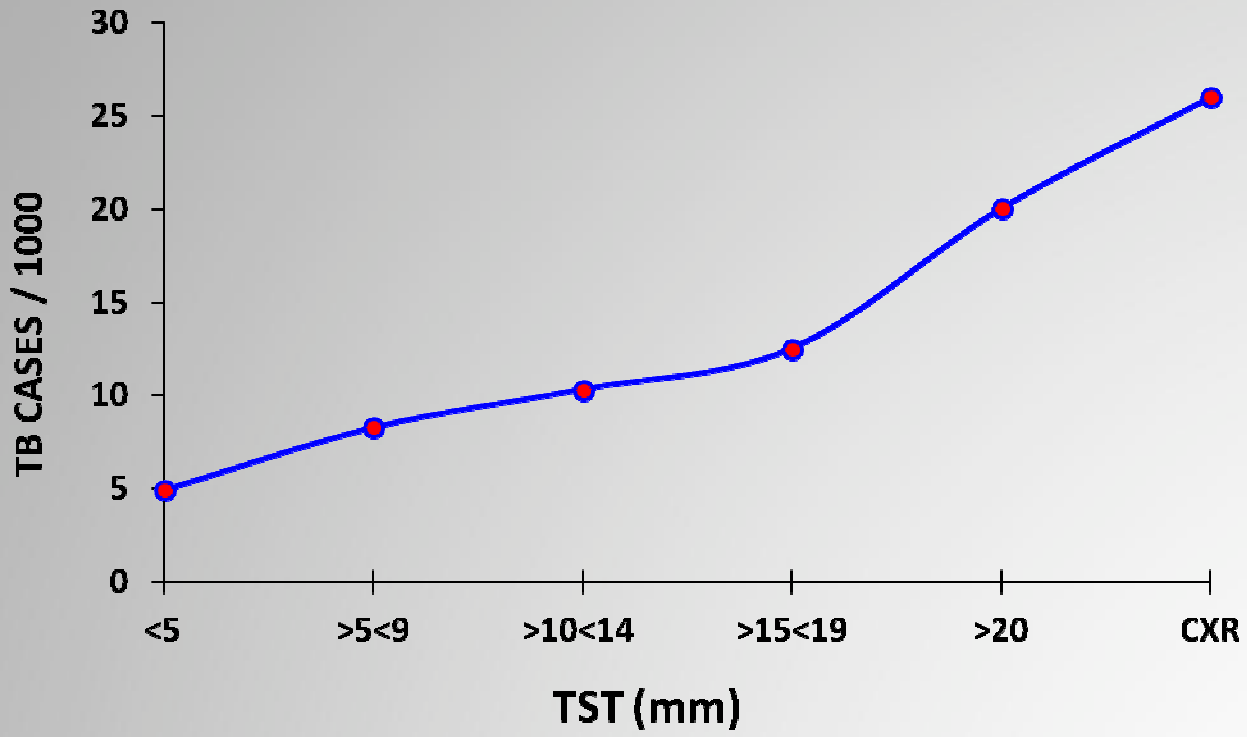
## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

## TST > 20 MM RECEIVING PLACEBO

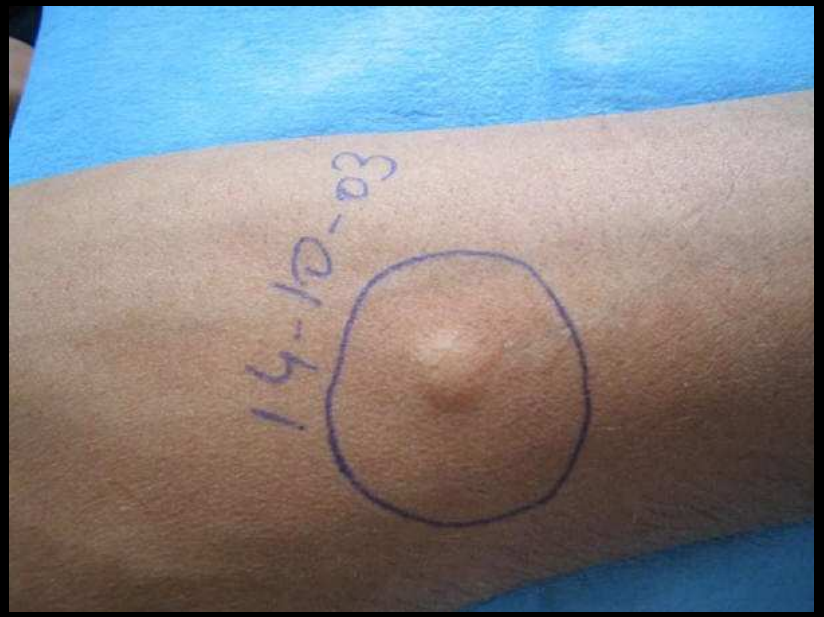

Rate per 1,000: **20.0**

## RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

## POPULATION RECEIVING PLACEBO




S Ferebee et al *Am Rev Respir Dis* 1962

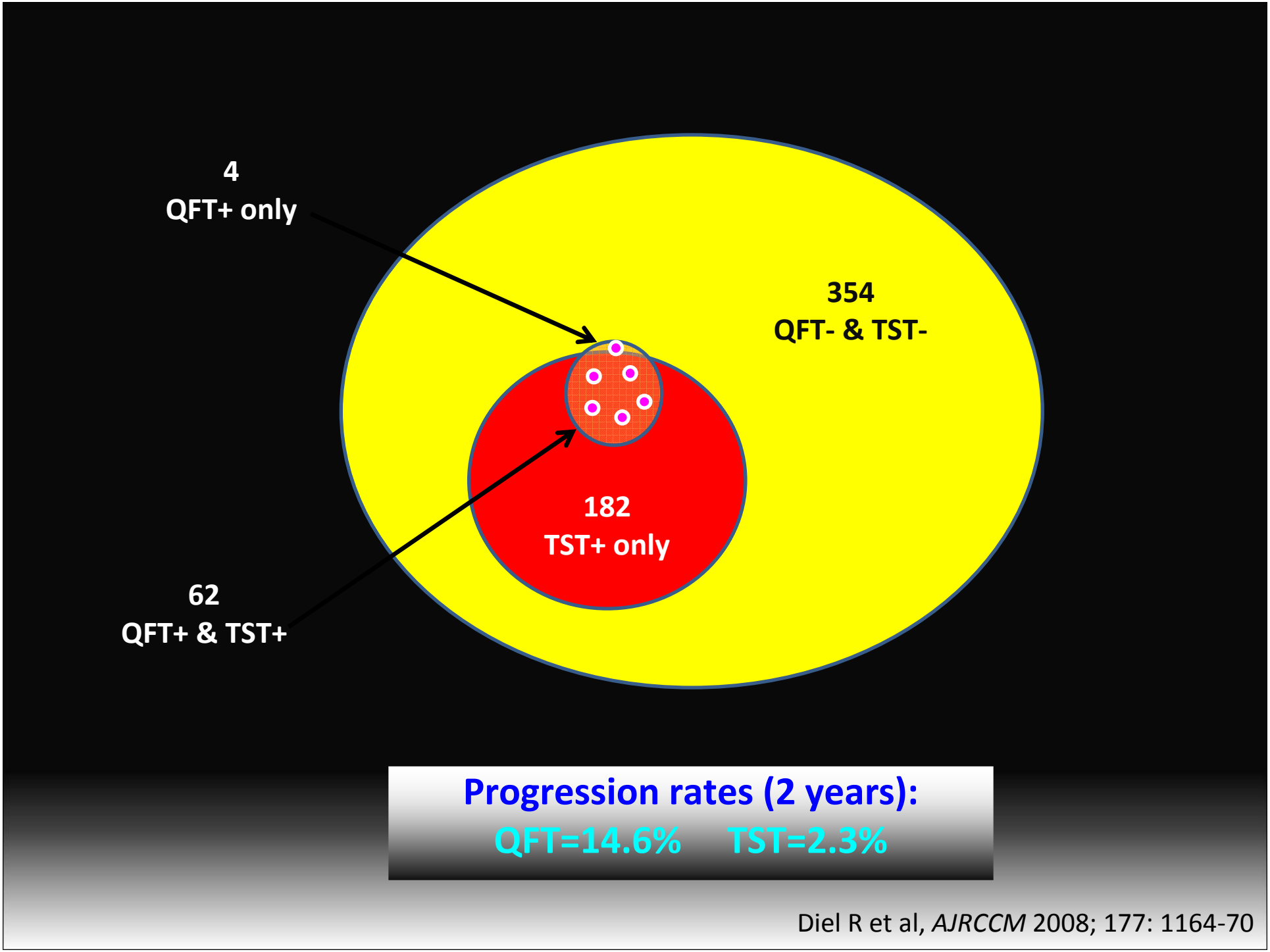

14-12-03

# Predictive Value of a Whole Blood IFN-γ Assay for the Development of Active Tuberculosis Disease after Recent Infection with *Mycobacterium tuberculosis*

Roland Diel[1], Robert Loddenkemper[2], Karen Meywald-Walter[3], Stefan Niemann[4], and Albert Nienhaus[5]

- **601 close contacts** (28% foreign-born, 46% BCG-vaccinated) of TB patients tested with both **TST** and **QFT.**
- **40%** TST-positive (5 mm) *vs* **11%** QFT-positive
- QFT-positives only associated with **exposure time.**
- INH offered to QFT-positive; only **38%** accepted.
- 2 years of follow-up
- **6** (untreated) contacts progressed to **active TB.**

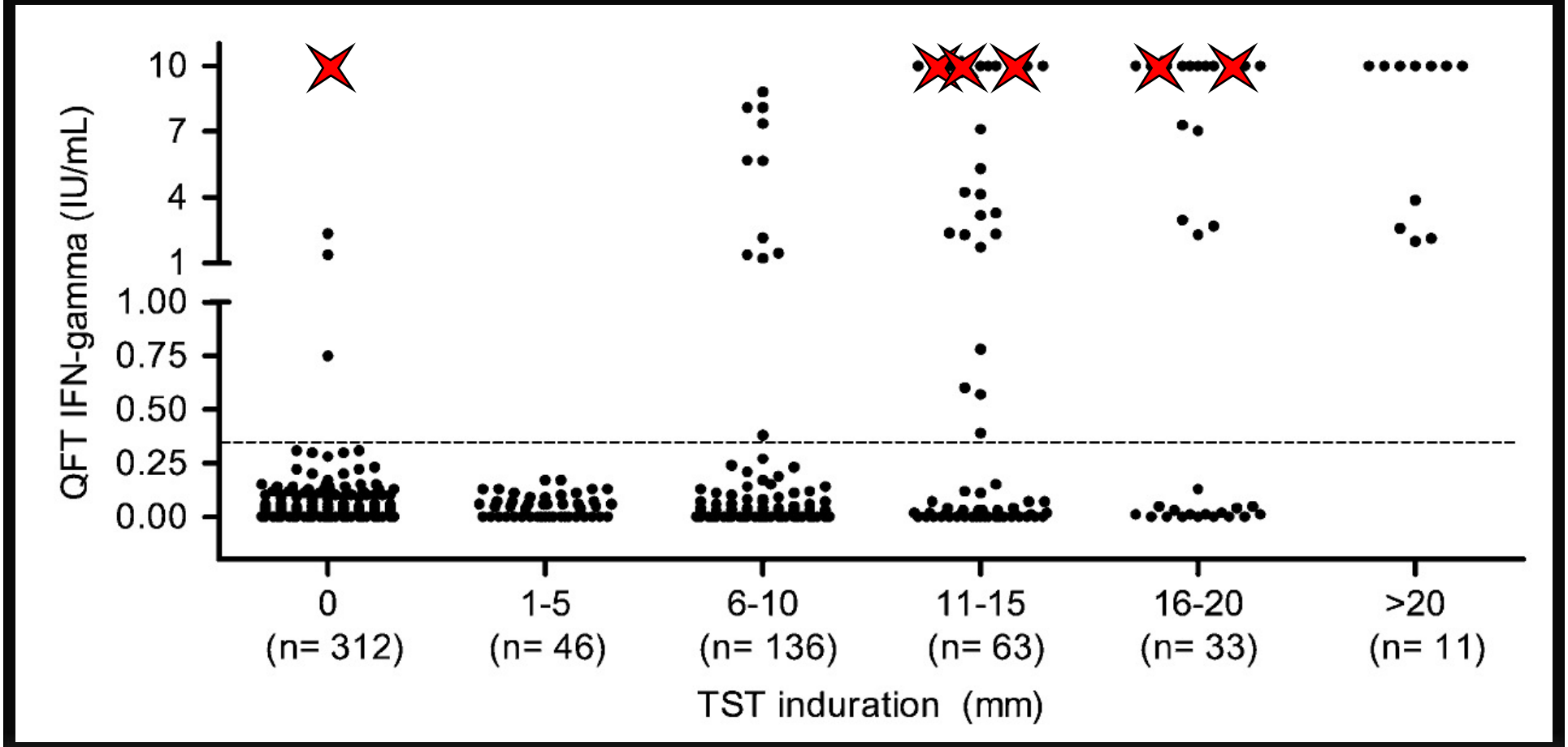
Diel R et al, *AJRCCM* 2008; 177: 1164-70




Diel R et al, *AJRCCM* 2008; 177: 1164-70

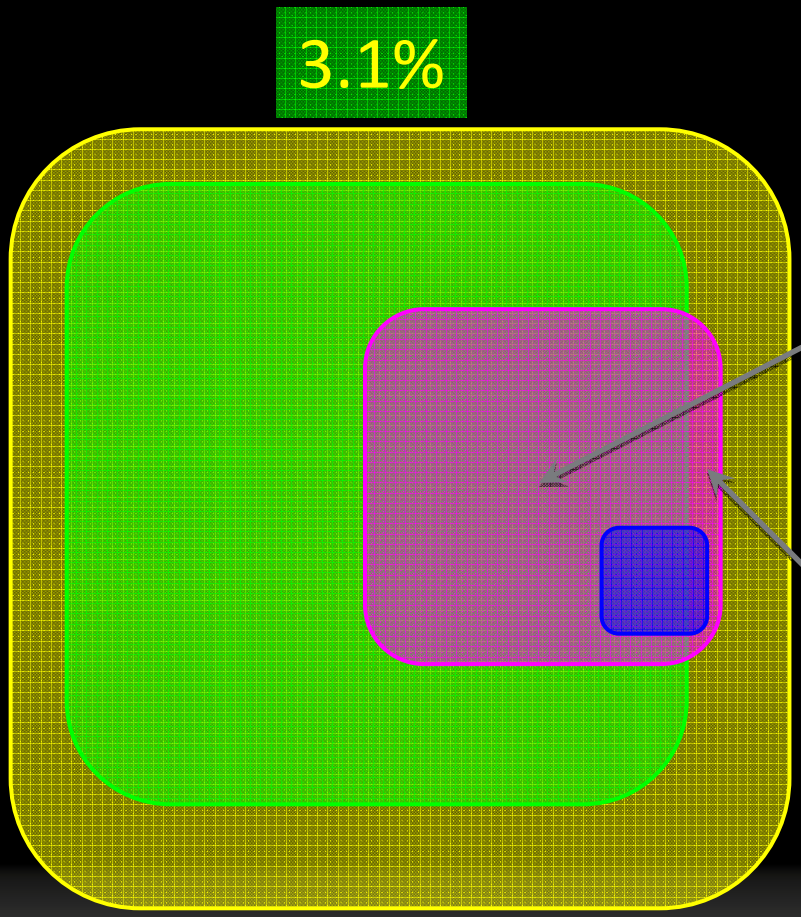
## *2-year progression rates*

**TST 2.3%  QFT 14.6%**




Diel R et al, *AJRCCM* 2008; 177: 1164-70

**Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis**
An Update




TST >5 mm: 604 (63.3%)

TST+/QFT+: 191 (**31.6%** of TST+)

**TB: 89.5% household contacts**

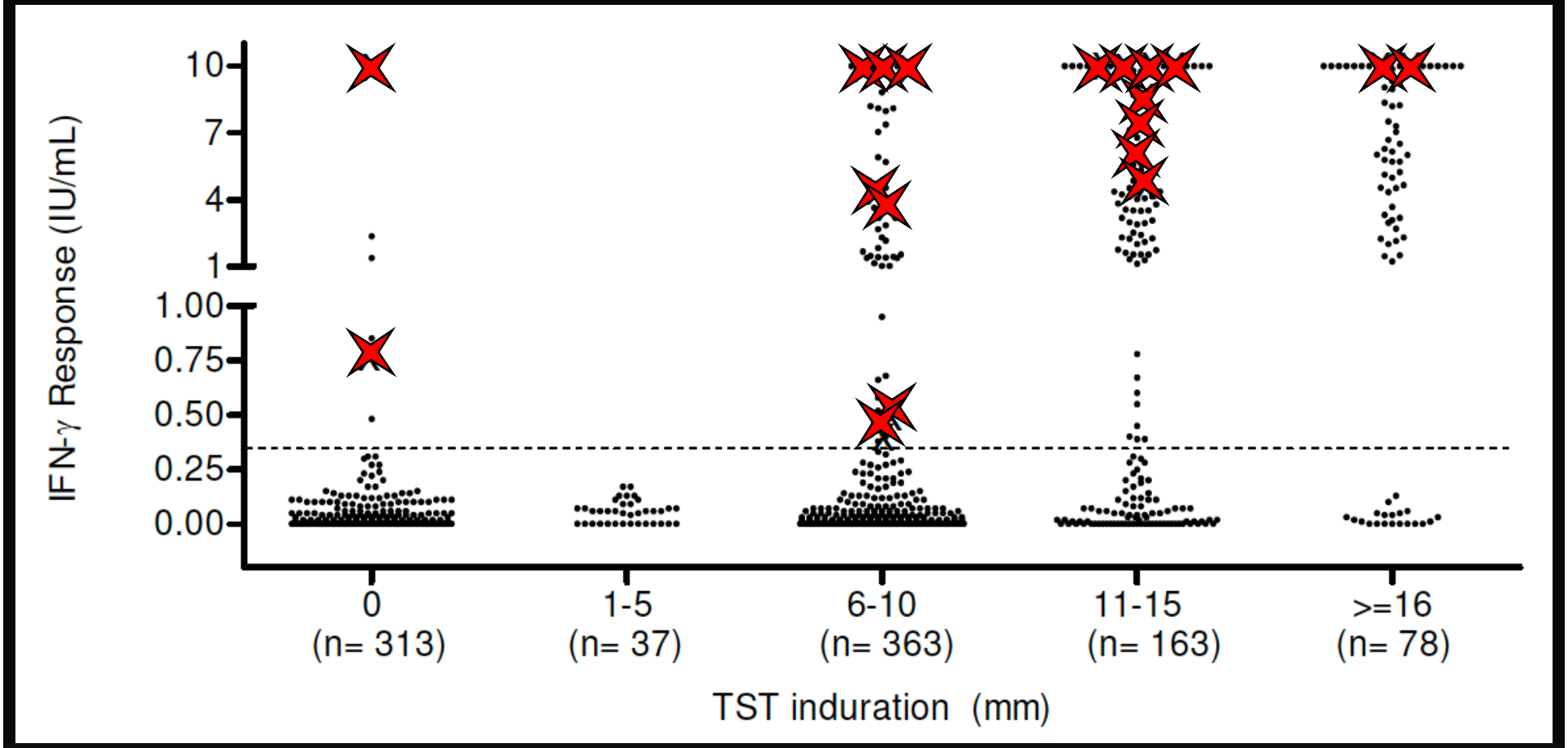
QFT+/TST-: 7 (**3.5%** of QFT+)

QFT-IT >0.35: 198 (20.8%)

Diel R et al, *Am J Respir Crit Care Med* 2011; 83; 88-95

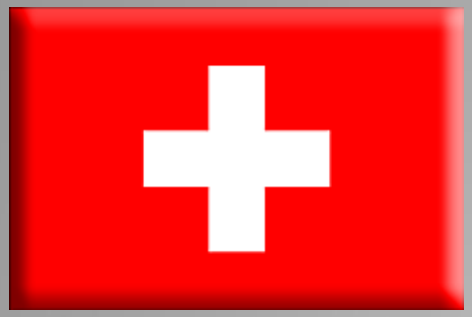
## *Progression rates*

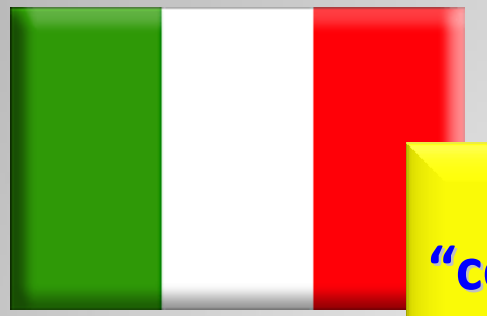
**TST 3.1%  QFT 12.9%**




Diel R et al, *AJRCCM* 2011; 183: 88-95

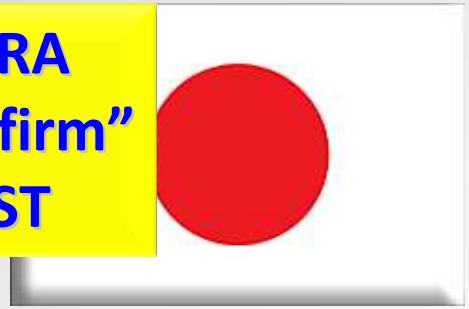
# GUIDELINES ON IGRA USE

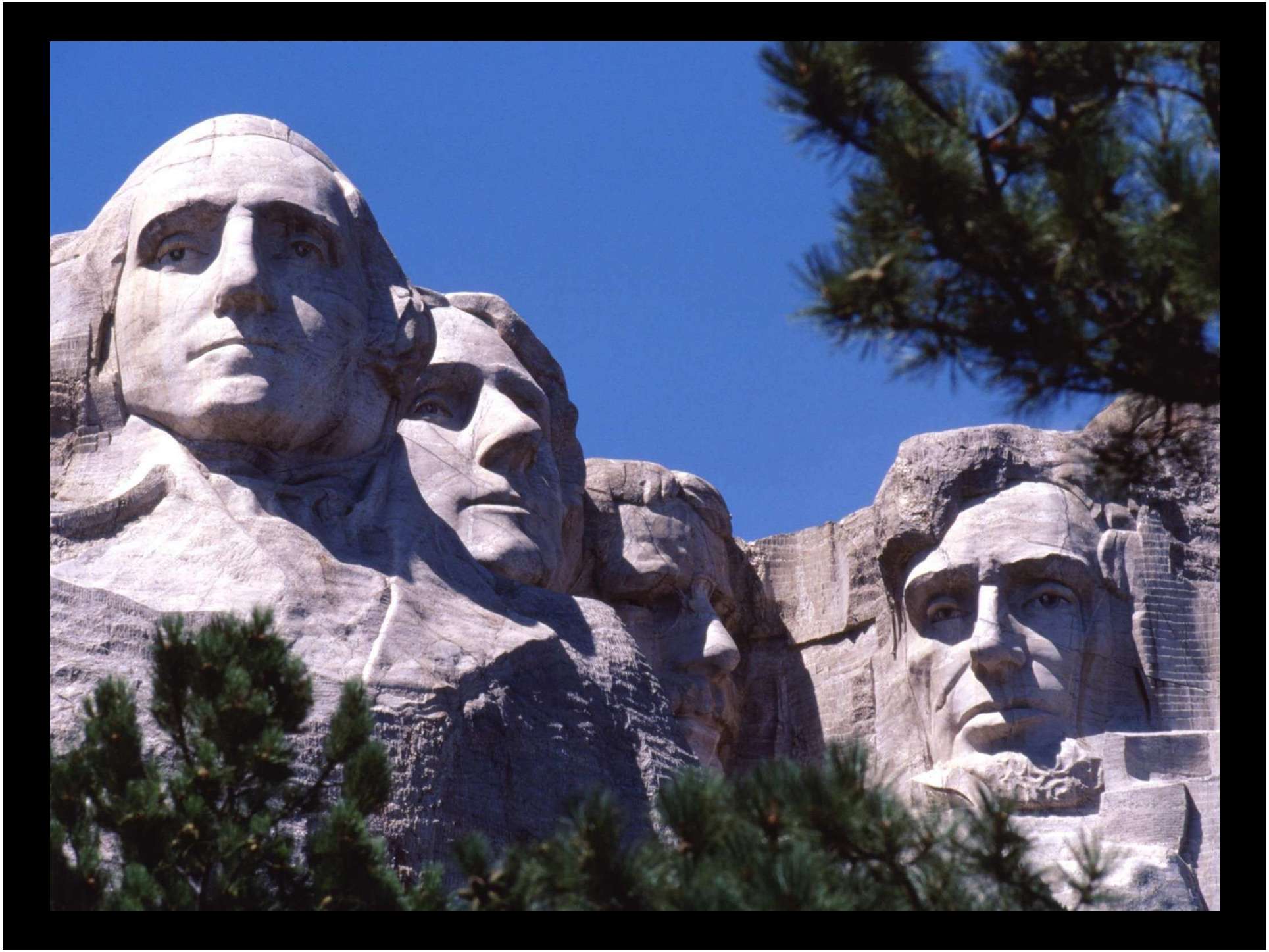




IGRA "replace" TST

IGRA "confirm" TST





CDC

MMWR™

Morbidity and Mortality Weekly Report

www.cdc.gov/mmwr

Recommendations and Reports

June 25, 2010 / Vol. 59 / No. RR-5

# Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010

# KEEP IN MIND THE GOOD "OLD" TIMES

*"Regardless of the test used to identify latent tuberculosis infection, testing should be primarily targeted at diagnosing* ***infected patients who will benefit from treatment****."*

Mazurek & Villarino *MMWR* 2002

Persons at increased risk* for progression of infection to active tuberculosis include

- persons with human immunodeficiency virus (HIV) infection;†
- infants and children aged <5 years;†
- persons who are receiving immunosuppressive therapy such as tumor necrosis factor–alpha (TNF-α) antagonists, systemic corticosteroids equivalent to ≥15 mg of prednisone per day, or immune suppressive drug therapy following organ transplantation;†
- persons who were recently infected with *M. tuberculosis* (within the past 2 years);
- persons with a history of untreated or inadequately treated active tuberculosis, including persons with fibrotic changes on chest radiograph consistent with prior active tuberculosis;
- persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck, or lung;
- persons who have had a gastrectomy or jejunoileal bypass;
- persons who weigh <90% of their ideal body weight;
- cigarette smokers and persons who abuse drugs or alcohol; and
- populations defined locally as having an increased incidence of active tuberculosis, possibly including medically underserved or low-income populations

An IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection, with preferences and special considerations noted below. Despite the indication of a preference in these instances, use of the alternative test (FDA-approved IGRA or TST) is acceptable medical and public health practice.

# *Keep in mind …*

**Asses individual risk for both MTB infection and progression and use the most reliable test(s) in the individuals with the highest TB risk.**

Avoid testing those which you wouldn't treat

**A DECISION TO TEST IS A DECISION TO TREAT**

*Thorax* doi:10.1136/thoraxjnl-2012-202824

**PostScript**

**Research letter**

# Inclusion of latent tuberculosis infection as a separate entity into the international classification of diseases

**Marc Tebruegge[1,2,3], Eeva Salo[4], Nicole Ritz[3,5], Beate Kampmann[6,7], On behalf of the Paediatric Tuberculosis Network European Trialsgroup (ptbnet)**

+ Author Affiliations

**Correspondence to**

Dr Marc Tebruegge, National Institute for Health Research Clinical Lecturer, Wellcome Trust Clinical Research Facility (Mailpoint 218), University Hospitals Southampton NHS Trust, Tremona Road, Southampton SO16 6YD, UK; m.tebruegge@soton.ac.uk

**Accepted** 5 October 2012

**Published Online First** 5 November 2012

## Abstract

The 11th revision of the International Classification of Diseases (ICD-11) proposed by the WHO is currently in the consultation phase. In common with previous versions of the ICD this revised version does not contain a code for latent tuberculosis infection (LTBI), contrasting with the inclusion of a large number of codes for various manifestations of active tuberculosis (TB). Inclusion of a separate code for LTBI into ICD-11 is critically important for epidemiological, clinical and research purposes. On behalf of the Paediatric Tuberculosis Network European Trialsgroup, we encourage colleagues worldwide who are caring for TB patients or are involved in TB research to join us in supporting the case for a long overdue ICD code for LTBI.


**Network di Microbiologia e Virologia del Nord Est**

*Incontro di Aggiornamento*

INTERFERON GAMMA RELEASE ASSAYS (IGRAs) NELLA DIAGNOSI E MONITORAGGIO DELLE MALATTIE INFETTIVE

Trento, 19 aprile 2013

# IGRAs TEST NELLA DIAGNOSI DELL'INFEZIONE TUBERCOLARE

Luca Richeldi

AOU Policlinico di Modena