TB Prevention – Who and How to Screen

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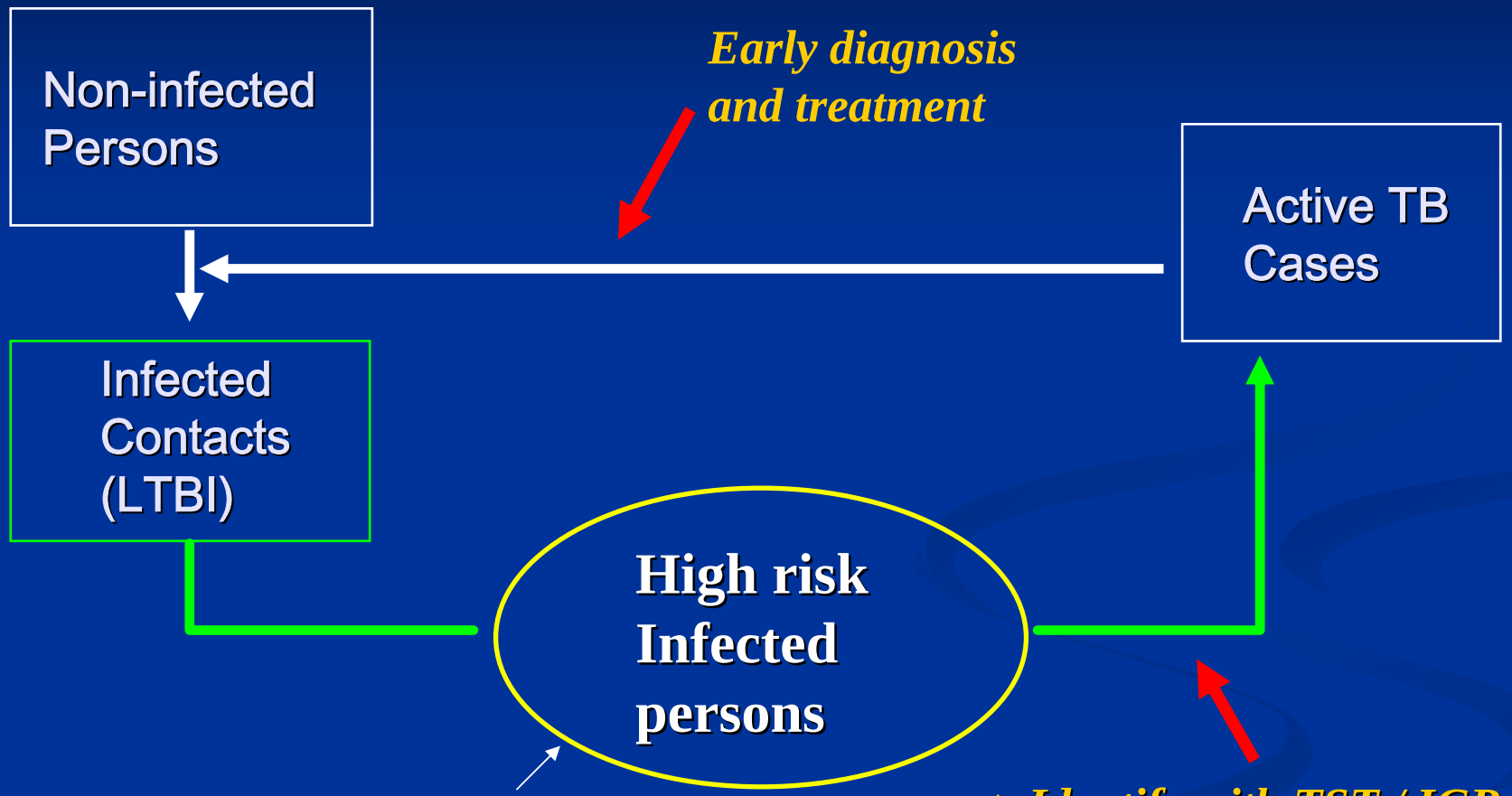
Cycle of Infection - Interventions



Risk of progression of TB infection to disease

- Life-time risk of 10% in immunocompetent adults; 5% risk in first 2 years after infection
- Risk especially high in early childhood
- Risk increased in certain medical conditions

Risk factors for tuberculosis following infection

Risk Factor	Measurement of incidence	
	Absolute / 1000 Person-years	Relative risk
Infection > 7 years past	0.7	
Infection < 1 year past	10.4	
HIV Infection	79	
AIDS		170.3
Fibrotic lesion	2.0-13.6	
Silicosis		30
Immunosuppressive treatment		11.9
Diabetes		2.0-3.6
Carcinoma of head or neck		16
Haemodialysis		10-15
Jejunoileal bypass		27-63
Gastrectomy		5

Adapted from H L Rieder et al, *Epidemiol Rev* 1989;11:79-98

Decision for LTBI Rx (Preventive therapy)

- ***Likelihood of recent infection***
  - close contact with active case
  - recent TST conversion
- ***Risk for development of active disease***
  - HIV / medical conditions
  - fibrotic disease on CXR
- ***Risk of Isoniazid hepatitis***
  - age > 35 yrs
  - background of liver disease
- ***Likelihood of adherence to completion of therapy***

Who to Screen?

- Screening should lead to therapeutic consequences where indicated

- Therefore only selected high-risk persons / groups in whom LTBI treatment is acceptable and feasible should be screened

Screening close contacts of infectious TB cases

- Contact screening data from the US:
  - 1 – 2% have active disease; one-third have recent LTBI
    - *Am J Respir Crit Care Med* 2000;162:2033-2038
  - Estimated rate of clinically active TB among contacts: 700 / 100,000 population
    - *Int J Tuberc Lung Dis* 1999;3:663-674
- High-yield activity which provides opportunity to intervene with preventive therapy in accessible group of high-risk individuals
- BUT highly resource intensive; may be efficacious and effective (in industrialized countries) but not efficient

Screening of high risk persons for LTBI and preventive therapy (PT)

- **High TB burden countries**
  - ***LTBI screening is inappropriate use of resources which should be directed towards detecting, treating and curing the infectious case***
    - **Lack of capability to exclude active disease before starting PT**
    - **PT does not prevent disease associated with re-infection after completion of treatment, an important consideration in areas with annual risk of infection > 2%**
  - **IUATLD recommends PT for asymptomatic children < 5 years old living in household of newly diagnosed smear positive cases (without TST screening)**

Screening of high risk persons for LTBI and preventive therapy (PT)

- **Low TB burden, resource rich countries**
  - Contact investigation and PT central to TB control efforts in many such countries
  - Screening expanded outside of household eg. workplace, school, social, aircraft exposures
  - Congregate settings eg. prisons, mental health institution, nursing homes
  - Other high-risk groups : healthcare workers, HIV-infected, immunosuppressed

Screening of high risk persons for LTBI and preventive therapy (PT)

- **Intermediate TB burden countries**
  - Contact screening for LTBI and PT not widely practised
    - Difficulty in TST interpretation in BCG-vaccinated population
    - Inability of TST to distinguish recent from remote LTBI (relatively high background prevalence of remote LTBI likely in such settings)
  - As TB rates decline, this may be an important strategy

How to Screen?

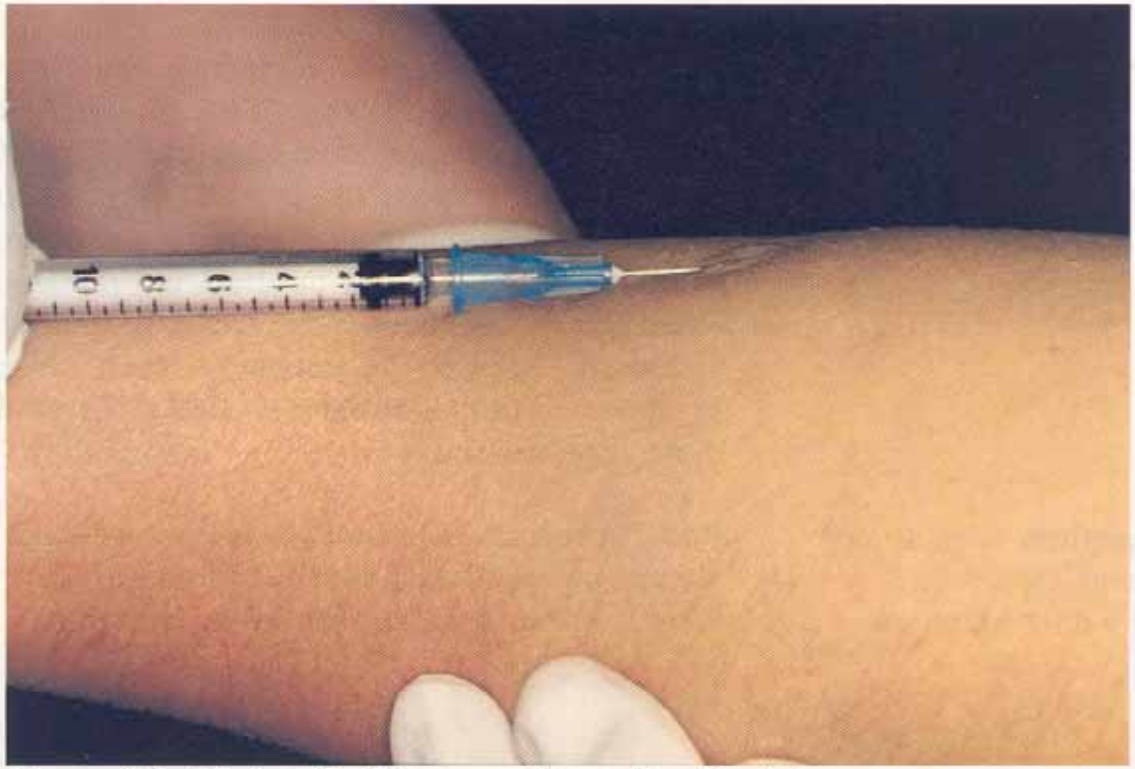


Figure 3.1 Giving the Mantoux tuberculin skin test.

The Tuberculin Skin Test (TST)

- Measures cell-mediated immunity in the form of delayed type hypersensitivity reaction to purified protein derivative (PPD)

- PPD = crude mixture of > 200 antigens shared among *M tuberculosis*, *M bovis* BCG, NTMs

- ***Advantages***
  - ***Inexpensive, simple test***
  - ***Interpretation based on rich body of scientific literature***

The TST - Drawbacks

- Specificity reduced by BCG vaccination and NTM exposure
- Low sensitivity in immunosuppressed persons
- Does not identify recent (vs remote) LTBI
- Boosting phenomenon
- Technical and operational
  - Wide inter and intra-reader variability
  - Return visit required

TST Interpretation
ATS / CDC recommendations

Am J Respir Crit Care Med 2000;161:S221-S243

- ≥ 5 mm *considered +ve in*
  - persons with HIV or at risk for HIV
  - close contacts of infectious TB case
  - radiographic evidence of old, healed TB
- ≥ 10 mm *considered +ve in*
  - persons with medical risk factors other than HIV
  - persons from high-incidence area
- ≥ 15 mm *considered +ve in*
  - persons with none of the above risk factors

NB: Above recommendations ignore BCG status

- *For BCG-vaccinated persons, higher cut-off points probably indicated*

A Meta-analysis of the Effect of BCG vaccination on Tuberculin Skin Test Measurements

Wang L et al

***Thorax* 2002;57:804-809**

- 26 articles included in analysis
- Conclusions
  - Persons with BCG vaccination more likely to have positive skin test
  - Effect of BCG on TST was less after 15 years
  - TST > 15 mm more likely to be result of tuberculous infection than BCG vaccination

False-positive TSTs: What is the absolute effect of BCG and Non-Tuberculous Mycobacteria?

M Farhat, C Greenaway, M Pai, D Menzies

Int J Tuberc Lung Dis **2006:10(11)1192-1204**

- Conclusions:
  - The effect on TST of BCG received in infancy is minimal, especially >= 10 years after vaccination.
  - BCG received after infancy produces more frequent, more persistent and larger TST reactions
  - NTM is not a clinically important cause of false-positive TST, except in populations with a high prevalence of NTM sensitization and a very low prevalence of TB infection

Contact screening using TST in Singapore

- Singapore : intermediate TB burden country
- Since 1950s:
  - BCG vaccination at birth
  - School health policy of BCG re-vaccination for tuberculin non-reactors at age 12 yrs or 16 years (policy stopped 2001)
- 1998: Preventive therapy for TST +ve close contacts of infectious TB cases
- Close contacts with TST reading >=15 mm advised PT; TST 10-14 mm advised on a case-by-case basis

Relative risk of developing TB between ages 17 to 20 years according to TST reading at age 16 years in Singapore schoolchildren (2nd BCG received at age 12 years)

TST reading (mm)	No. of TB cases	Person-Years	Relative risk (95% confidence interval) of developing TB	P value
0 - 4	6	57,318.0	1.00	
5 - 9	8	48,384.0	1.58 (0.55 – 4.55)	0.39
10 - 14	25	145,533.5	1.64 (0.67 – 4.00)	0.27
15 - 17	21	36,664.5	5.47 (2.21 – 13.56)	<0.001
≥ 18	16	8,351.0	18.34 (7.17 – 46.87)	<0.001

P-Values from Pearson Chi-Square or Fisher's Exact Test

Am J Respir Crit Care Med 2001; 164:968-961

Relative risk of developing TB between the ages of 13 to 16 years according to TST reading at age 12 years in Singapore schoolchildren (BCG at birth)

TST reading (mm)	No. of TB cases	Person-years	Relative risk (95% confidence interval) of developing TB	P value
0 - 4	19	563,414.5	1.00	
5 - 9	3	120,817.5	0.74 (0.22 – 2.45)	0.79
10 - 14	21	127,707.5	4.88 (2.62 – 9.07)	<0.001
15 – 17	10	10,997	26.99 (12.55 – 58.05)	<0.001
≥ 18	6	3,718	47.93 (19.13-120.08)	<0.001

P-Values from Pearson Chi-Square or Fisher's Exact Test

Am J Respir Crit Care Med 2001; 164:968-961

Interferon-gamma Release Assays (IGRAs)

- Late 1990s: Discovery of region of difference-1 (RD-1) of the *M tuberculosis* genome not present in all BCG substrains and most NTM species
- Two proteins encoded within RD 1 : early secretory antigenic target 6 (ESAT 6) and culture filtrate protein 10 (CFP 10) are strong targets of T-cells in patients with *M tb* infection
- In-vitro T-cell based assays based on principle that T cells of individuals sensitized with TB antigens produce IFN gamma when they encounter mycobacterial antigens; *M tuberculosis* specific proteins ESAT 6 and CFP 10 used to stimulate T- cell IFN gamma production which is measured by ELISA or ELISPOT technology
- Incubation period of 16 – 24 hours to stimulate effector T-cells

Commercially available IGRAs

- **QuantiFERON® Gold assay (Cellestis, Carnegie, Australia)**
  - **whole blood assay that measures IFG response to ESAT6 and CFP10 with ELISA**
  - **FDA-approved; endorsed by US CDC to replace TST**
- **QuantiFERON®-In-Tube assay : also includes TB7.7 antigen**

- **T SPOT-*TB*® assay (Oxford Immunotec, Oxford, UK)**
  - **uses peripheral blood mononuclear cells, detects by use of enzyme-linked immunospot (ELISPOT) method to measure the number of T cells producing IFG in response to ESAT6 and CFP10 antigens**

IGRAs vs TST for LTBI testing

- **ELISPOT and ELISA : Higher specificity than TST**
  - **Approaching 100% specificity**
- **ELISPOT : Better correlation than TST with hours of exposure (as a surrogate marker for sensitivity) in point source contact investigation in low-incidence settings**

Comparison of Two Interferon-gamma Assays and TST for Tracing Tuberculosis Contacts

Arend et al.

***Am J Resp Crit Care Med* 2007; 175:618-627**

- 785 *non-BCG vaccinated* supermarket customers in low TB incidence country exposed to infectious index case
- Conclusions:
  - Positive TST associated with age
  - Positive IGRA results associated with exposure (QFT-IT > T-SPOT.TB) whereas TST >= 15 mm was not
  - Among those with TST >= 15 mm, sensitivity of QFT-IT was 42.2% and T-SPOT.TB was 51.3%
  - Authors suggest further investigation into alternative cut-off values of IGRA assays needed

IGRAs to replace TST?

- **Only gold standard for LTBI is the subsequent development of active TB**
  - **Do the IGRAs identify those at risk for progression to active TB disease?** ***Results of large-scale longitudinal studies awaited***
  - **Do the IGRAs (unlike the TST) indicate recent (vs remote) LTBI?**
- **Scarcity of data on**
  - **Use for LTBI testing in immunosuppressed persons and young children**
  - **Its interpretation in serial testing**
- **High cost of assay relative to TST**

Priorities in TB Control

- *Early identification and treatment (until cure) of persons with active TB disease is the highest priority*
- *Widespread implementation of LTBI screening and preventive therapy should only be considered in the context of efficient case finding and high rates of treatment completion of patients with disease*
- *Targeted LTBI screening should only be performed for persons who would benefit from, and who are likely to accept (and adhere to) preventive therapy*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Singapore Tuberculosis
Elimination Programme
Thank You