Targeted Screening and Treatment of Latent Tuberculosis Infection in Hong Kong

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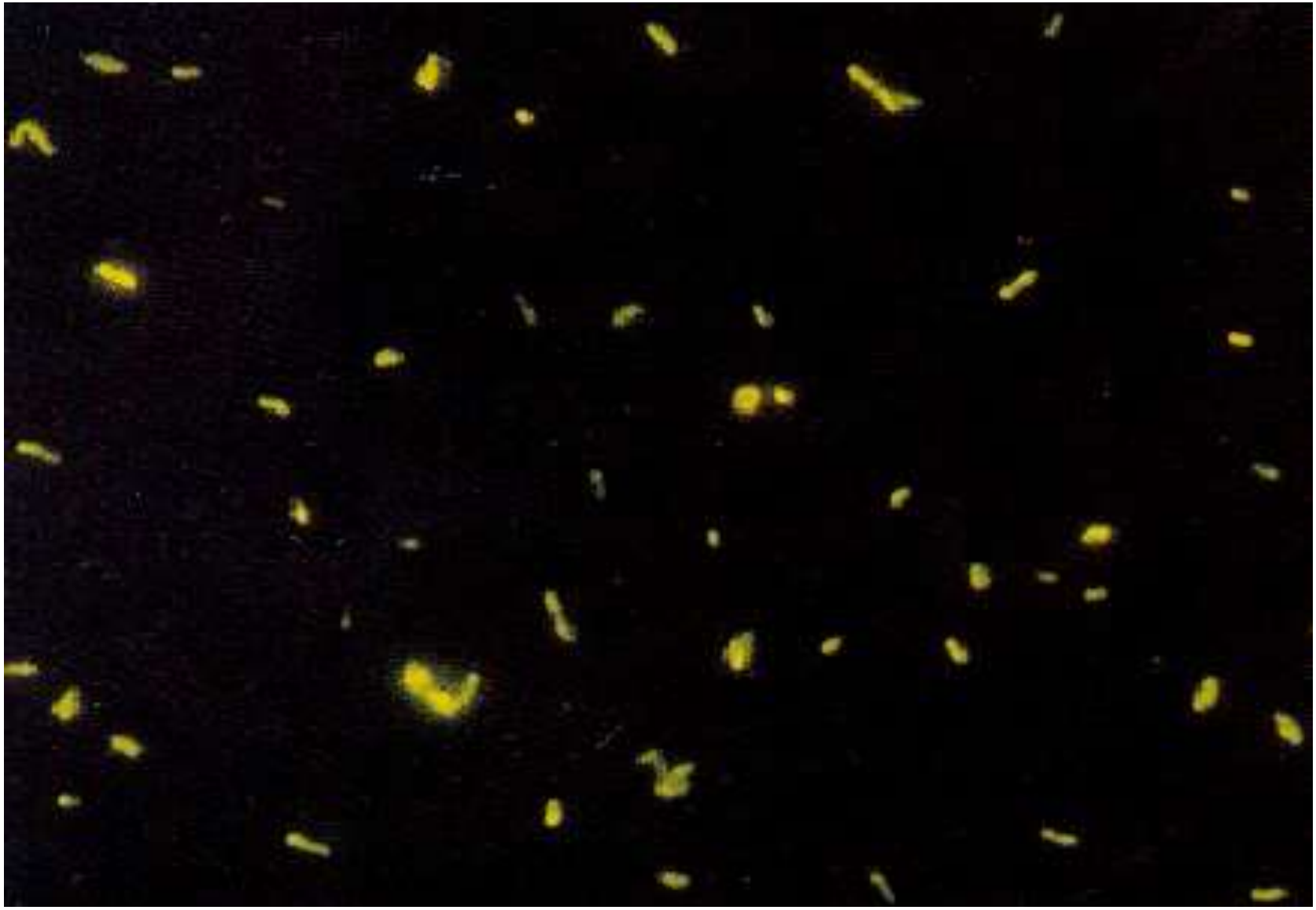
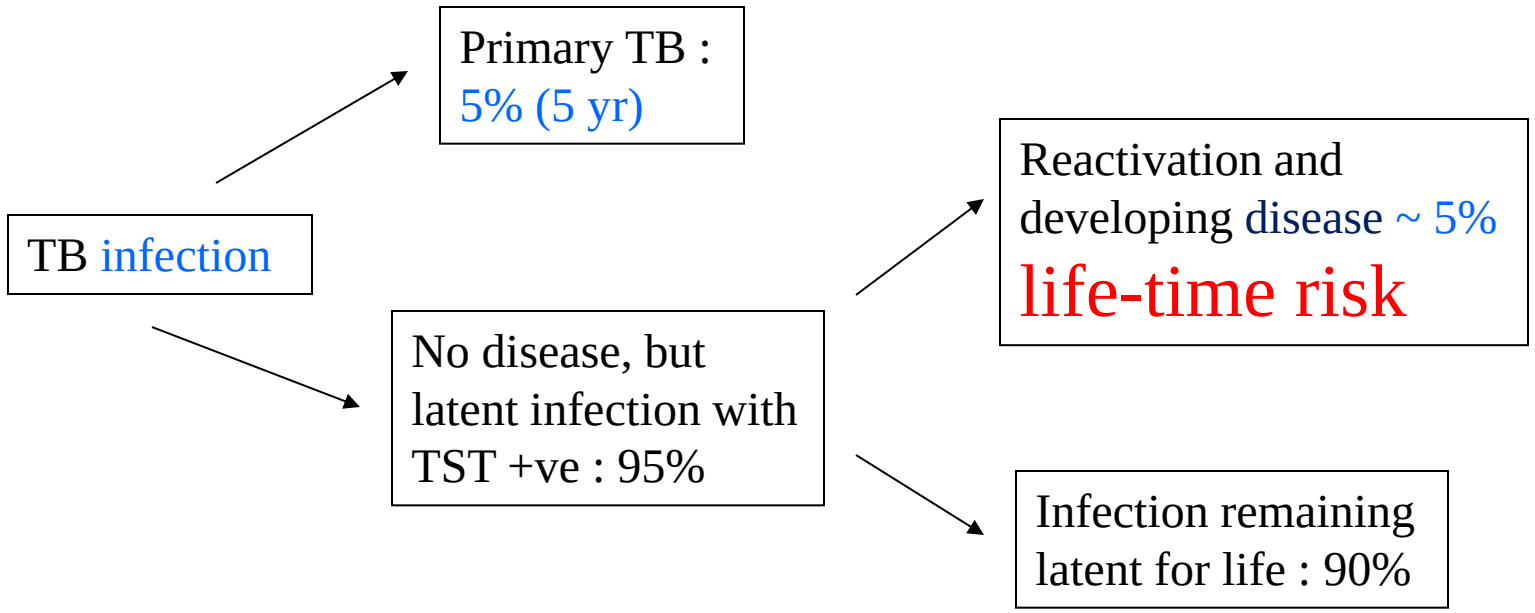


Auramine-O staining of AFB under Fluorescence Microscopy

Natural history of tuberculosis

Exposure → Infection → Disease



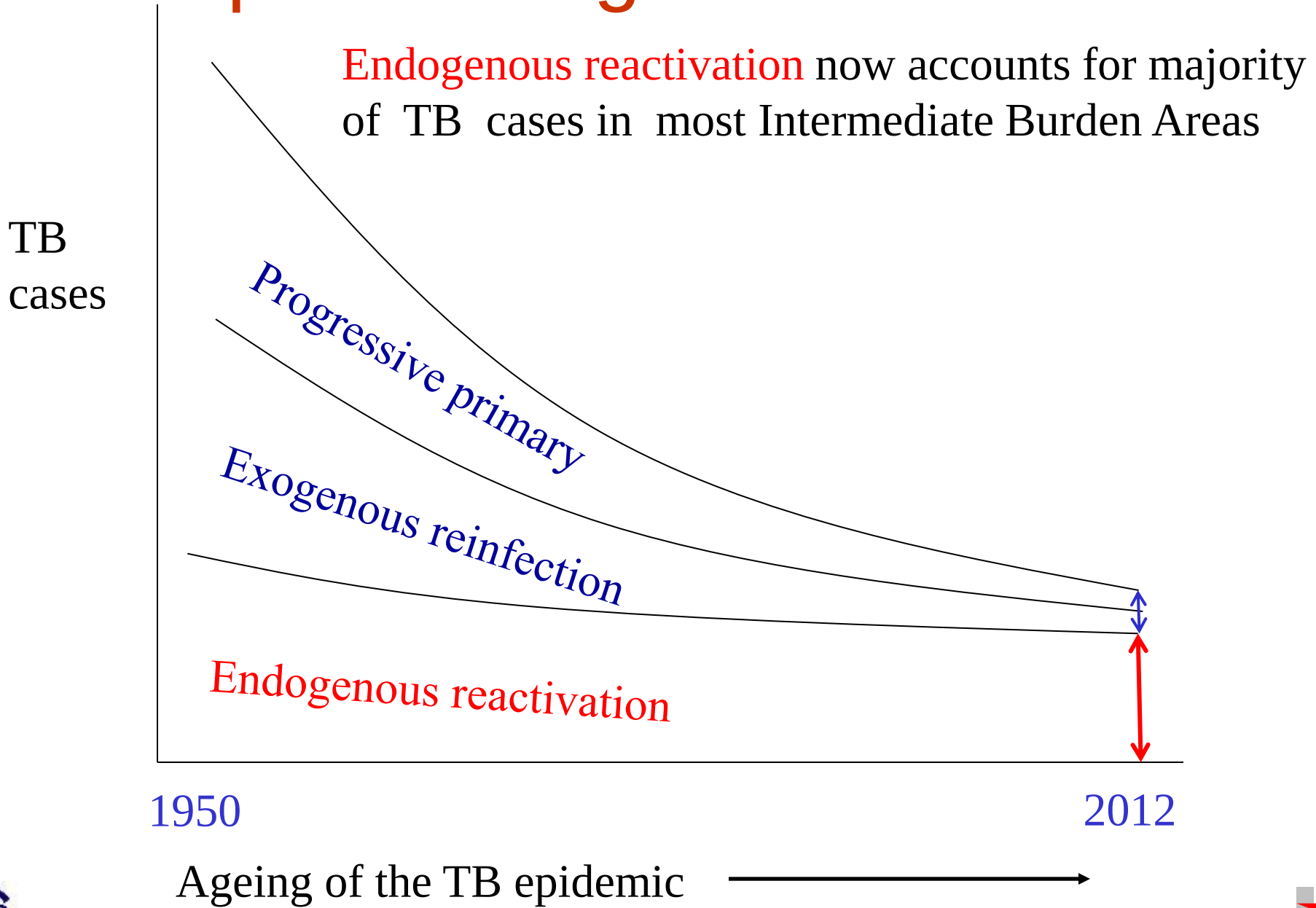
Tuberculosis (TB) notification rates

Year	TB notification		TB deaths	Death / Notifications (%)	TB notification rate (per 100,000 population)
	Total	Chinese immigrants < 7 years			
2010	5093	80	191	3.75	72.5
2011	4794	81	187	3.90	67.8
2012	4858	100	199	4.10	67.9
2013	4664	92	178	3.82	64.9
2014	4705	85	187	3.97	65.0
2015*	4498	81	167	3.71	61.6

* Provisional Figure

Ref: Annual Report 2013. TB & Chest Service, Department of Health, Hong Kong

Epidemiological Transition



TB notification rates by age groups

Age Group	TB notification rate (per 100,000 population) in 2015 *
< 10	< 2
10-14	6.82
15-19	28.48
20-49	39.83-45.18
50-54	51.33
55-59	71.77
60-64	87.06
65-69	100.47
70-74	138.06
75-79	159.62
80-84	212.75
≥ 85	277.35

* Provisional Figure

Ref: http://www.chp.gov.hk/en/data/1/10/26/43/5104.html

What is latent infection with *M. tuberculosis* (LTBI)*?*

LTBI is a spectrum

Clinical disease

Subclinically active infection: Bacterial replication maintained at a subclinical level by the immune system

Quiescent infection: Infection controlled with some bacteria persisting in a non-replicating form

Infection **eliminated** by acquired immunity in associated with T cell priming

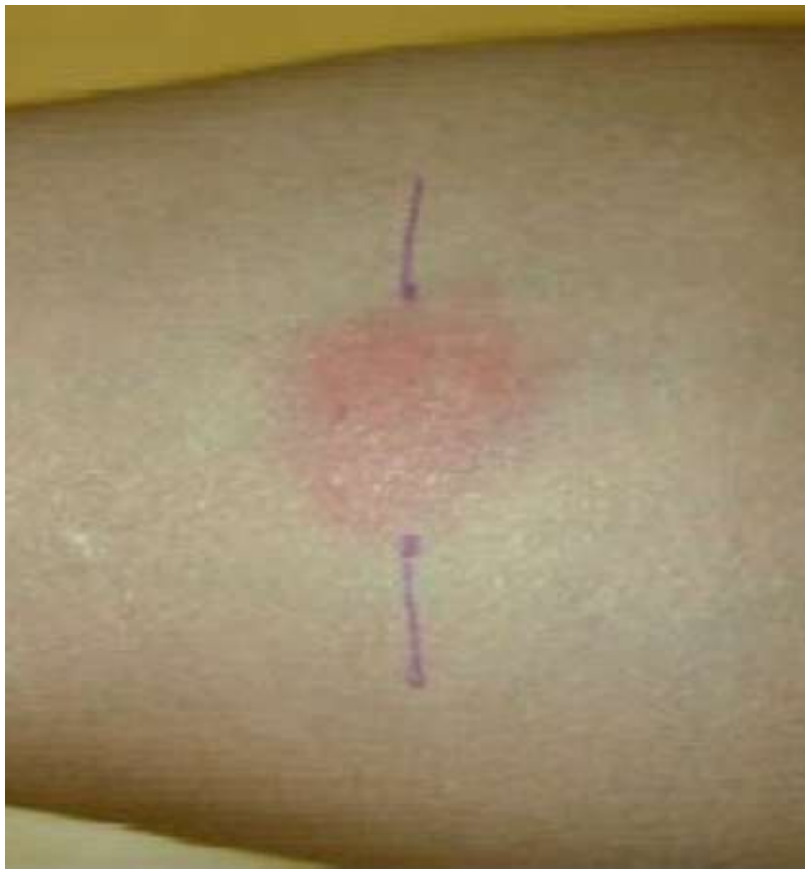
Infection **eliminated** by innate immunity without priming antigen-specific T cells

Reference: Barry et al. Nat Rev Microbiol 2009; 7: 845-855

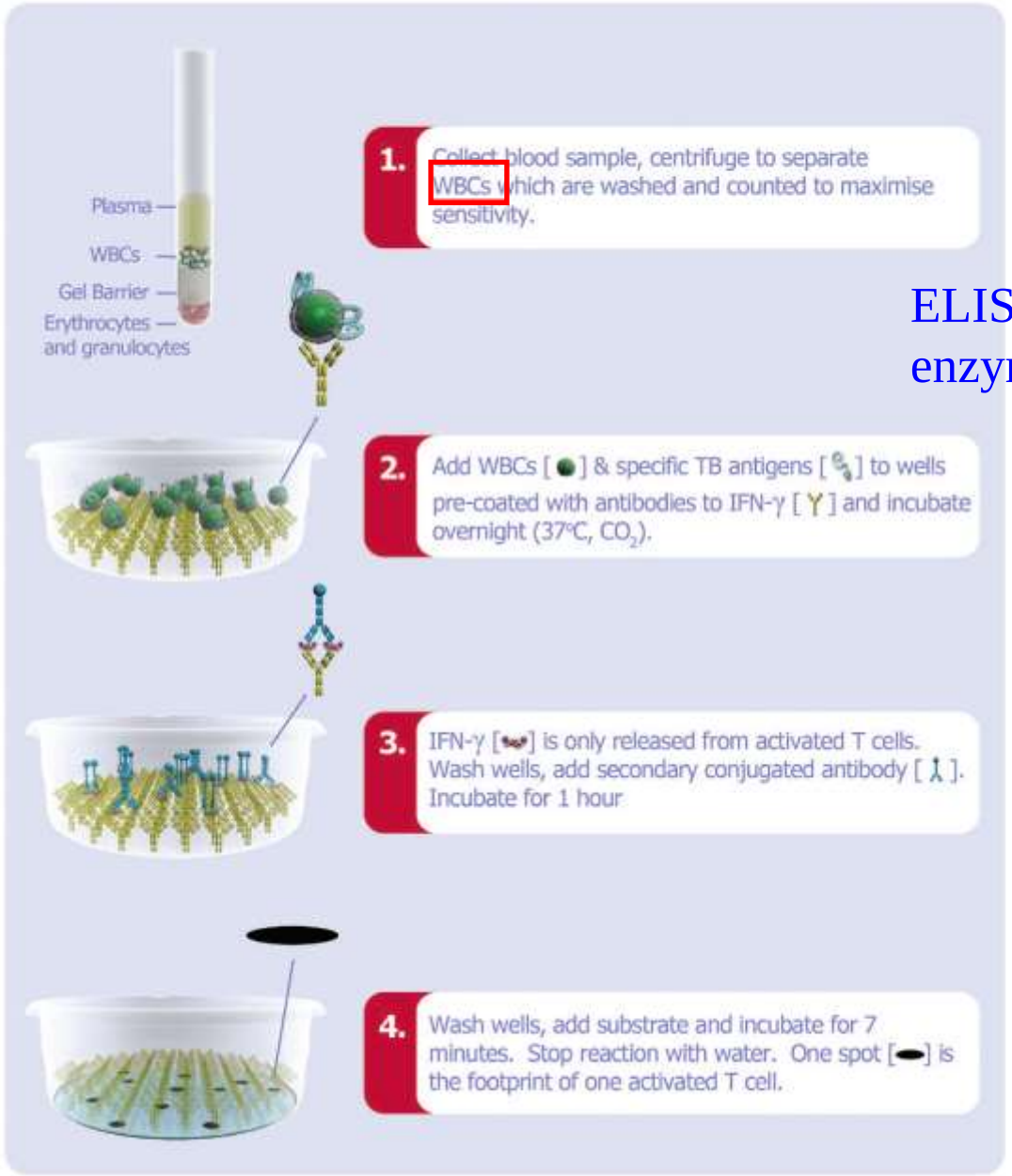
Diagnostic tools for LTBI

- Measurement of specific host immune responses
- Methods
  - **Tuberculin skin test (traditional standard)**
    - Use PPD RT 23 two units
  - **Interferon-γ release assay (IGRA)**
    - More specific antigens: ESAT6, CFP10, (TB 7.7)
      - T-Spot.*TB*® (Oxford Immunotec) (Separate monocyte layer from fresh blood)
      - QuantiFERON® -TB Gold / In-tube (Cellestis) (Fresh whole blood)
  - Serological tests: not useful

Mantoux test: intradermal injection of Tuberculin Purified Protein Derivative



Principles of the T-SPOT® Assay System



ELISPOT =
enzyme-linked immunospot

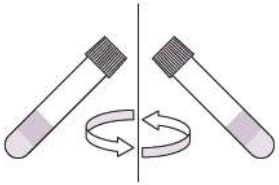
Reference: Oxford Immunotec

Blood sampling and incubation

Collect patient blood into blood collection tubes and **SHAKE** vigorously to mix.

Incubate tubes **upright** at 37°C for 16 to 24 hours.

Following incubation, centrifuge tubes for 15 minutes at 2000 to 3000g RCF (g) to separate the plasma and the red cells.



Following centrifugation, harvest plasma sample from each tube for IFN-γ quantification.

Equilibrate ELISA components, with the exception of the Conjugate 100X Concentrate, to room temperature for at least 60 minutes.

Reconstitute the Kit Standard to 8.0 IU/mL with distilled or deionised water. Prepare four (4) standard dilutions.

Reconstitute freeze-dried Conjugate 100X Concentrate with distilled or deionised water.

Prepare working strength conjugate in Green Diluent and add 50µL to all wells.

Add 50µL of test plasma samples and 50µL of standards to appropriate wells. Mix using shaker.

Incubate for 120 minutes at room temperature.

Wash wells at least 6 times with 400µL/well of wash buffer.

Add 100µL Enzyme Substrate Solution to wells. Mix using shaker.

Incubate for 30 minutes at room temperature.

Add 50µL Stop Solution to all wells. Mix using shaker.

Read results at 450nm with a 620 to 650nm reference filter.

Analyse Results.

IFN-gamma ELISA

ELISA = enzyme-linked immunosorbent assay

Reference: Qiagen

Latent infection with *M. tuberculosis*

- Pragmatically defined as presumptive infection with M. tuberculosis complex, as evidenced by a positive tuberculin skin test (TST) reaction and/or a positive interferon-ϒ release assay (IGRA) result without any sign of clinically or radiologically manifest disease.
- Asymptomatic and NON-INFECTIOUS
- Do not notify LTBI.

TST vs. IGRA: differences (1)

	TST	QuantiFERON TB (QFT) Gold/ In-Tube (IT)	T-SPOT.TB
Nature	In vivo	Ex vivo	Ex vivo
Antigens	Mixture in PPD; shared by BCG	More TB-specific: ESAT-6, CFP-10, (TB7.7)	More TB-specific: ESAT-6, CFP-10
Interference by BCG	Yes	No	No
Exposure correlation	Some, especially if not BCG-vaccinated	Higher	Higher/ highest?
Method	Manually measuring induration, read 48-72 hours later	ELISA (can be automated), plasma can be stored for ~ 8 weeks at 4 ^{o}C	ELISPOT (can be automated), completed within 2 days
Need of support by laboratory	No	High; fresh blood delivery	Highest; fresh blood and cell separation
Inter-reader variability	Can be substantial	Minimal	Minimal
No. of visits	2	1	1

ELISA = enzyme-linked immunosorbent assay ELISPOT = enzyme-linked immunospot

Reference: Leung CC et al. Eur Respir J. 2011;37:690-711

TST vs. IGRA: differences (2)

	TST	QFT TB Gold/ IT	T-SPOT.TB
Choice of cutoff	5, 10, 15 mm by clinical scenario; higher disease risk with larger induration	Single	Single
Sensitivity specificity trade-off	Yes	Not fully clarified	Not fully clarified
Advanced age	Significantly affected	Less affected	Less affected
Immune compromise	Significantly affected	Less affected	Less affected/ Least?
Proxy sensitivity	71-82%	QFT-Gold: 73-82% QFT-Gold IT:63-78%	86-93%
Proxy specificity	No BCG: 95-99% BCG: low, heterogeneous	No BCG: 98-100% BCG: 94-98%	86-100%
Conversion	Criteria established	Not fully clarified	Not fully clarified
Booster effect	Yes	No (prior TST may affect)	No (prior TST may affect)
Longitudinal data	Abundant	Less	Less

Reference: Leung CC et al. Eur Respir J. 2011;37:690-711

TST vs. IGRA: similarities

- Both are indirect measures of TB infection
- NEITHER rules in active TB
- NEITHER rules out
  - active TB or LTBI in the immunocompromised
- NEITHER tells
  - recent vs. remote infection
- NEITHER determines
  - treatment efficacy

Species Specificity of IGRA TB Antigens

Species	ESAT-6	CFP-10	TB7.7
M. tuberculosis	+	+	+
M. africanum	+	+	+
M. bovis	+	+	+
BCG strains	-	-	-
Most NTM	-	-	-
M. kansasii	+	+	+
M. marinum	+	+	+
M. szulgai	+	+	+

ESAT-6 = 6-kDa early secretory antigenic target

CFP-10 = 10-kDa culture filtrate protein

Screening for LTBI
Universal vs. Targeted

Targeted screening is the currently recommended approach.

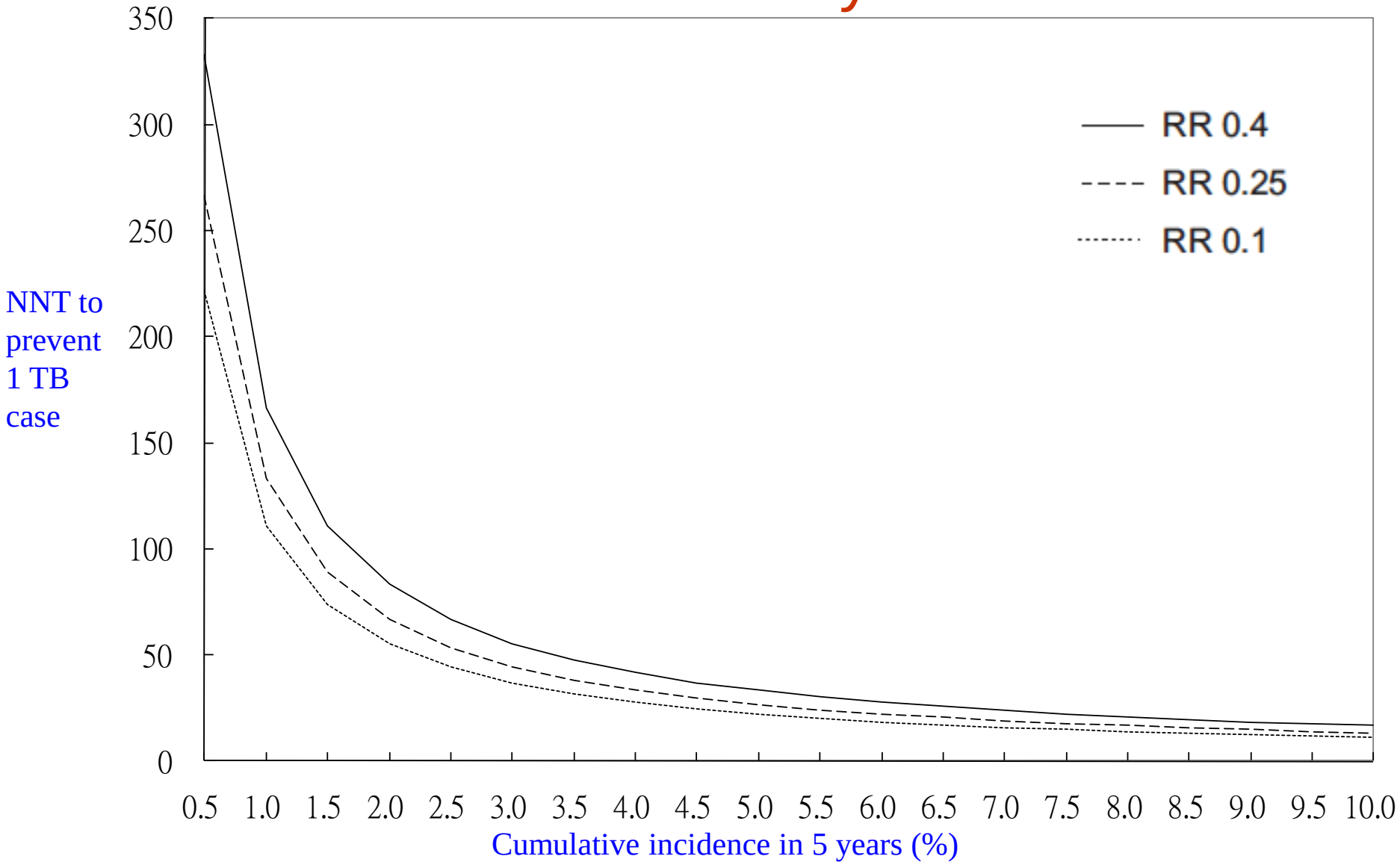
Ref: Leung CC, et al. Eur Respir J. 2011;37(3):690-711

Targeted screening for LTBI

- Target = high-risk groups
- Screening = intention to treat in order to prevent TB disease

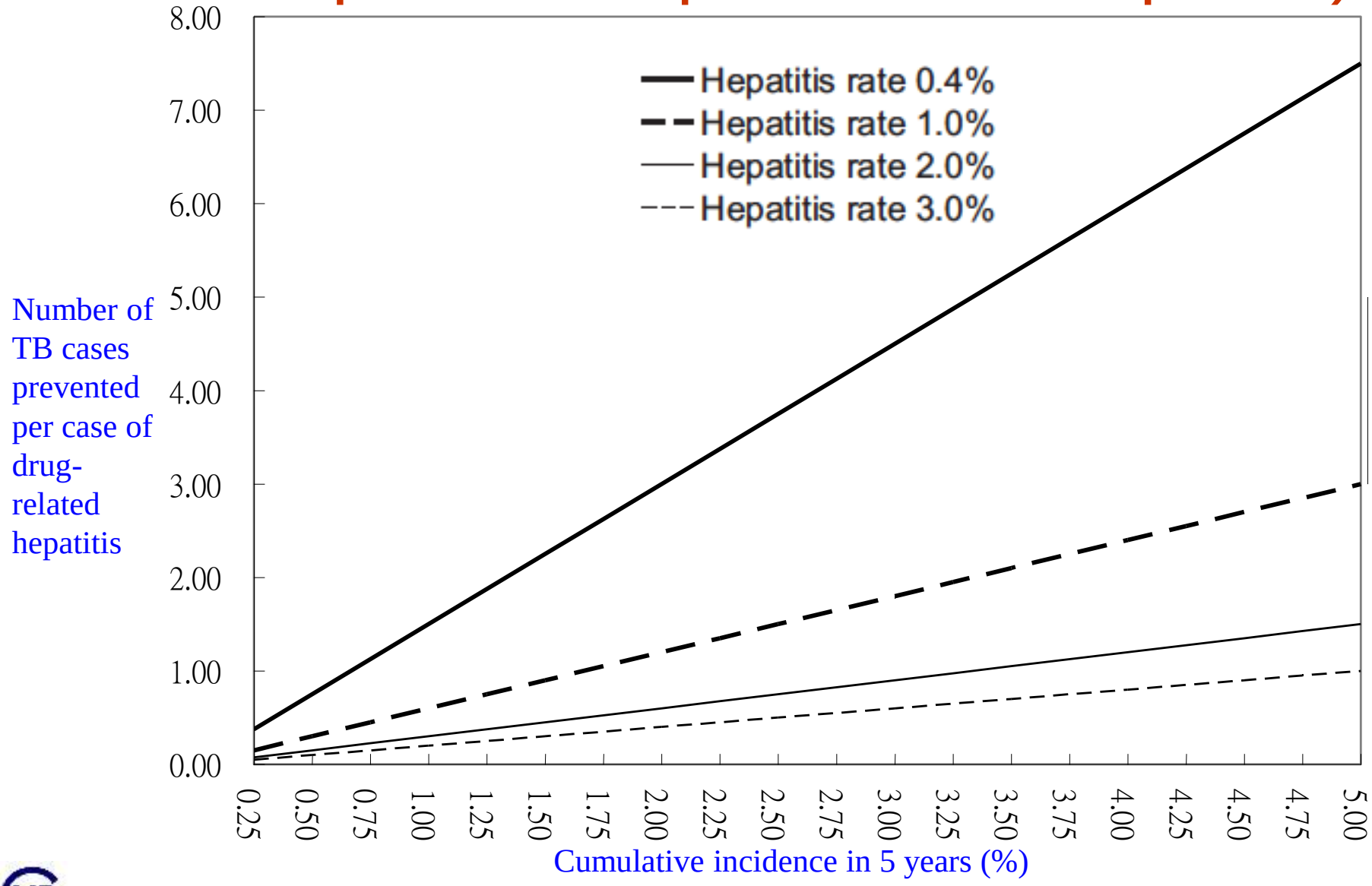
Ref: Leung CC, et al. Eur Respir J. 2011;37(3):690-711

Number needed to treat (NNT) to prevent 1 TB case in 5 years



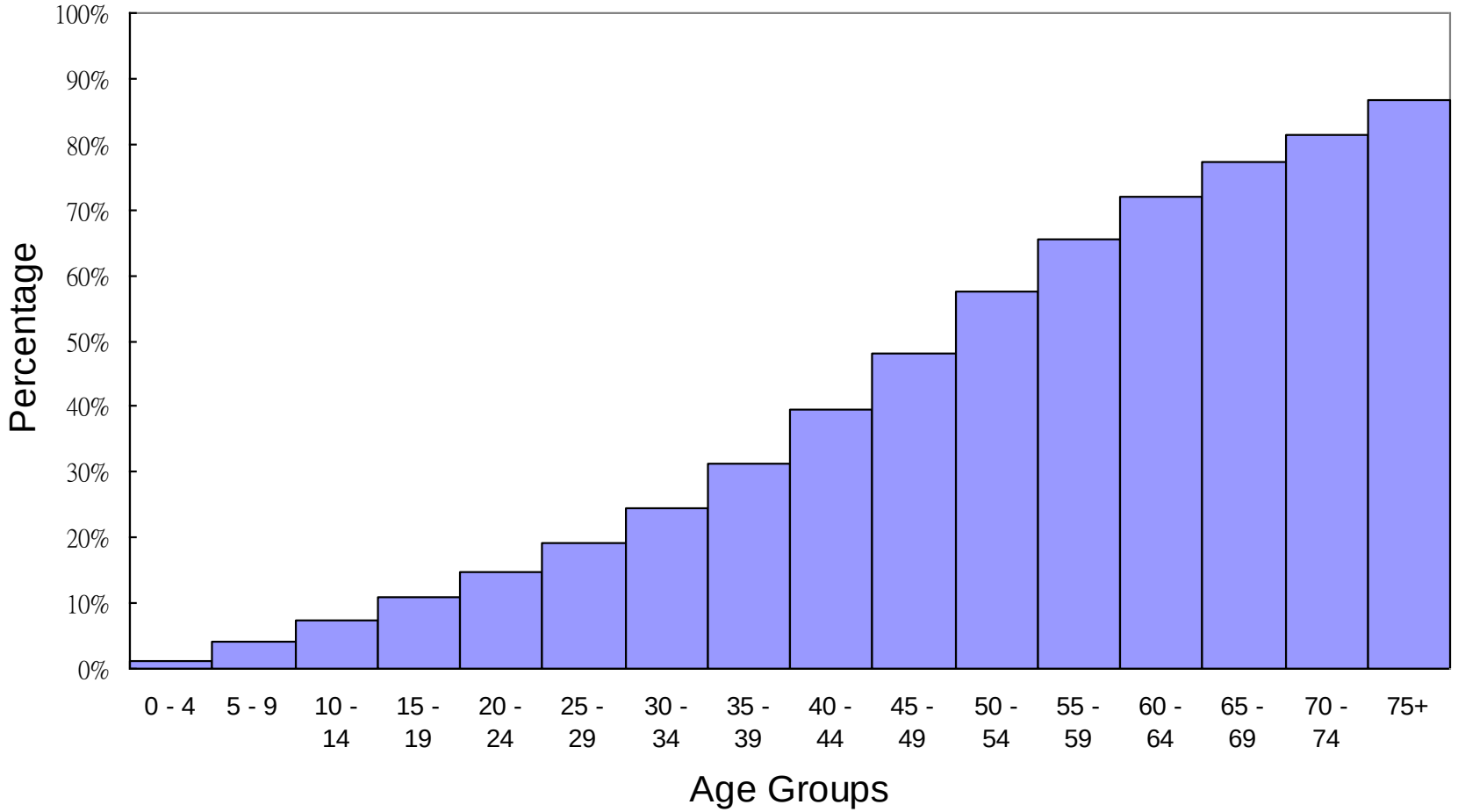
Reference: Leung CC et al. Eur Respir J. 2011;37:690-711

Benefit versus Risk Ratio (Number of TB cases prevented per case of hepatitis)



Reference: Leung CC et al. Eur Respir J. 2011;37:690-711

Estimated Infection Rate (HK)



*Estimation based on: Incidence (smear-positive cases) = ARI * Styblo ratio

Who are the TB high-risk groups that we may target?

Ref: Leung CC, et al. Eur Respir J. 2011;37(3):690-711

Incidence/ relative risk of active TB

		Incidence of disease among tuberculin-positive subjects (per 1000 person-years	Relative Disease Risk
Recent TB infection	Infection < 1 year past	12.9	
	Infection 1-7 year past	1.6	
Old TB scar		2.0-13.6	
HIV infection		35.0-162	
Body Mass Index	< 18.5		2.11
Diabetes mellitus (DM)	DM vs no DM		1.8-4.1
	HbA1c ≥ 7% vs. < 7%		3.1
Chronic renal failure			10.0-25.3
Renal Transplant			37
Heart Transplant			20-74
Head and neck carcinoma			16
Silicosis		68	30
Smoking	Current smokers		2.63
	Ex-smokers		1.41
	Never smokers		1.00
Passive smoking			1.49

Ref: Leung CC, et al. Eur Respir J. 2011;37(3):690-711

TB Risk in RA (2004-08 HK cohort)

RA cohorts	No of patients at risk	Observed TB cases	*Expected TB cases	#Population denominator	SIR	95% CI	p-value
RA combined	2441	20	6.954	6972	2.876	1.55-5.35	<0.001
TNF blockers naïve RA	2424	16	6.839	5706	2.354	1.17-4.67	0.013
TNF blockers treated RA	81	4	0.115	2829	34.922	8.89-137.20	<0.001

~15x RA

*Expected number of TB cases at the sex and age-adjusted rate of the Hong Kong population.
Size of hypothetical control population of same sex and age mix as the RA cohorts and with similar sex and age-adjusted TB rates as the Hong Kong population that would be expected to give the same number of observed TB cases within the same period.
Independent explanatory variables associated with an increase risk of active TB included older age at study entry (RR 1.05, p=0.013) a past history of pulmonary TB (RR 5.48, p=0.001), extra-pulmonary TB (RR 16.45, p<0.001), Felty's syndrome (RR 43.84, p=0.005), prednisolone >10mg daily (RR 4.44, p=0.009) and the use of TNF blockers (RR 12.48, p<0.001).

Reference: Tam LS, et al. Clin Exp Rheumatol 2010;28:679-85.

Targeted screening and treatment of LTBI

Target group	TST cutoff
1. Household contacts (esp. < 35 years old) of a smear+ source	Age > 1 year: 15 mm Age < 1 year: 5 mm
2. Silicosis	10 mm
3. HIV-infected	5 mm
4. Immunosuppression/ Use of biologics especially TNF blocker	Before immunosuppression: 10 mm After immunosuppression: 5 mm*

* if not screened at baseline, or > baseline when screened again for a new indication

Ref: TB & Chest Service, Department of Health of Hong Kong SAR. Guidelines on targeted tuberculin testing and treatment of latent tuberculosis infection (Internal guidelines). 2015.

How good are TST/ IGRA for predicting TB disease?

Which test to use?

Field performance of a test: factors

- **Test characteristics**
  - Sensitivity and specificity
- **Predictive values**
  - Positive Predictive Value (PPV)
  - Negative Predictive Value (NPV)
  - Sensitivity, specificity, prevalence
- **Risk ratio (RR)** or **Incidence rate ratio (IRR)**
  - RR = TB disease risk among test-positive/ TB disease risk among test-negative
  - IRR: censoring, follow-up duration
  - RR = PPV/(1-NPV)

Systematic review: IGRA vs. TST

Test	Pooled unadjusted IRR (95% CI)
IGRA	2.11 (1.29–3.46)
TST (cutoff = 10 mm)	1.60 (0.94–2.72)
TST (cutoff = 5 mm)	1.43 (0.75–2.72)

IRR = incidence rate ratio

- Compared with test-negative results, IGRA-positive and TST-positive results were much the same with regard to the risk of tuberculosis in five studies that used both methods.
- Until more predictive biomarkers are identified, existing tests for LTBI should be chosen on the basis of relative specificity in different populations, logistics, cost, and patients' preferences rather than predictive ability alone.
- Performance of IGRA could be better in high income areas, but potential bias prevent firm conclusion.

Ref: Rangaka MX et al. Lancet Infect Dis 2012; 12:45-55

T-SPOT.TB vs. TST in predicting active TB among patients with silicosis in Hong Kong

	T-SPOT.TB	TST (Cutoff = 5mm)	TST (Cutoff = 10mm)	TST (Cutoff = 15mm)
Test positive [a]	151	161	136	89
Test negative [a]	90	80	105	152
Active TB cases predicted [b]	12	9	9	4
Active TB cases missed [b]	1	4	4	9
Sensitivity % (95% CI)	92.3 (64.6-100.0) [c]	69.2 (42.0-87.7)	69.2 (42.0-87.7)	30.8 (12.4-58.0)[c]
Specificity % (95% CI)	39.0 (32.9-45.5) [c]	33.3 (27.5-39.7)	44.3 (38.0-50.8)	62.7 (56.3-68.7)[c]
PPV % (95% CI)	7.9 (4.5-13.5)	5.6 (2.8-10.4)	6.7 (3.4-12.3)	4.5 (1.4-11.4)
Positive results per case predicted	13 (8-23)	18 (10-36)	16 (9-30)	23 (9-72)
NPV % (95%CI)	98.9 (93.4-100.0)	95.0 (87.5-98.4)	96.2 (90.3-98.8)	94.1 (89.0-97.0)
Negative results per case missed	90 (16- >10000)	20 (8-63)	27 (11-84)	17 (10-34)
IRR (test positive/ test negative)	8.50 (1.11-65.4)[d]	1.00 (0.31–3.25)	1.69 (0.52–5.50)	0.72 (0.22–2.33)[d]

a. Excluding subjects treated for LTBI.
b. Prevalence of TB disease = 13/241 = 5.4%
c. T-SPOT.TB vs. TST (cutoff) with $P < 0.001$
d. T-SPOT.TB vs. TST (cutoff) with $P < 0.05$

Ref: Leung CC et al. Am J Respir Crit Care Med 2010;182:834-840

T-SPOT.TB vs. TST in predicting active TB among household contacts in Hong Kong

	T-SPOT.TB	TST (Cutoff = 5mm)	TST (Cutoff = 10mm)	TST (Cutoff = 15mm)
Test positive [a]	244	503	337	119
Test negative [a]	621	362	528	746
Active TB cases predicted [b]	15	18	17	8
Active TB cases missed [b]	5	2	3	12
Sensitivity % (95% CI)	75.0 (50.9–91.3) [c]	90.0 (68.3–98.8)	85.0 (62.1–96.8)	40.0 (19.1–63.9) [c]
Specificity % (95% CI)	72.9 (69.8–75.9) [d]	42.6 (39.2–46.0) [d]	62.1 (58.8–65.4) [d]	86.9 (84.4–89.1) [d]
PPV % (95% CI)	**6.1(3.5–9.9)**	**3.6 (2.1–5.6)**	**5.0 (3.0–8.0)**	**6.7 (2.9–12.8)**
Positive results per case predicted (95% CI)	16 (10–29)	28 (18–47)	20 (13–34)	15 (8–34)
NPV % (95%CI)	**99.2(98.1–99.9)**	**99.4 (98.0–99.9)**	**99.4 (98.3–99.9)**	**98.4 (97.2–99.5)**
Negative results per case missed (95% CI)	124 (54–382)	181 (50–1493)	176 (61–853)	62 (36–120)
IRR (test positive vs. test negative)	7.7 (2.8–21.2)	6.4 (1.5–27.5)	8.8 (2.6–30.1)	4.2 (1.7–10.3)

a. Excluding subjects treated for LTBI.
b. Prevalence of TB disease = 20/865 = 2.3%
c. T-SPOT.TB vs. TST (cutoff) with $P < 0.05$
d. T-SPOT.TB vs. TST (cutoff) with $P < 0.001$

Ref: Leung CC et al. Respirology 2015;20:496-503

Targeted screening for LTBI among the HIV-infected in Hong Kong

- TST: cutoff at 5 mm
  - Treatment is indicated for HIV infected patients with significant recent exposure to an infectious source of TB regardless of TST results.
- IGRA is an acceptable alternative.
- Dual testing by TST and IGRA:
  - Advisable when CD4 count <100/μL
  - A positive result with either test is an indication for treatment.
  - Blood should be drawn for IGRA before or on the same day as placing the TST to avoid potential PPD sensitisation.

Ref: Scientific Committee on AIDS and STI (SCAS), Centre for Health Protection, Department of Health. Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection. March 2015

Treatment of LTBI:
assuming no drug resistance in the source case

LTBI: Isoniazid (INH) Preventive Treatment

- 6-12 m: Efficacy
  - Meta-analysis
    - 73375 subjects, 11 RCT, HIV/non-HIV, 6-12 months
    - Risk reduction: 60% [Risk ratio 0.40 (95% CI 0.31-0.52)]
  - IUAT trial
    - 1970s, Eastern Europe, 28000 subjects, previously untreated fibrotic lesions
    - Risk reduction: 21% (3H), 65% (6H), 75% (12H)
    - Risk reduction (good compliance): 30% (3H), 69% (6H), 93% (12H)
    - Cost-effectiveness analysis: 6H best (adopted by most public health programmes)
  - Comstock (1999):
    - 9-10H conferred optimal protection
    - Efficacy (9H) ~ 90% (ATS/ US CDC recommends)

References: 1. Leung CC et al. Eur Respir J 2011; 37: 690–711
2. Chee CB et al. Respirology 2013;18:205–216

LTBI: Isoniazid (INH) Preventive Treatment

- Prolonged INH therapy
  - Non-HIV infected: > 12m NOT useful
  - HIV-infected: CONFLICTING findings from RCTs

Treatment regimen	Studies	Efficacy
6H vs. 36H	RCT (Botswana) [Ref: Samandari T et al Lancet. 2011;377:1588-98]	▪ ART was provided to those with CD4 <200/mL. ▪ 36H was more effective than 6H for preventing TB in those who were TST-positive. ▪ ART independently reduced TN incidence by 50%.
3HP vs. 3HR vs. continuous H (up to 6 years) vs. 6H	RCT (South Africa) [Ref: Martinson NA et al N Engl J Med 2011;365:11-20]	▪ Median CD4 484/mL ▪ ART not given ▪ None of the alternative regimens were superior to 6H. ▪ Serious adverse reactions more common in the continuous H group than in the other groups (18.4 per 100 person-years vs. 8.7–15.4 per 100 person-years).

References: 1. Leung CC et al. Eur Respir J 2011; 37: 690–711
2. Chee CB et al. Respirology 2013;18:205–216

LTBI: Isoniazid (INH) Preventive Treatment

- Primary INH prophylaxis
  - RCT: No improvement
    - HIV-infected children: TB disease-free survival
    - HIV-uninfected BCG-vaccinated children: TB infection-free survival

    [Madhi SA et al. N Engl J Med. 2011;365:21-31]

References: 1. Leung CC et al. Eur Respir J 2011; 37: 690–711.

Risk of INH-related hepatitis

Age group	Risk
20 - 34	0.3%
35 - 49	1.2%
50 - 64	2.3%
> 64	4.6%

Ref: Kopanoff DE, et al. Am Rev Respir Dis 1978;117:991.

LTBI: Alternative regimens (1)

- Rifampicin monotherapy (4 months): 4R
  - 4 RCT (vs. 9H): well-tolerated (3), efficacy data (1)
  - Meta-analysis of 4 RCT
    - non-completion (relative risk 0.53; 95% CI 0.44–0.63)
    - hepatotoxicity (relative risk 0.12; 95% CI 0.05–0.30)
    - cost-effective, US$213 savings per patient treated
  - A multicentre trial comparing 4R vs. 9INH
    - ongoing

References: 1. Leung CC et al. Eur Respir J 2011; 37: 690–711
2. Chee CB et al. Respirology 2013;18:205–216

LTBI: Alternative regimens (2)

- Isoniazid + rifampicin (3 months): 3HR
  - Hong Kong Silicosis Study
    - RCT (6H vs. 3HR vs. 3R vs. placebo),
    - Risk ratio (95% CI): 6H = 0.58 (0.36-0.94) vs. 3HR = 0.64 (0.39-1.03) vs. 3R = 0.48 (0.29-0.80)
    - Efficacy ~ 36%
  - Meta-analysis of 5 RCT (3-4 months HR)
    - 6H (3), 9H (1), 12H (1, HIV-infected)
    - 3HR not different from 6-12 INH therapy by efficacy, severe side-effects and mortality
  - Overall efficacy ~ 65%

References: 1. Leung CC et al. Eur Respir J 2011; 37: 690–711
2. Chee CB et al. Respirology 2013;18:205–216

LTBI: Alternative regimens (3,4)

- Isoniazid + rifapentine (weekly for 12 weeks): 3HP
  - RCT (Schechter M et al, 2006): largely HIV-uninfected
  - RCT (Martinson NA et al, 2011): HIV-infected
  - RCT (Sterling TA et al, 2011): largely HIV-uninfected
- Rifampicin plus pyrazinamide (2 months)
  - [NOT recommended]
  - excess hepatotoxicity in non-HIV infected

RCT: 3HP (Sterling TA et al, 2011)

- US, Canada, Brazil, Spain
- 3HP vs. 9H
- 7731 subjects, largely HIV-uninfected, followed for 33 months
- Non-inferiority trial: non-inferiority margin=0.75%
- Cumulative TB incidence
  - 0.19% (3HP) and 0.43% (9H)
  - Difference = 0.24%
  - 3HP is non-inferior to 9H
- Effective in immunocompentent and HIV-infected
- Rifamycin resistance: no evidence (too few isolates)

Treatment completion is more likely with 3HP than 9H

Permanent drug discontinuation	Isoniazid daily for 9 months (n = 3759)	Isoniazid and Rifapentine once weekly for 12 weeks (n = 4040)	P value
For any reason	1160/3745 (31.0%)	713/3986 (17.9%)	<0.001
Because of an adverse event	139/3745 (3.7%)	196/3986 (4.9%)	0.009

Reference: Sterling TR et al. N Engl J Med 2011;365:2155-66

3HP is less hepatotoxic than 9H

Adverse events attributable to drug	Isoniazid daily for 9 months (n = 3759)	Isoniazid and Rifapentine once weekly for 12 weeks (n = 4040)	P value
Related to drug	206 (5.5%)	332 (8.2%)	<0.001
Hepatotoxicity	103 (2.7%)	18 (0.4%)	<0.001
Rash	21 (0.6%)	31 (0.8%)	0.26
Possible hypersensitivity	17 (0.5%)	152 (3.8%)	<0.001
Others	65 (1.7%)	131 (3.2%)	<0.001

Reference: Sterling TR et al. N Engl J Med 2011;365:2155-66

Treatment of LTBI:
assuming drug resistance in the source case

Preventive treatment for contacts of drug-resistant TB

Scenario	Evidence	Options
H-resistant TB contacts	Case series ▪ Contacts given 6R did not develop active TB ▪ Contacts given isoniazid monotherapy had the same rate of active TB as those not given treatment.	▪ 4R or 6R ▪ 2RZ (generally not recommended)
MDR-TB contacts	Systematic review ▪ It is not possible to support or reject the use of preventive treatment.	▪ At least two drugs (combinations of Z, E and/or FQ) for 6–12 months according to source case's DST results (US CDC) ▪ Fluoroquinolone monotherapy ▪ High-dose H and a FQ (ideally levofloxacin) for ≥ 6 months in children under 5 or HIV-infected. ▪ Close observation for ≥ 2 years for contacts who are otherwise healthy and do not have risk factors for rapid disease progression and dissemination (UK health authorities, WHO, and European CDC)

Reference: Chee CB et al. Respirology 2013;18:205–216

Summary

- Operational definition of LTBI
- Targeted screening of LTBI
  - It is unrealistic to screen and treat all.
  - Target at high-risk groups, more for personal protection than public health
  - Screening is with an intent to treat.
- Diagnostic tools
  - TST vs. IGRA
  - Parameters for evaluating diagnostic tools
- Treatment options

Thank you