Diagnosis and Treatment of Latent TB Infection (LTBI)

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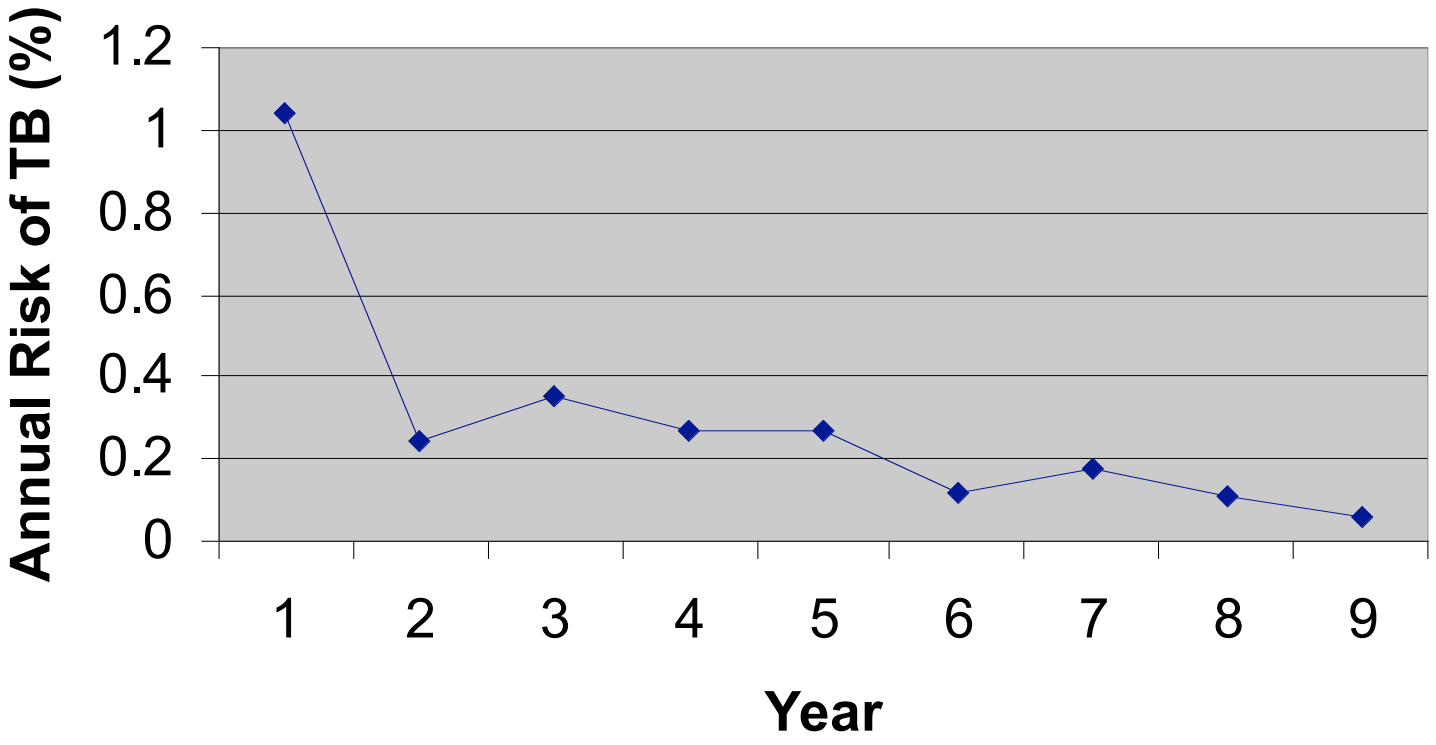
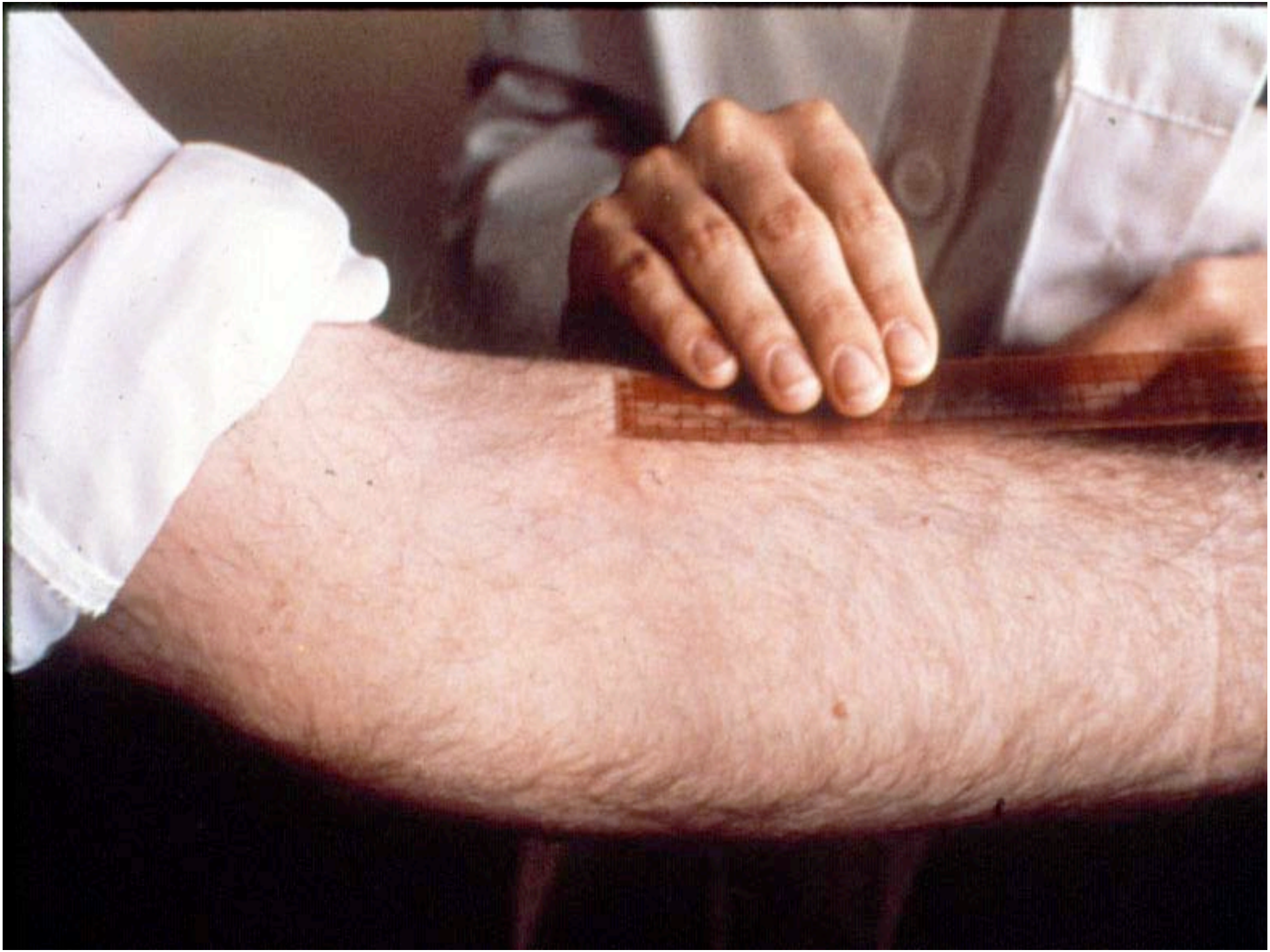
Reactivation TB by year after TST conversion

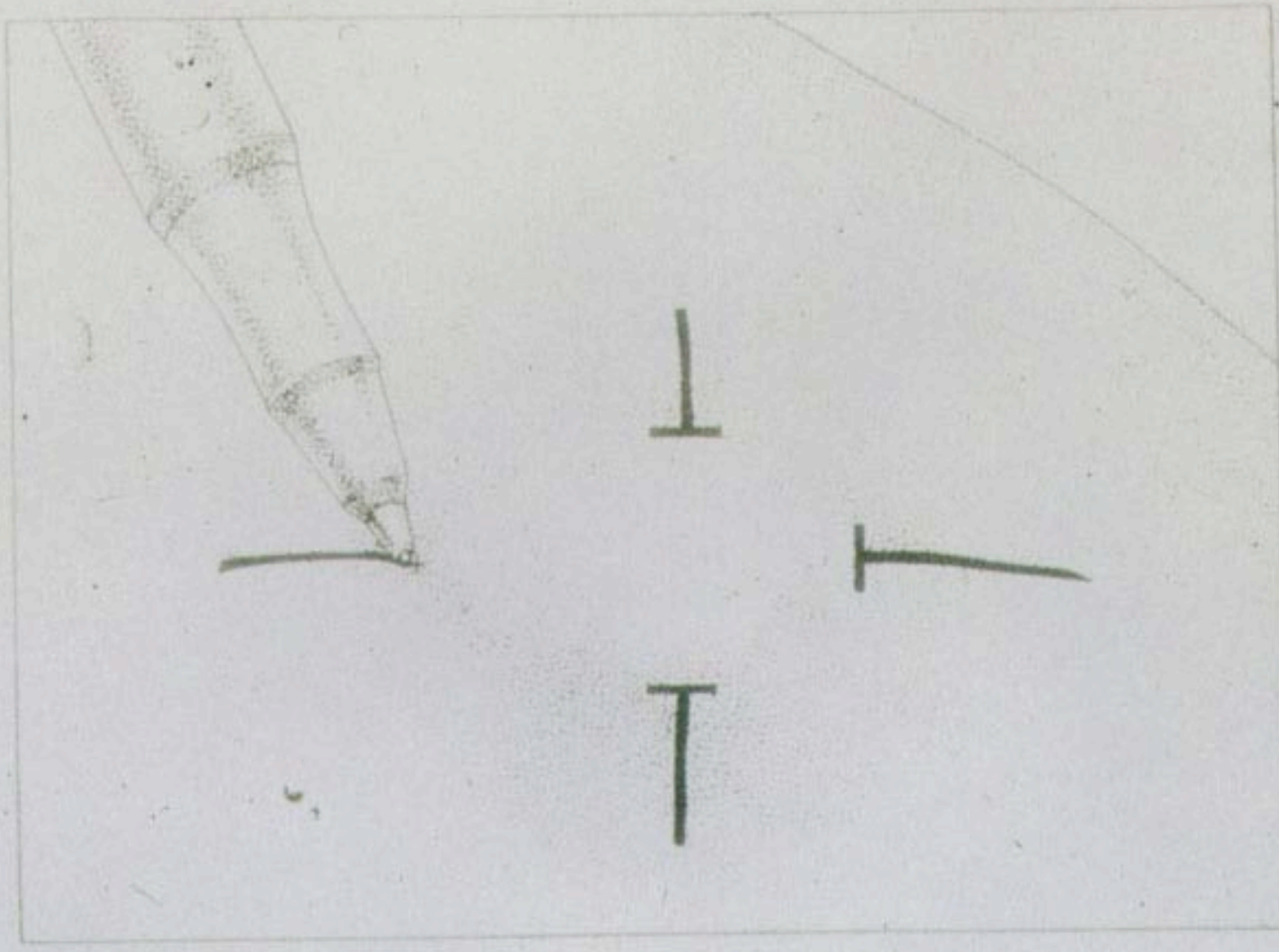


Bibl Tuberc 1970; 53

Tuberculin Skin Testing

- Intradermal Mantoux test
- 0.1 mL of 5 TU PPD tuberculin
- Read 48 – 72 hours after application





Classification of the Tuberculin Reaction

A reaction of ≥ 5 mm is positive in:

- Close contacts to patients with infectious tuberculosis
- Persons with HIV infection
- Persons who have chest radiographs with fibrotic lesions

Classification of the Tuberculin Reaction (contd.)

A reaction of ≥ 10 mm is positive in:

- Persons with medical risk factors which increase the risk of tuberculosis once infection has occurred
- Intravenous drug users
- Residents of long term care facilities (such as correctional institutions and nursing homes
- Recent Immigrants from high prevalence countries (within last 5 years)

Classification of the Tuberculin Reaction (contd.)

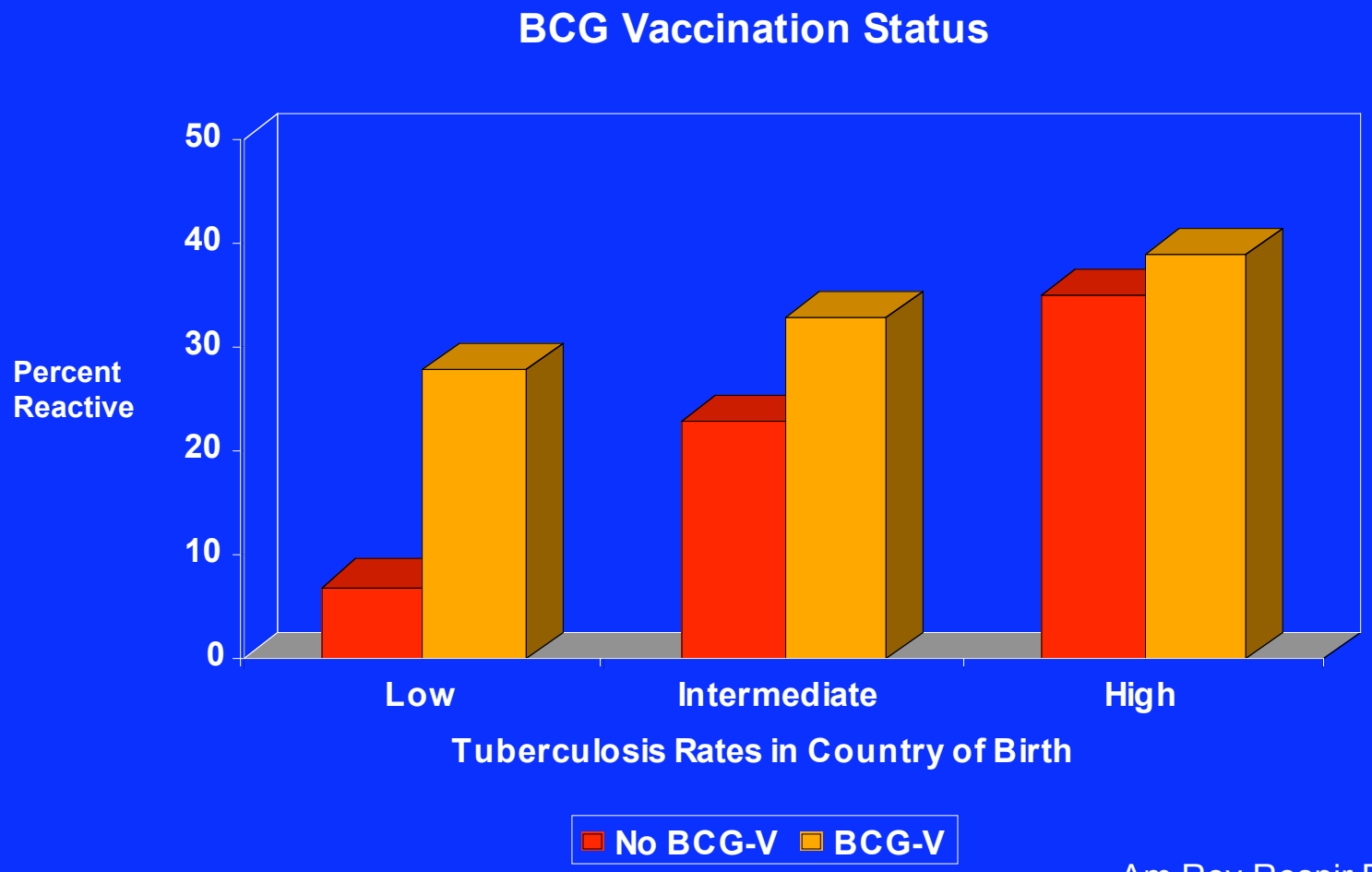
A reaction of ≥ 15 mm is positive in:

- Persons with no additional risk factors for tuberculosis

Limitations of Tuberculin Skin Testing

- Non-specific (false positive)
  - infection with non-tuberculosis mycobacteria
  - BCG vaccine
  - problems with standardization
- Lack of sensitivity (false negative)
  - Anergy (HIV, other immunosuppressive illnesses, drugs, age, active TB)
  - Problems with administration, storage or factors related to reading the PPD.
- Booster Effect
  - Cannot sensitize non-infected person with repeated testing
  - Increase in skin reactivity 1 week to 1 year after initial negative test, due to immunologic recall

BCG Vaccination status and PPD skin test reactivity by Prevalence of TB Disease

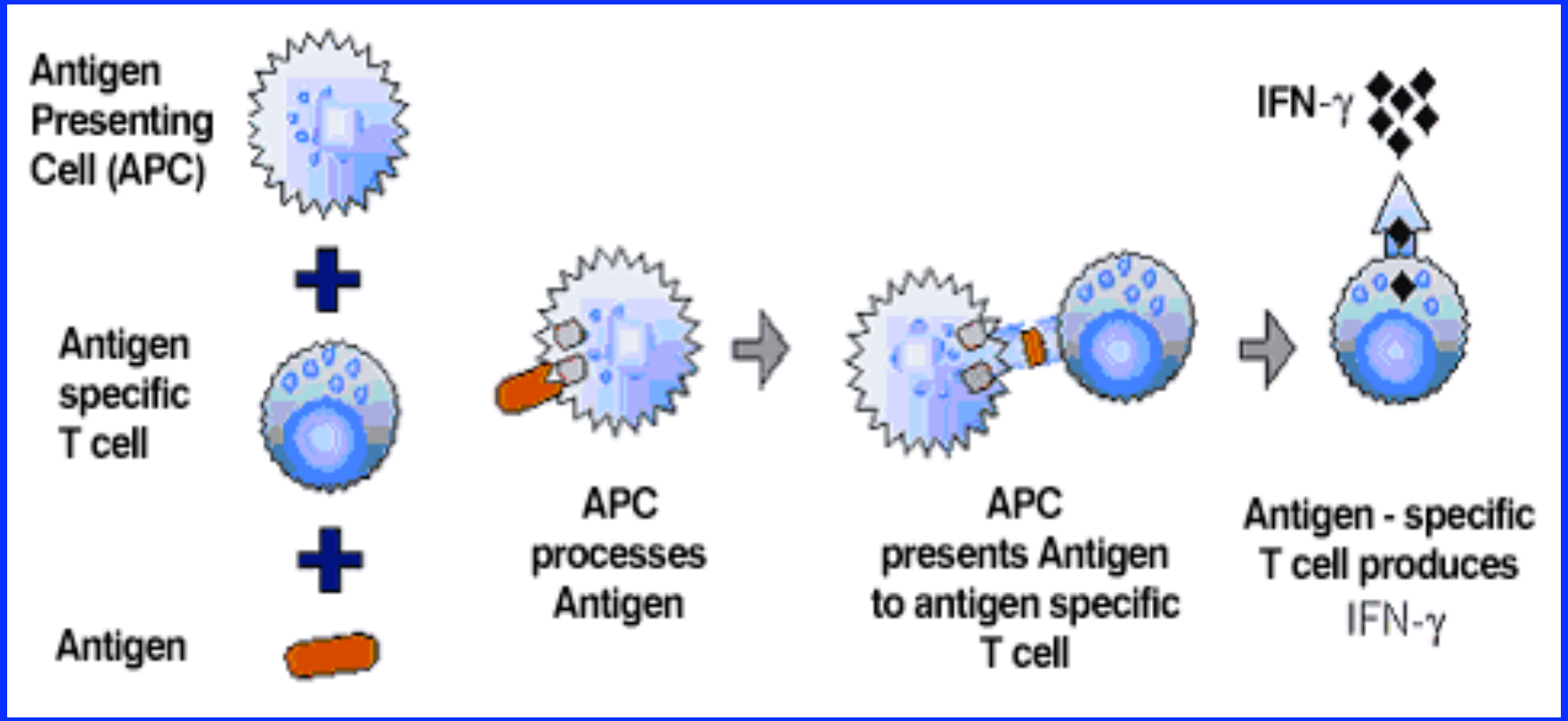


Am Rev Respir Dis 1992;146:754

T Cell-Based Technologies

- Whole-blood tests used to detect LTBI
- QuantiFERON Gold Test (QFTG) approved in 2005
- T-SPOT TB Test under FDA review
- Blood incubated 16-24 hours with
  - TB specific antigens ESAT-6 and CFP-10
  - *M. avium* antigens
  - Controls
- Cells that recognize antigen release interferon-γ
- Amount of Interferon released in response to TB Ags compared to amount released in response to other Ags

Interferon Gamma Release



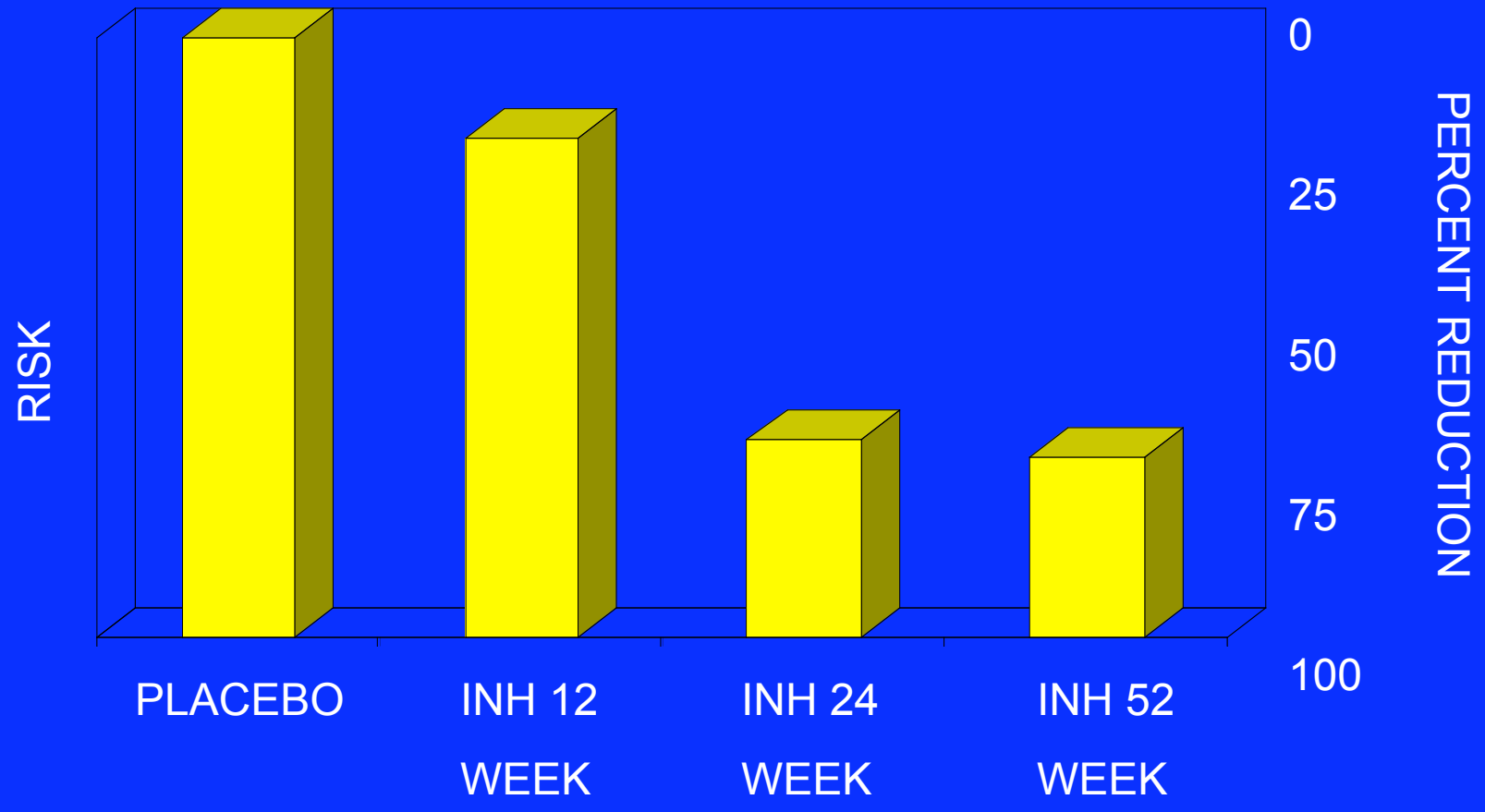
Advantages

- Requires single patient visit
- Does not cause booster phenomenon
  - No two-step necessary
- Less reader bias than TST
- Improved specificity
- Adequate sensitivity

Disadvantages

- Blood sample must be processed in 12hrs
- Detects
  - *M. africanum, bovis, kansasii, marinum, szulgai*
- T-Spot approved in Europe – not US
- QFTG approved but not available in MA
  - State Lab to begin offering 1/07
- New technology: research needed
  - Comparison between technologies
  - Cost effectiveness

FIVE YEAR INCIDENCE OF CULTURE-POSITIVE TUBERCULOSIS PER 100 PERSON-YEARS BY TREATMENT GROUP

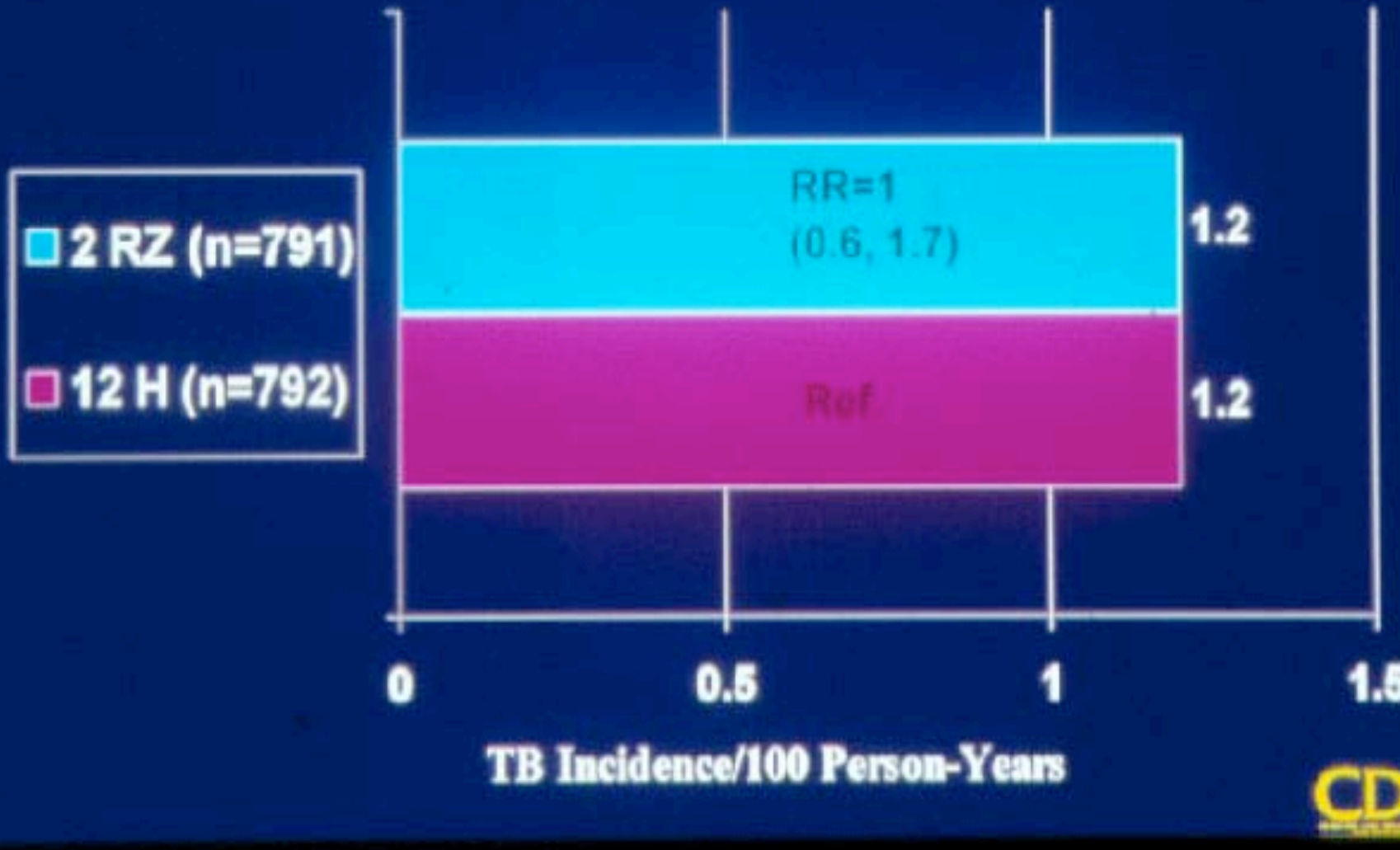


Preventive Therapy Regimens in HIV+PPD+Persons

Group	TB Cases/100 py	Adjusted RR	Adverse events (%)
Placebo	3.4	1.0	5.0
INH (6)	1.1	0.33 (0.14-0.77)	11.2
INH+RIF (3)	1.3	0.40 (0.18-0.86)	9.7
INH+RIF+PZA (3)	1.7	0.51 (0.24-1.08)	24.7

Whalen, et al. NEJM 1997;337:801

Multinational Preventive TB Therapy Trial in HIV+/PPD+ (Gordin, et al.)



Treatment of Latent Tuberculosis Infection

Drugs	**Duration (months)**	**Interval**
Isoniazid	9	Daily Twice weekly
Isoniazid	6	Daily Twice weekly
Rifampin	4	Daily

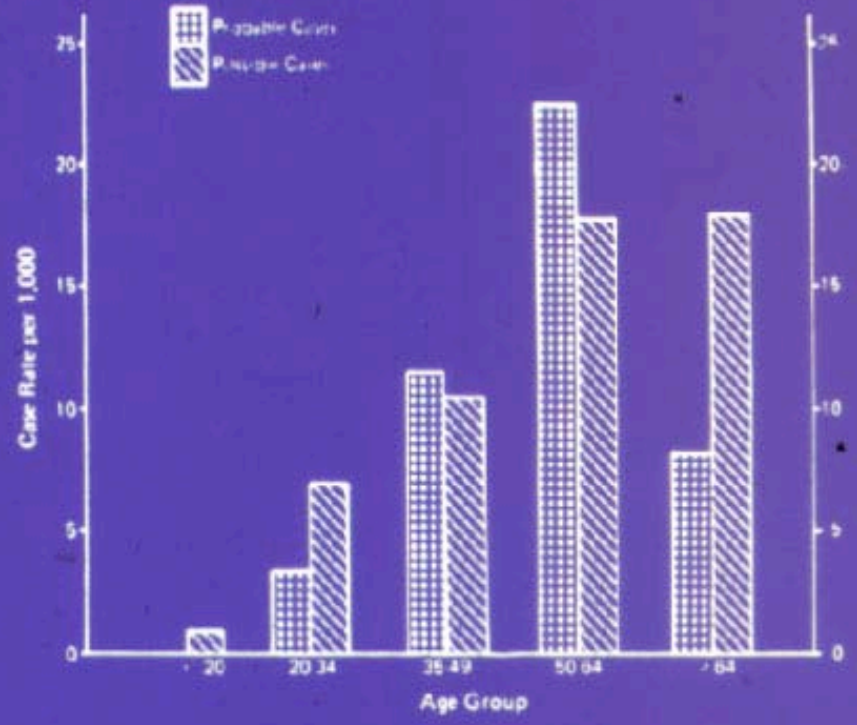
MMWR 2000; 49 (RR-6):2

Screening for TB disease

- HIV-infected patients with a positive tuberculin skin test must have chest radiograph to exclude active TB
- In some African countries, prevalence of TB disease is 8-15%
- Patients being treated for LTBI must be monitored closely for active disease and for toxicity

ISONIAZID TOXICITY

Major:	Hepatitis
Moderate:	Peripheral neuropathy
Minor:	Central nervous system
	gastrointestinal
	rash



*Rates have been adjusted for length of time in study

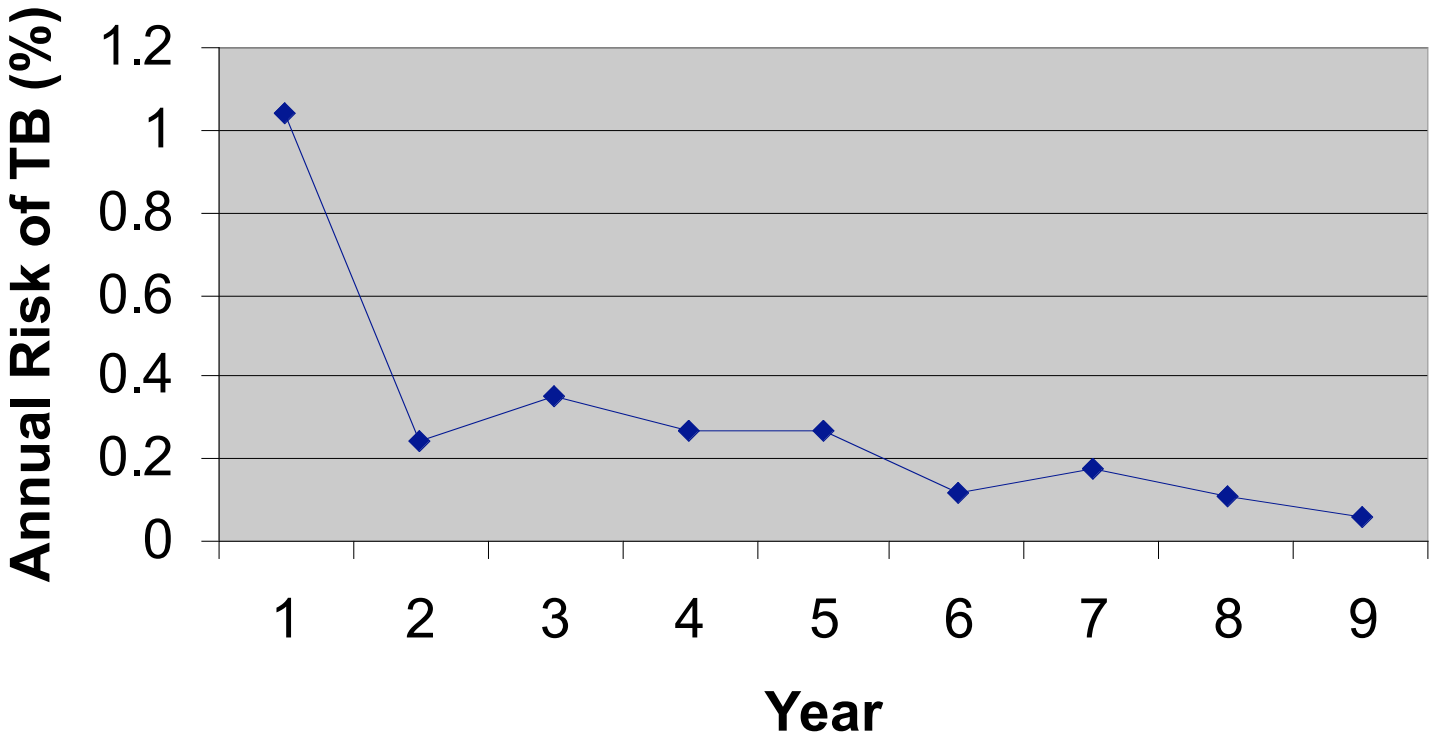
Fig. 1. Comparison of probable and possible isoniazid-related hepatitis case rates per 1,000 participants, by age group. Case rates have been adjusted for length of time in study.

Relative Risk of Reactivation TB among Persons with Conditions That Impair Immune Control of TB

Condition	Relative Risk (95% CI)
Advanced HIV infection	9.9 (8.7-11.3)
	9.4 (3.5-25.1)
Old, healed tuberculosis	5.2 (3.4-8.0)
Chronic renal failure	2.4 (2.1-2.8)
Infliximab therapy	2.0 (1.7-2.4)
Poorly controlled diabetes	1.7 (1.5-2.2)
Silicosis	1.7 (1.3-2.1)
	1.3 (1.1-1.7)
	1.2 (1.0-1.5)
Underweight (≤10% below normal)	1.6 (1.1-2.2)
Gastrectomy	1.4 (1.1-1.9)
	1.3 (1.2-1.4)

NEJM 2004;350:2060-7

Reactivation TB by year after TST conversion



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Cost-effectiveness of TB and HIV Interventions in U.S. Dollars

Intervention	Cost per DALY Gained	Cost per Death Averted	Cost per TB Case Averted
Baseline Scenario	N/A	N/A	N/A
Improve TB Detection Rate	21.6	458	201
Improve TB Cure Rate	34.3	752	175
Improve TB Cure Rate and Case Detection Rate	17.8	379	123
TLTI, 6 months	84.7	1136	294
TLTI, Lifetime	373	3,630	1,374
ART, 50% dropout rate	258	20,461	37,569
ART, 20% dropout rate	410	14,370	28,064
ART, 5% dropout rate	533	11,294	23,403
ART to TB patients	462	13,846	62,578

BMC Public Health 2005; 5:130

Conclusions

1. LTBI treatment is cost effective, but not as cost-effective as case-finding and treatment
2. LTBI treatment is warranted in highest risk groups (recent infection, HIV+)
3. All HIV-infected persons should receive tuberculin skin testing as part of initial evaluation
4. All HIV-infected persons should have active TB excluded before beginning LTBI treatment
5. INH for 9 months is the optimal LTBI treatment regimen for HIV-infected persons