BCG對PPD檢驗結果的影響

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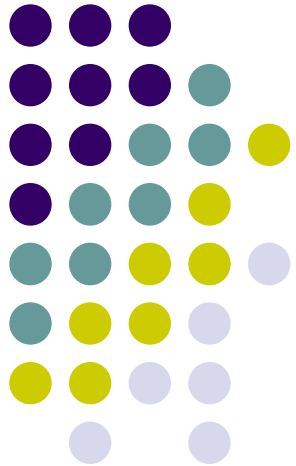
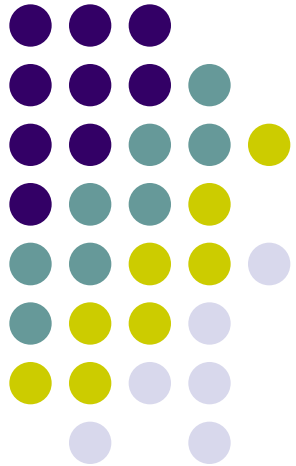
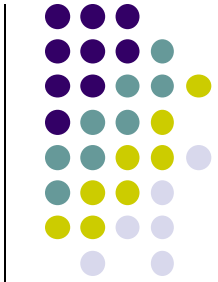


BCG



Introduction



- Immunization with bacillus Calmette–Guerin (BCG) is currently used in many parts of the world as a means of preventing tuberculosis
- It remains a highly controversial method of preventing TB despite more than 80 years of use

BCG Vaccine

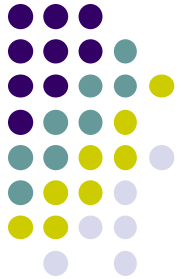
- Derived from an attenuated strain of *M.bovis*
- Vaccine efficacy only ≤80%
- More effective if given in childhood
- Prior vaccination can cause positive PPD skin test
- Side effects: prolonged ulceration at the vaccination site, lupoid reactions & death

BCG: Bacillus of Calmette and Guerin Vaccine

BCG: History

- BCG is named after the two French investigators responsible for developing the vaccine from an attenuated strain of *Mycobacterium bovis.*
- They presented their results to the Academie de Sciences in 1908

BCG: history



- BCG vaccines are the oldest of the vaccines in wide use today, having been derived between 1906 and 1919 by in vitro attenuation of an isolate of *Mycobacterium bovis.*

BCG: history

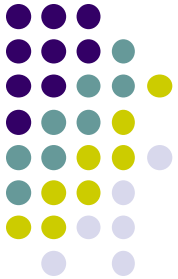
- The product of this attenuation was never cloned, but was distributed to many laboratories, which then propagated the vaccine strain under different conditions
- As a result, the bacteria marketed today by different providers as BCG are by no means bacteriologically identical

Fine. Rev Inf Dis 1989; 11:S353

BCG: history

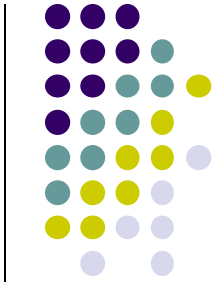
- BCG was first used as an antituberculosis vaccine in humans in 1921
- BCG vaccination was encouraged worldwide until these vaccine became –after the eradication of smallpox- the most widely used vaccine in the world
- Only the US and the Netherlands have not used BCG on a national scale

BCG History: The Lübeck disaster



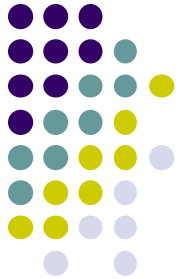
- Between 10 December 1929 and 30 April 1930, 251 of 412 infants born in Lübeck, Germany, received three doses of *BCG vaccine* by the mouth during the first ten days of life.
- Of these 251, *72 died of tuberculosis*, most of them in two to five months, and all but one before the end of the first year

BCG History: The Lübeck disaster



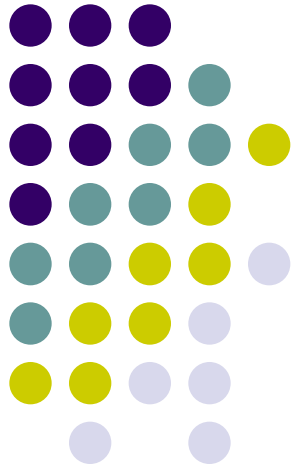
- In addition, 135 suffered from clinical tuberculosis but eventually recovered
- 44 became tuberculin-positive but remained well
- Of 251 children, 207 (82.5%) died or developed tuberculosis

Expanded Program on Immunization (WHO)

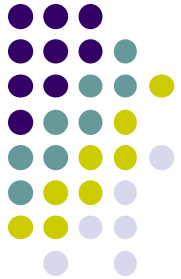


- In 1974 when EPI was launched by WHO, <5% of the world children were immunized against 5 infectious diseases including TB
- By 1995, BCG had the highest vaccination coverage, 87%

Is BCG effective?

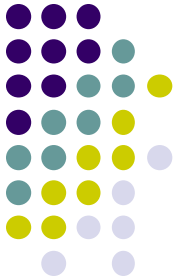


Is BCG effective?

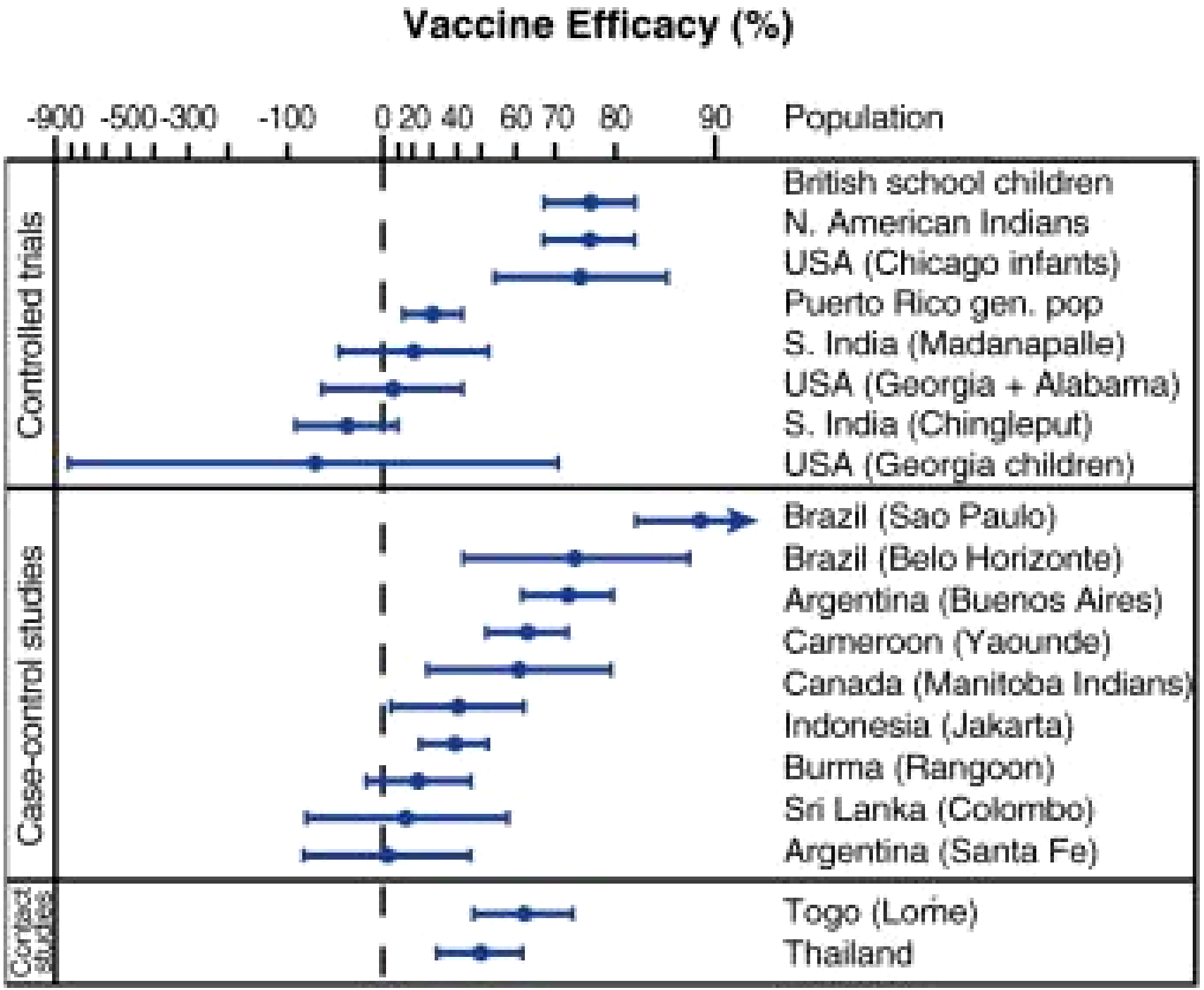


- Millions of people around the world have been vaccinated with BCG, but even so, the efficacy of the vaccine is uncertain.

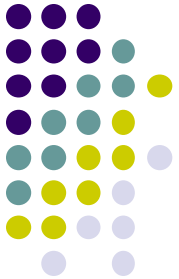
Is BCG effective?



- Results of randomized controlled trials (RCT) and case control studies (CCS) showed the protective efficacy against tuberculosis as uncertain and unpredictable, as protective efficacy varied from 0 to 80%


Vaccine Efficacy (%)
-900 -500 -300 -100 0 20 40 60 70 80 90
Population
Controlled trials
British school children
N. American Indians
USA (Chicago infants)
Puerto Rico gen. pop
S. India (Madanapalle)
USA (Georgia + Alabama)
S. India (Chingleput)
USA (Georgia children)
Case-control studies
Brazil (Sao Paulo)
Brazil (Belo Horizonte)
Argentina (Buenos Aires)
Cameroon (Yaounde)
Canada (Manitoba Indians)
Indonesia (Jakarta)
Burma (Rangoon)
Sri Lanka (Colombo)
Argentina (Santa Fe)
Contact studies
Togo (Lome)
Thailand

BCG: a meta-analysis



- Meta-analysis of over 1,200 articles from international publications
- Only 14 prospective trials and 12 case-control studies met the selection criteria

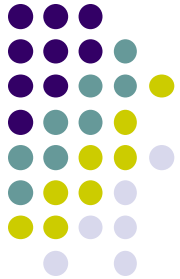
JAMA 1994; 271:698-702

BCG: a meta-analysis

- Combining data from the trials the RR for TB among those vaccinated with BCG was 0.49 (95%CI, 0.34 to 0.70); protective effect 51%
- Combining data from the case-control studies, the OR for BCG vaccination against TB was 0.50 (95%CI 0.39 to 0.64)

JAMA 1994; 271:698-702

BCG: a meta-analysis



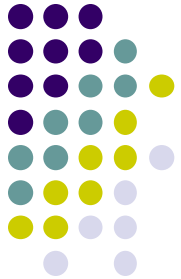
- Combining data from 7 trials the RR for death from TB among vaccinated was 0.29 (95%CI 0.16 to 0.53); 71% protective effect
- 5 CC studies showed a protective effect against meningeal TB of 64%
- 3 CC studies showed a protective effect against disseminated TB of 78%

JAMA 1994; 271:698-702

- However, the protection afforded by BCG against pulmonary disease in both children and adults is not proven

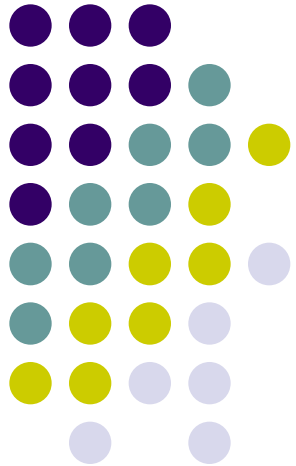
Clin. Infect. Dis. 1995; 20:982–991

Factors contributing to variability in BCG efficacy

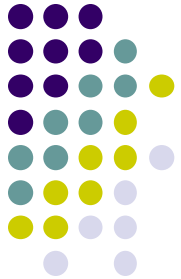


- Genetic variability of the subjects vaccinated
- Use of different strains of BCG for immunization
- Use of different doses of vaccine
- Different schedules of immunization

BCG and tuberculin reactivity



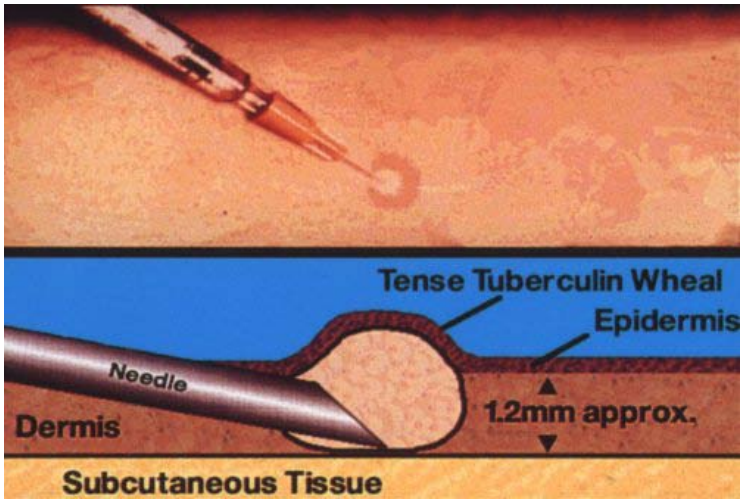
Standard Tuberculin Preparations

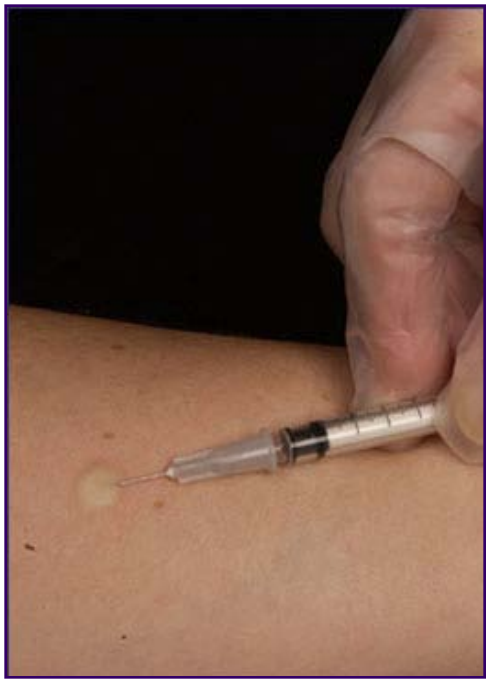


- Current preparations of tuberculin contain a purified protein derivative (PPD) of Koch's Old Tuberculin
- The two standard preparations are:
  - **PPD-S** – dose of 0.1 ml contains 5 tuberculin units (TU) of PPD
  - **RT-23** – dose of 0.1 ml contains 2 TU (equivalent to 5TU of PPD-S)

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

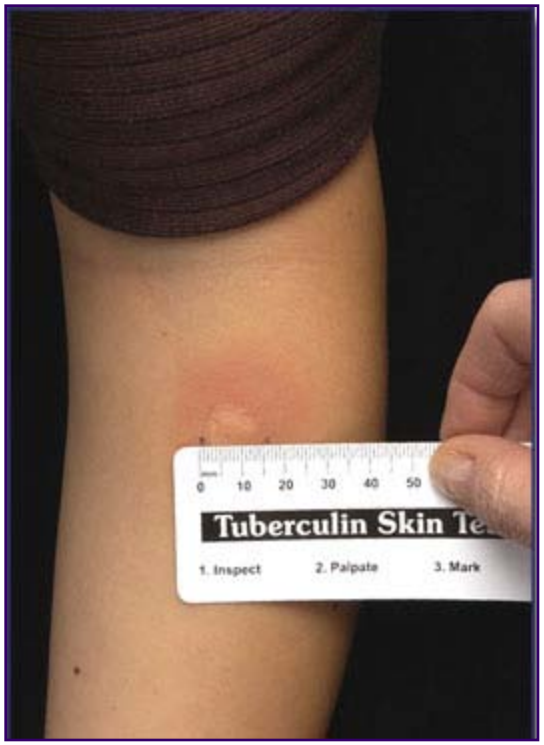




- Produce a wheal 6 - 10mm in diameter

Reading the TST

- Measure reaction in 48 to 72 hours
- Measure **induration**, not erythema
- Forearm: *Transversely to the long axis of the forearm*. Record in mm!
- Ensure trained health care professional measures and interprets the TST



TST Interpretation

≥ 5 mm

- HIV-infection
- Other immunosuppressed
- Recent contact
- Fibrotic CXR changes
- Organ transplant recipients

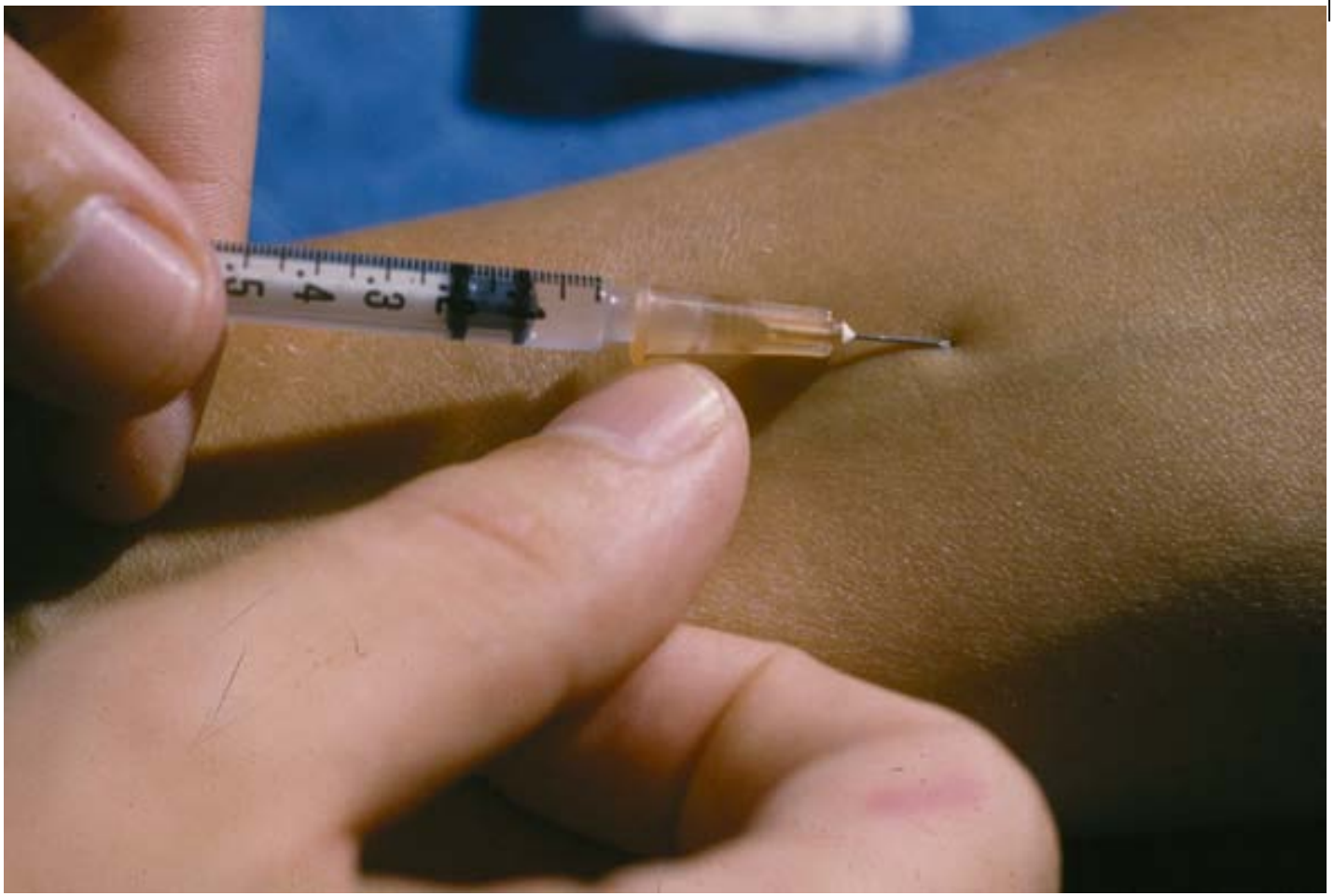
≥15 mm

- Consider significant “positive” for all

≥ 10 mm

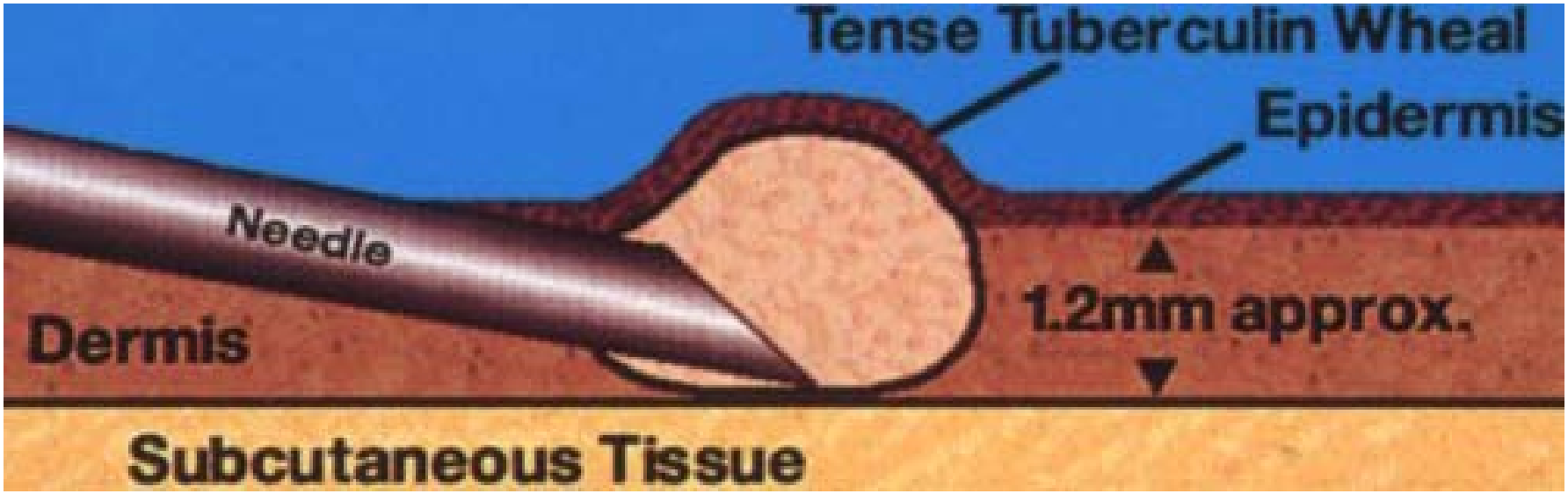
- Recent immigrants
- Injection drug users
- Lab personnel
- Residents/employees of congregate settings
- Persons with clinical risk factors
- Children < 5-years-old or child/adolescent exposed to high-risk adult

Applying the tuberculin skin test

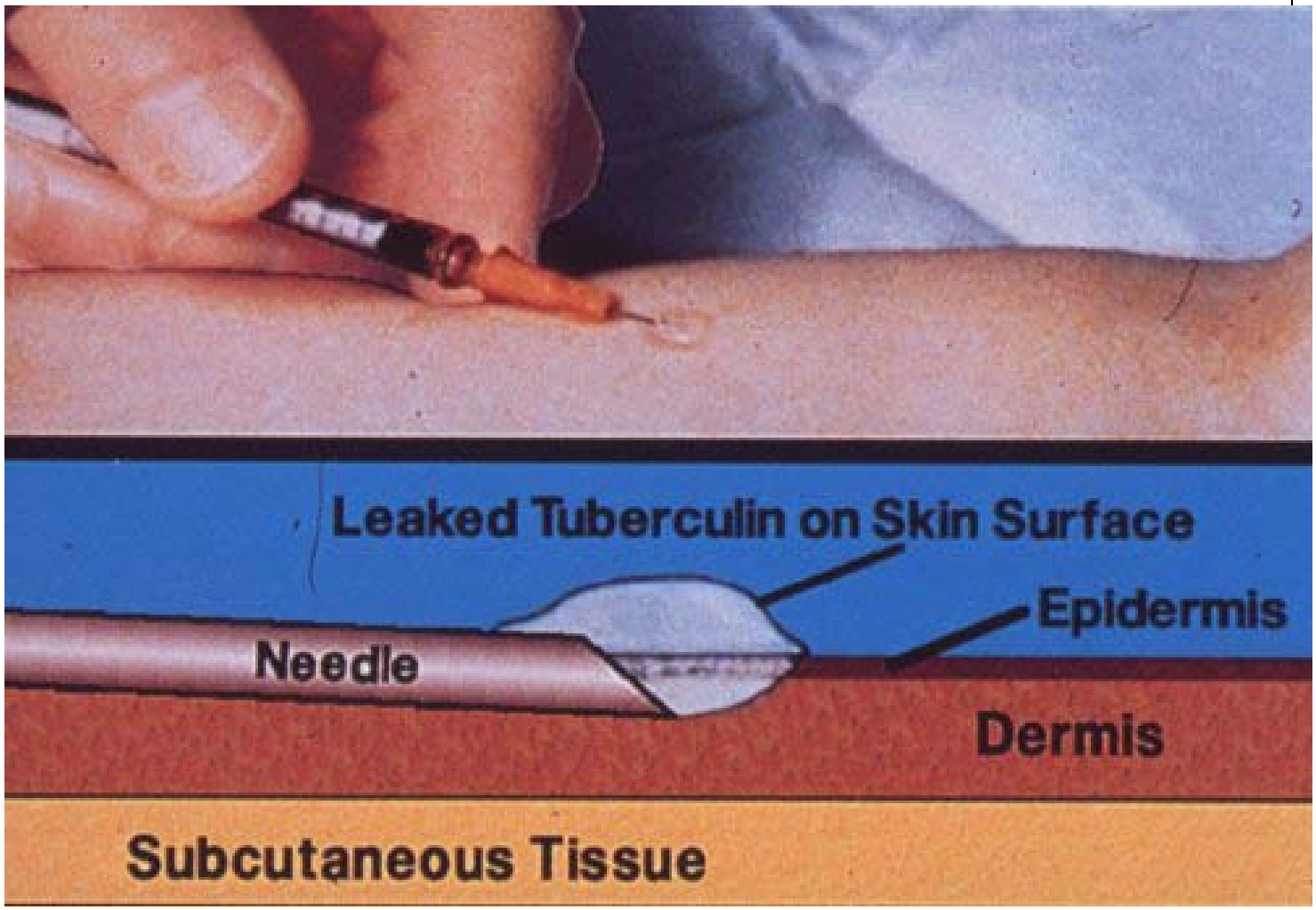


Courtesy of Dr. Marc Steben

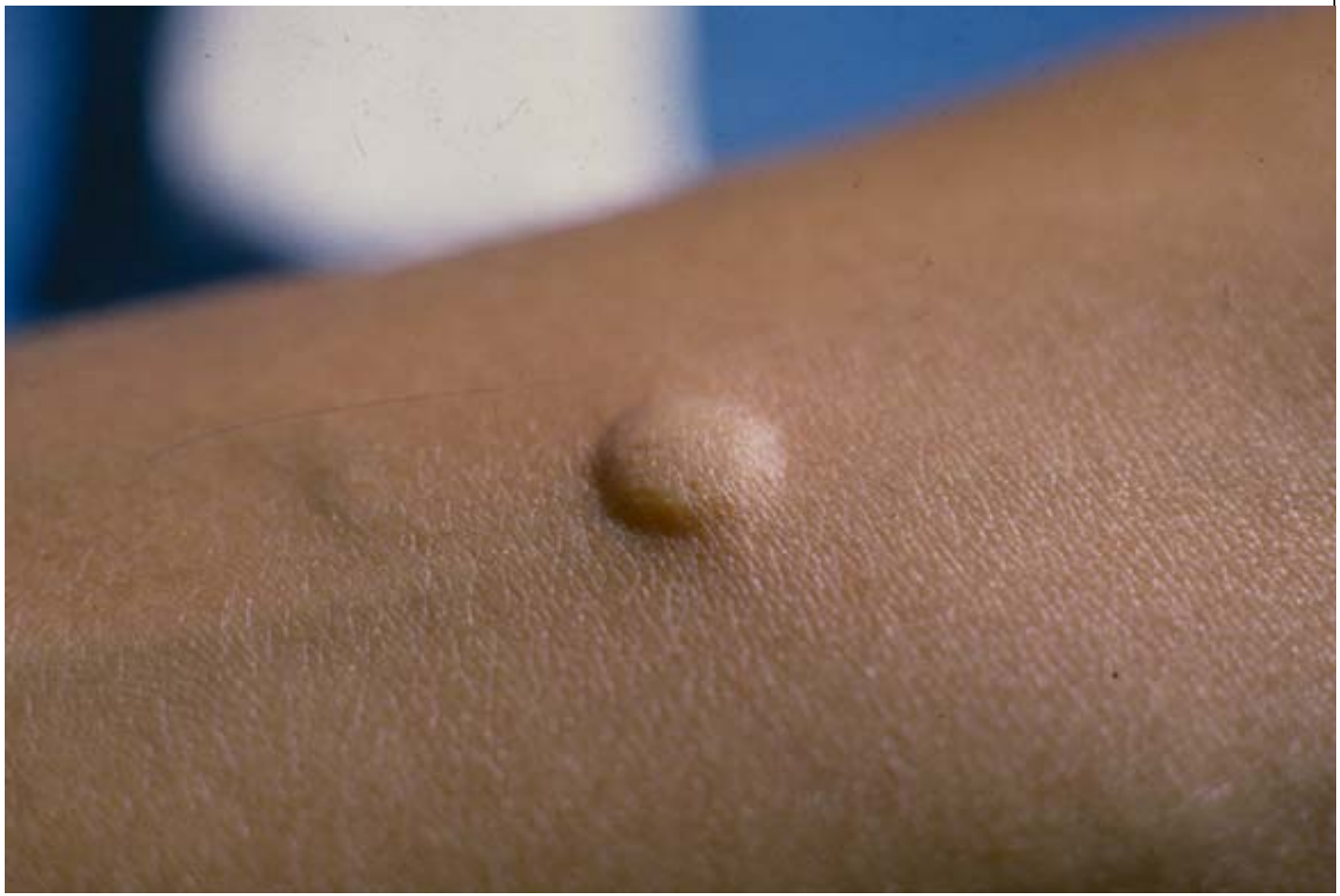
Applying the tuberculin skin test



PPD Skin Test

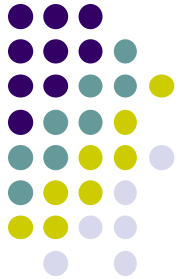


Applying the tuberculin skin test



Courtesy of Dr. Marc Steben

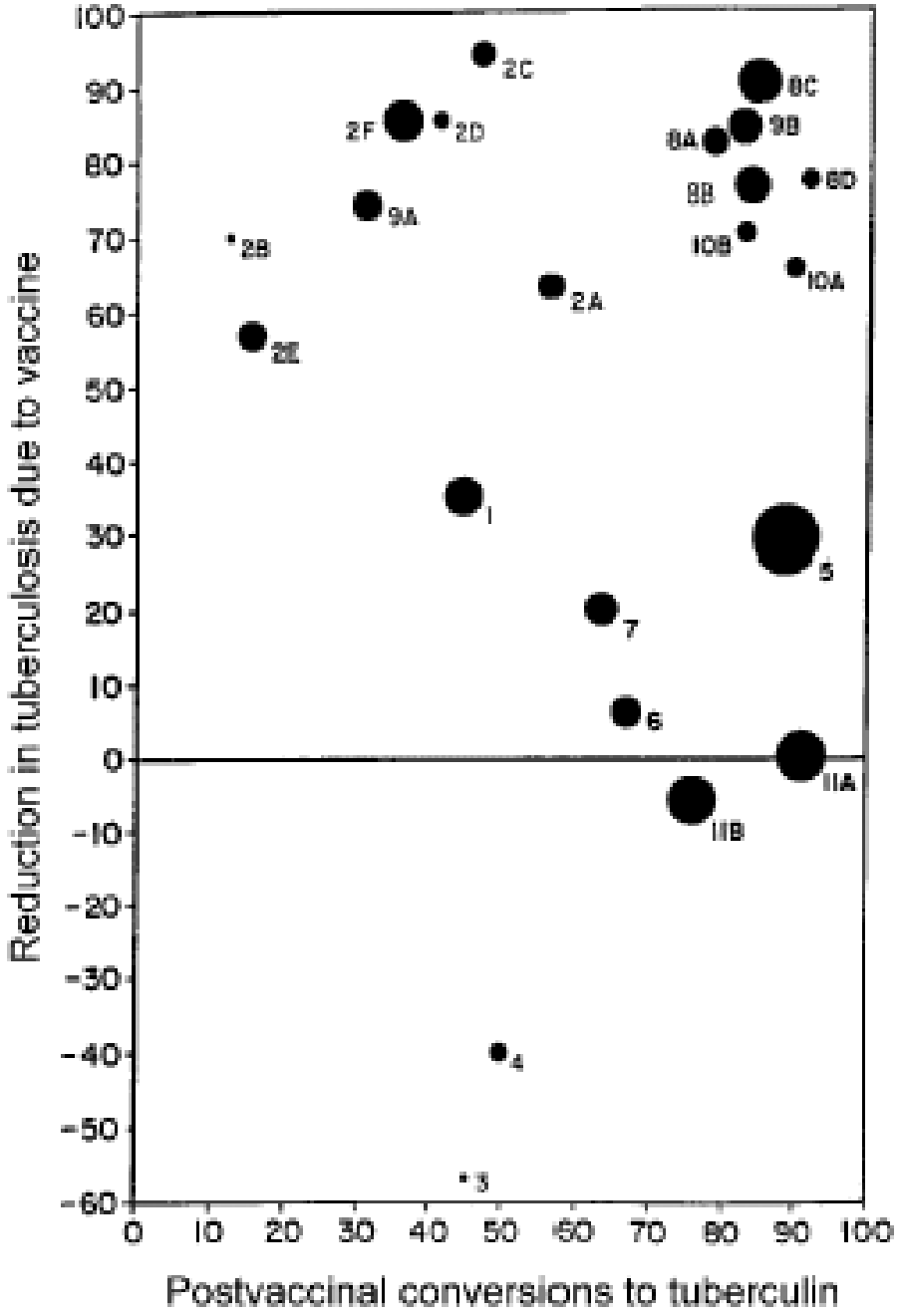
BCG and tuberculin reactivity



- Interestingly, skin test reactivity resulting from vaccination does not correlate with protection against tuberculosis
- Animal and human studies have shown that tuberculin reactivity after BCG vaccination is highly variable

CID 2000;30(Suppl 3):S262

- Tuberculin sensitivity and the ability to prevent tuberculosis are separate phenomena
- Postvaccinal tuberculin sensitivity does not predict efficacy.
- In fact, there is a slight negative correlation.



GW Comstock. CID 2000; 30:S250

BCG and tuberculin reactivity

- The type of BCG vaccine, the number of doses of vaccine, time lapsed since BCG vaccination, age at BCG vaccination, genetics of the host, exposure to NTM, and exposure to tuberculin can all influence tuberculin reactivity after BCG vaccination

CID 2000;30(Suppl 3):S262

- There is no reliable method of distinguishing tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections.

- In general, BCG given in infancy is unlikely to lead to a positive PPD response (induration of greater than 10 mm diameter) in later life
- Thus, a positive PPD test result in a BCG vaccinated person probably indicates concurrent or previous TB infection

Prevalence of tuberculosis infection in schoolchildren from Tijuana, Mexico

- 1,131 school children in Tijuana, Mexico
  - mean age 11.43 ± 0.10 years
- The proportion of immunized children with a positive tuberculin reaction was significantly higher than that of non-immunized children ($p<0.001$)

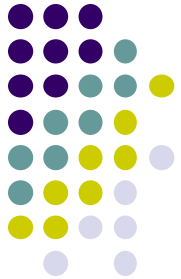
CUADRO II

NÚMERO Y PORCENTAJE DE REACTORES DE ACUERDO CON EL ANTECEDENTE DE INMUNIZACIÓN CON BCG. TIJUANA, MÉXICO, 1996

	Reactor				
Inmunización con BCG	*Positivo*	*%*	*Negativo*	*%*	*Total*
Sí	556	59.7	376	40.3	932
No	82	45.6	98	54.4	180
Total	638	57.4	474	43	1 112

Salud Publica Mex 1998;40:47

Prevalence of tuberculosis infection in schoolchildren from Tijuana, Mexico



- The proportion of positive reactors in first grade was identical for both groups (46.4% *vs.* 47.7%)
- By 9th grade, the proportion of positive reactors was significantly higher among the immunized subjects (69.7% *vs.* 49.9%)
- Diameter of induration was positively correlated with age ($r=0.16$, $p<0.001$)

Salud Publica Mex 1998;40:47

- It is usually prudent to consider “positive” reactions to 5 TU of PPD tuberculin in BCG vaccinated persons as indicating infection with *M. tuberculosis*, especially among persons from countries with a high prevalence of tuberculosis

- Because most persons who have received BCG are from high-prevalence areas of the world, it is important that vaccinated persons who have a positive reaction to a tuberculin skin test be evaluated for tuberculosis and treated accordingly

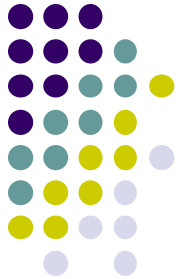
MMWR 1996; 45:RR-4

However.....

- A study of a large group of contacts of several active cases of TB, showed that ignoring BCG history may lead to overuse of chemoprophylaxis
- 18.3% of non-BCG contacts were offered chemoprophylaxis, whereas 43.8% of contacts who had received BCG were offered chemoprophylaxis ($p < 0.001$).

Int J Tuberc Lung Dis 1998; 2:S149

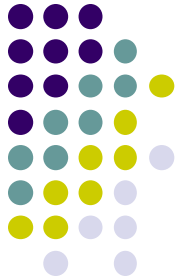
BCG and TST Interpretation



- BCG is the most widely used vaccine in the world
- Wang, et al – meta-analysis
  - Effect of BCG vaccination on TST results was less after 15 years
  - Positive TST with indurations of >15 mm more likely to be result of TB infection than of BCG vaccination

L Wang, et al. Thorax 2002;57:804-809

Effect of TB exposure on TST results in a BCG vaccinated population



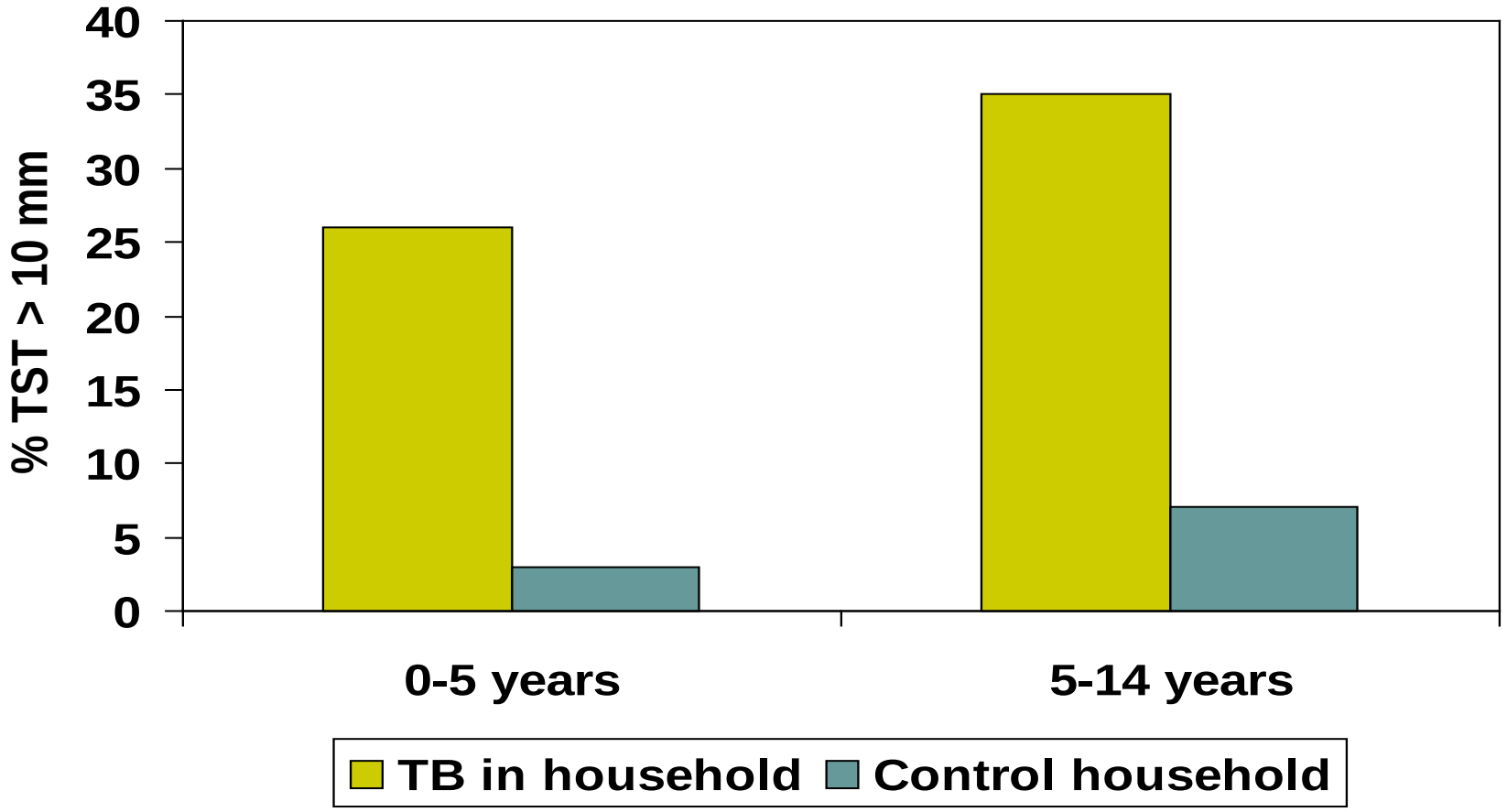
- Setting - village in Ghana, country with universal BCG just after birth (96% coverage rate)

- Study - tuberculin skin testing of two kinds of households:

  1) household with recently-diagnosed case of active pulmonary TB

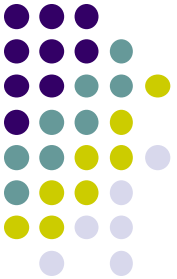
  2) neighboring households without active TB

TST results and TB exposure in area using BCG vaccination - results in infants/children



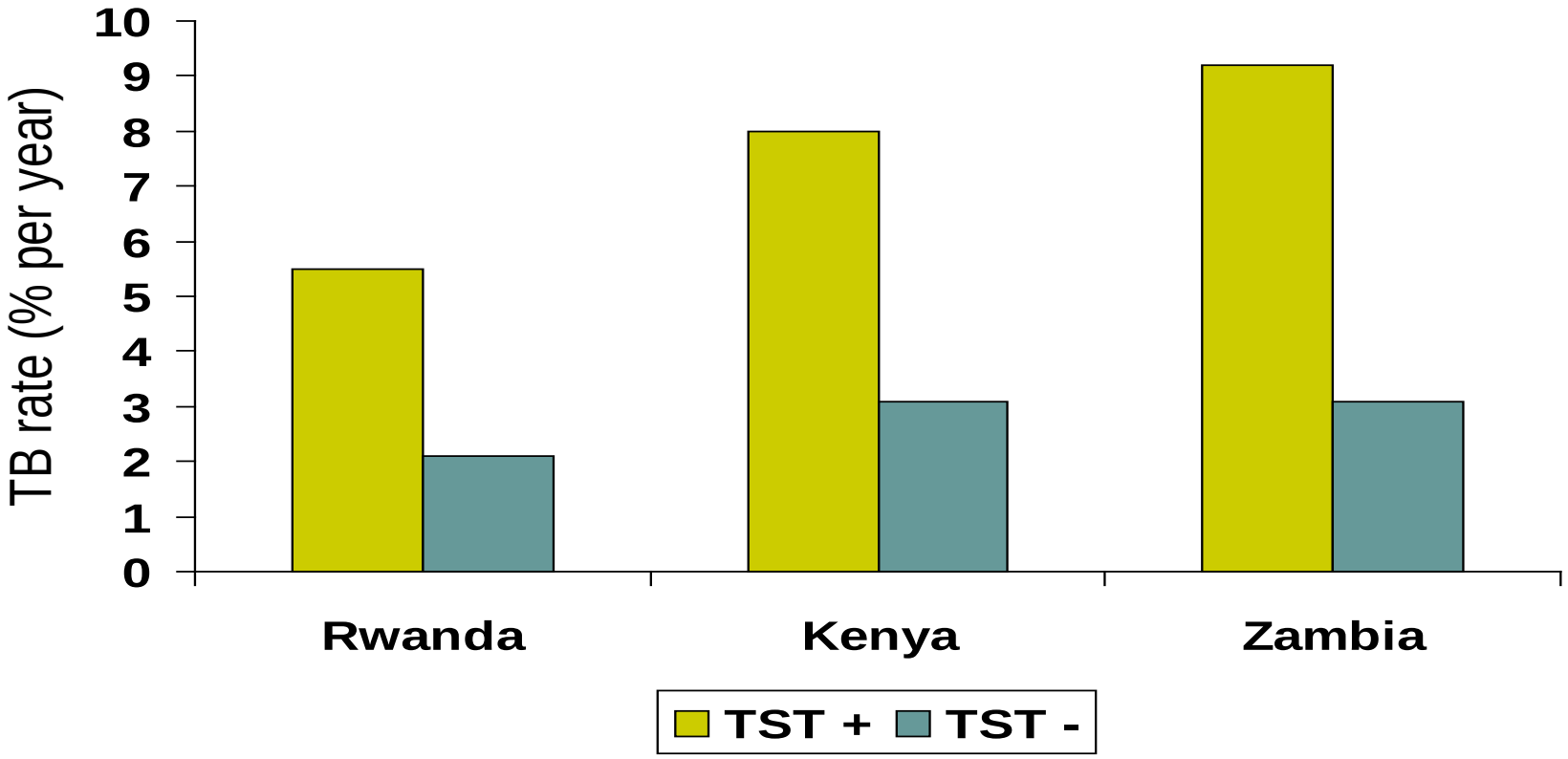
Am J Respir Crit Care Med 2003; 168: 448-455

Conclusions – Use of TST where BCG vaccination is common

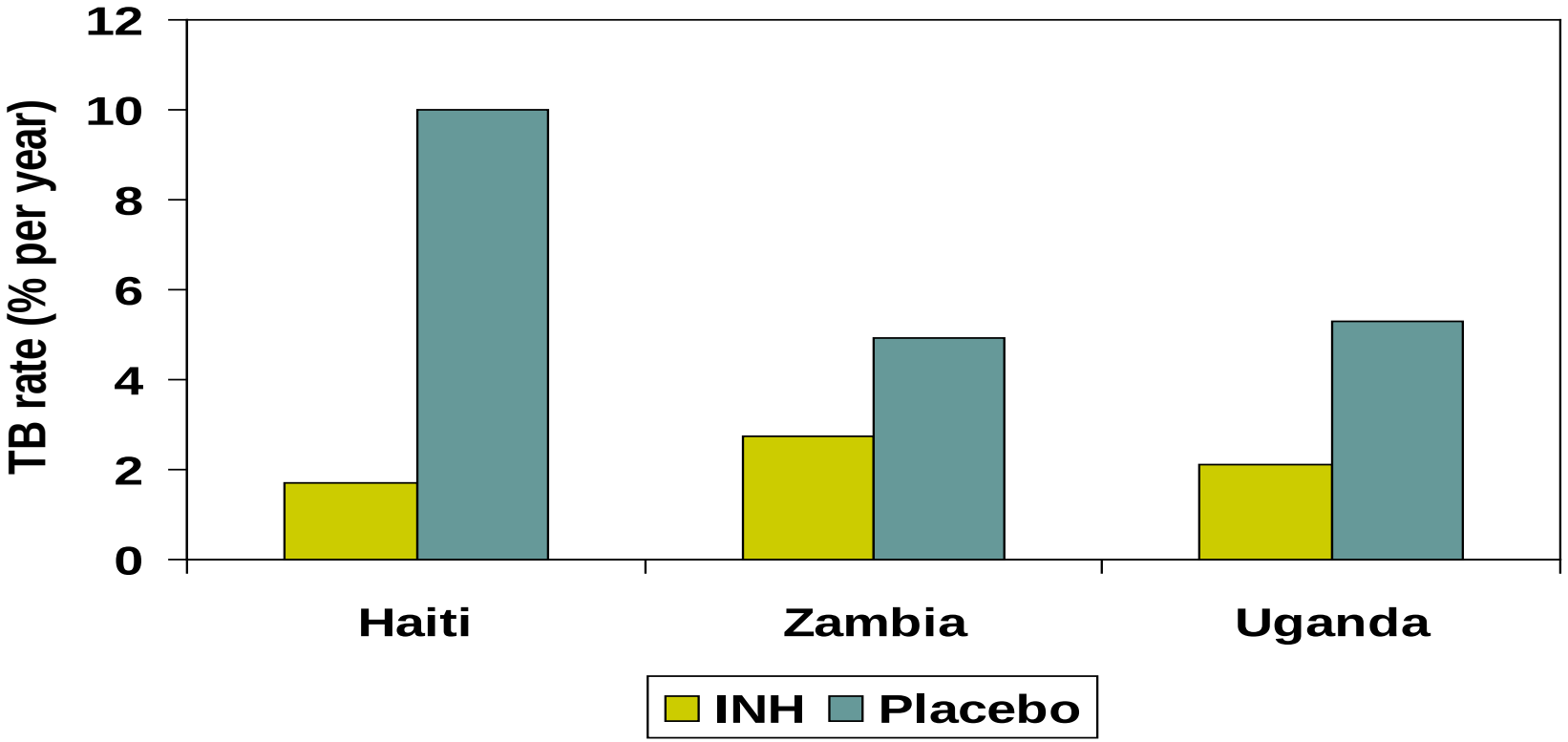


- In a setting of universal BCG
  - Positive TST is strongly associated with TB exposure
  - TST reaction is not associated with presence of BCG scar
  - True for children and adults
- Interpret TST the same whether BCG has been given or not
  - HIV-positive or recent contact – 5 mm
  - HIV-negative, not recent contact – 10 mm

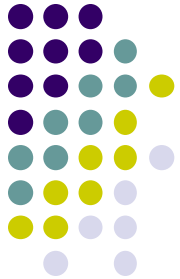
TST identifies persons at high risk of active TB



Isoniazid (INH) reduces active TB rate by 60% among patients with positive TST (≥ 5 mm)



Adverse events in studies of INH treatment of latent TB - Uganda



Group	*Mild*	*Moderate*	*Severe*	*DC meds*
Placebo	**5%**	**0**	**0**	**0.2%**
INH	**10%**	**0.7%**	**0**	**0.6%**

Conclusion - side effects were more common with INH, but most were mild

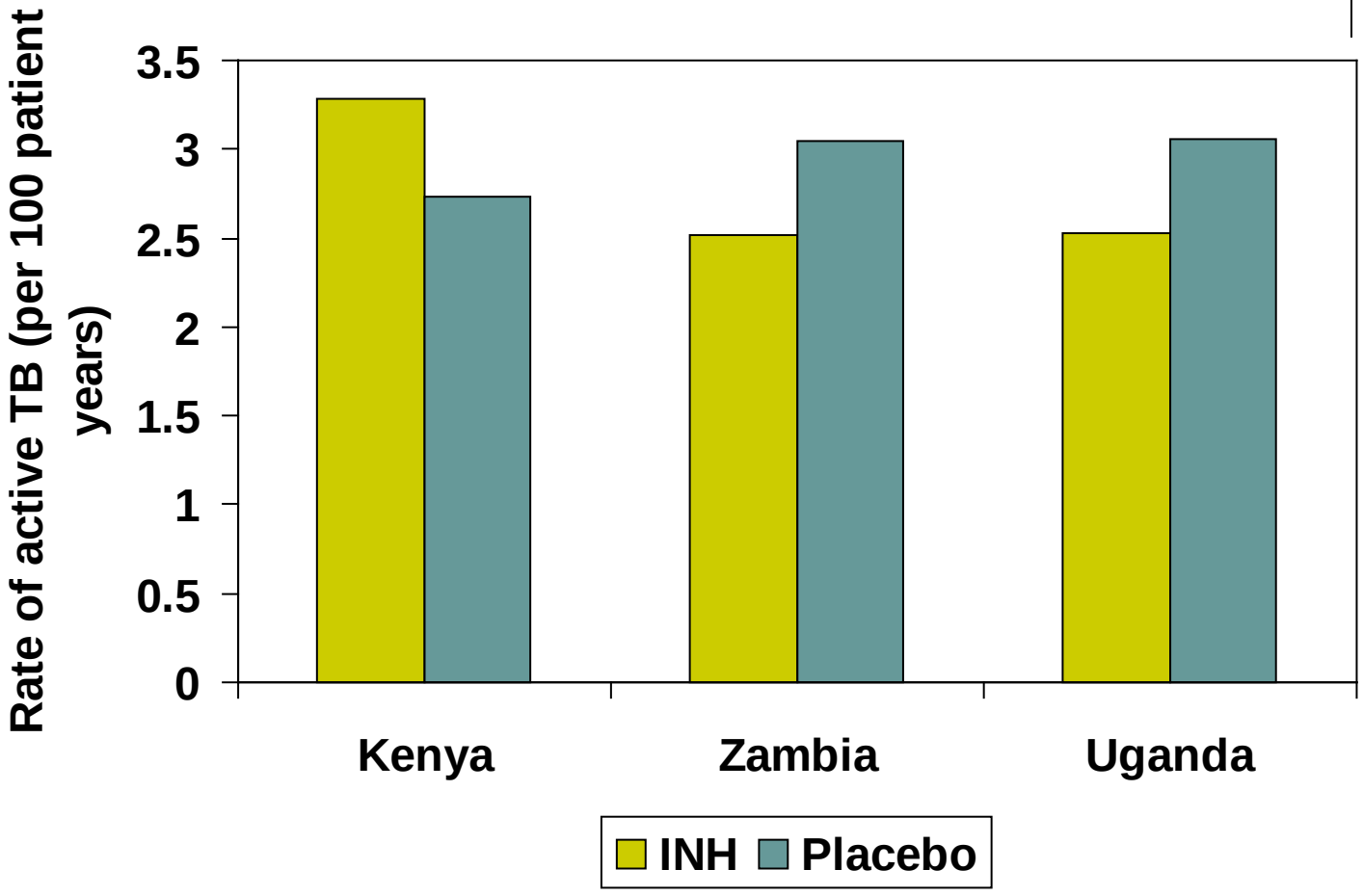
N Engl J Med 1997;337:801-8

Types of adverse events from INH for latent TB - Zambia

Adverse event leading to drug discontinuation	***Placebo*** *(n = 360)*	***INH*** *(n = 360)*
Hepatitis	0	3 (0.8%)
Rash	0	1 (0.3%)
GI symptoms	1 (0.3%)	5 (1.4%)
Others	2 (0.6%)	3 (0.8%)

AIDS 1998;12:2447-57

Efficacy of INH among HIV-positive, TST-negative persons in Africa

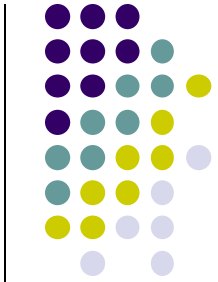


AIDS 1997;11:875-82, AIDS 1998;12:2447-57, N Engl J Med 1997;337:801-8

Risk of INH resistance after INH treatment for LTBI – data among HIV-positive patients

Trial site	**INH treatment** INH-resis / total	**Placebo** INH-resis / total
Kenya	2 / 17	0 / 21
Uganda	5 / 20	1 / 24
Haiti	0 / 4	0 / 15
Zambia	0 / 3	1 / 5
U.S.	0 / 3	0 / 5
Total	7 / 47 (14.9%)	2 / 70 (2.9%)

INH for LTBI and INH-resistance – data from placebo-controlled trials in the era prior to HIV



	INH	Placebo
INH-susceptible, n	43	64
INH-resistant, n (%)	2 (4.4%)	2 (3.0%)

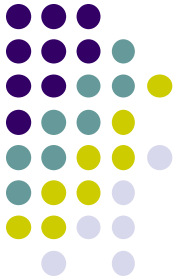
Bull Wld Hlth Org 1966;35:509-26

Effect of INH resistance on outcomes of treatment for active TB

	Failure	Died	Default/ transfer	Success
Drug-susceptible	2%	2%	11%	85%
IHN-resistant (any)	4%	2%	12%	82%
RIF-resistant (any)	11%	2%	13%	73%

JAMA 2000;283:2537-45

Common concerns about screening for and treating latent TB - responses



- TST results correlate with TB exposure even when BCG is used
- TST positive patients are at greatly increased risk of active TB
- Treatment of latent infection – effective in decreasing risk of active TB, but only among TST-positive patients
- INH-resistance may be more common in those who receive INH for latent TB, but treatment can still be effective

懇請賜教