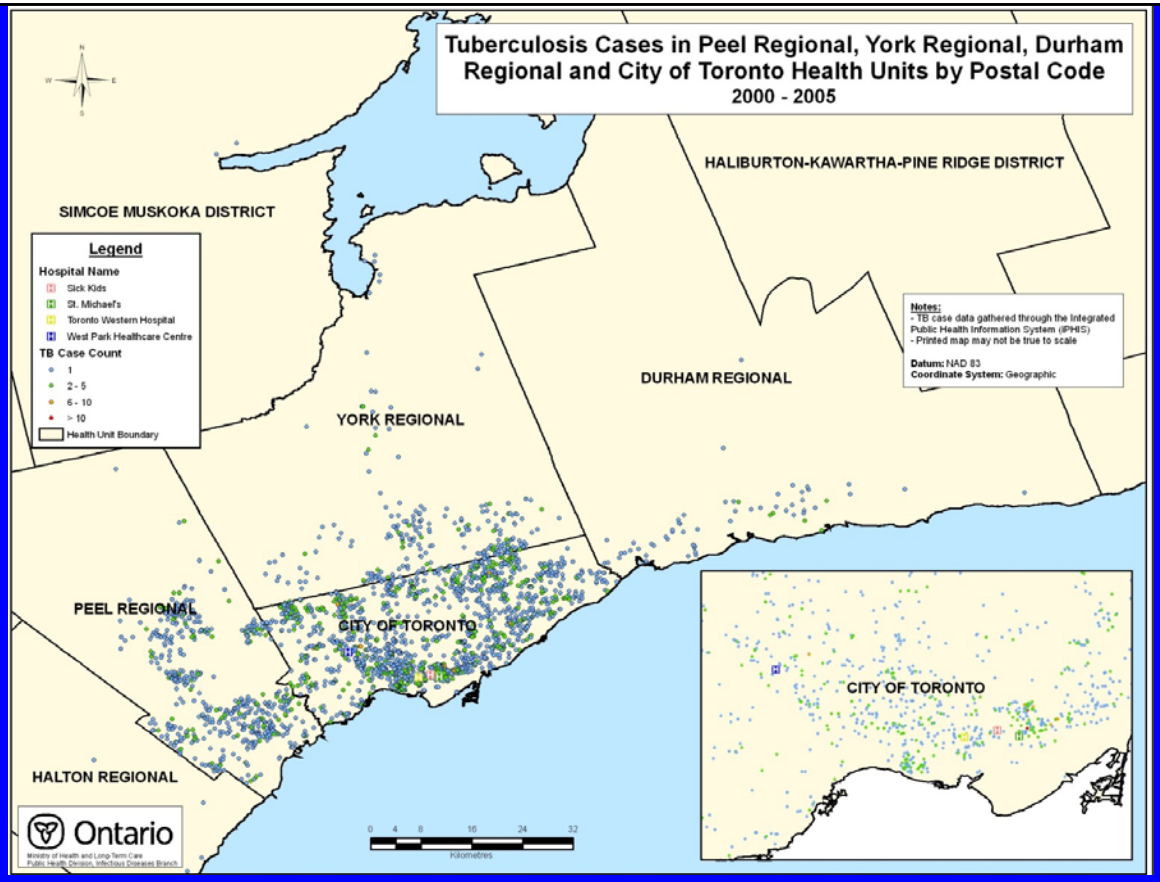


Tuberculosis in Primary Care
COC GTA Spring Symposium

Dr Elizabeth Rea April 2013

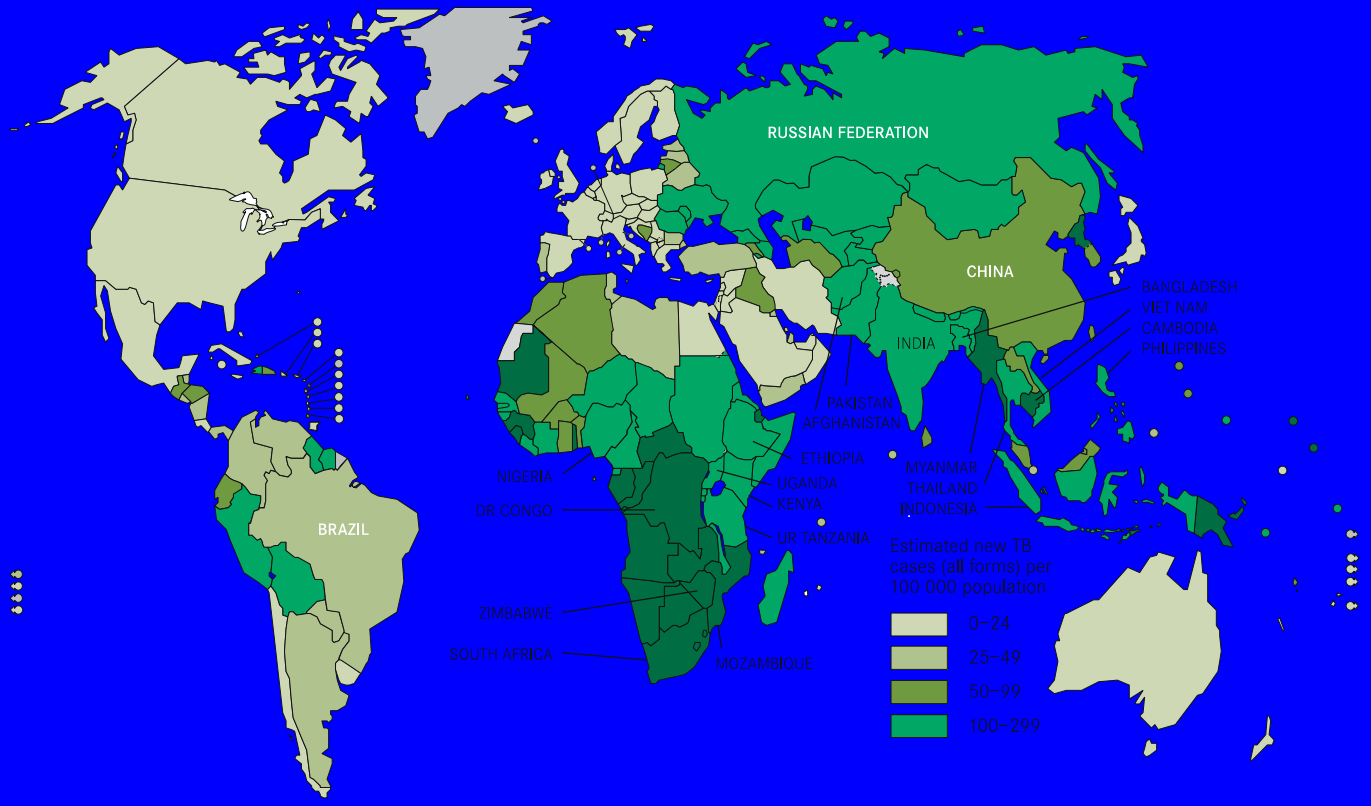
TORONTO Public Health

- TB in Toronto - risk groups
- Diagnosis of active TB
- LTBI – diagnosis and management
- Infection control

TB in Toronto Case #1

- 68 yr man from China – landed immigrant, lives with daughter, son-in-law, 3 grandchildren
- Diabetes, hypertension, ?renal failure
- 2m hx cough, chest pain, weight loss 20lb, fatigue
- Pleural effusion, nodules on CXR
- TB Smear 2+, culture positive
- 1 grandchild = secondary case

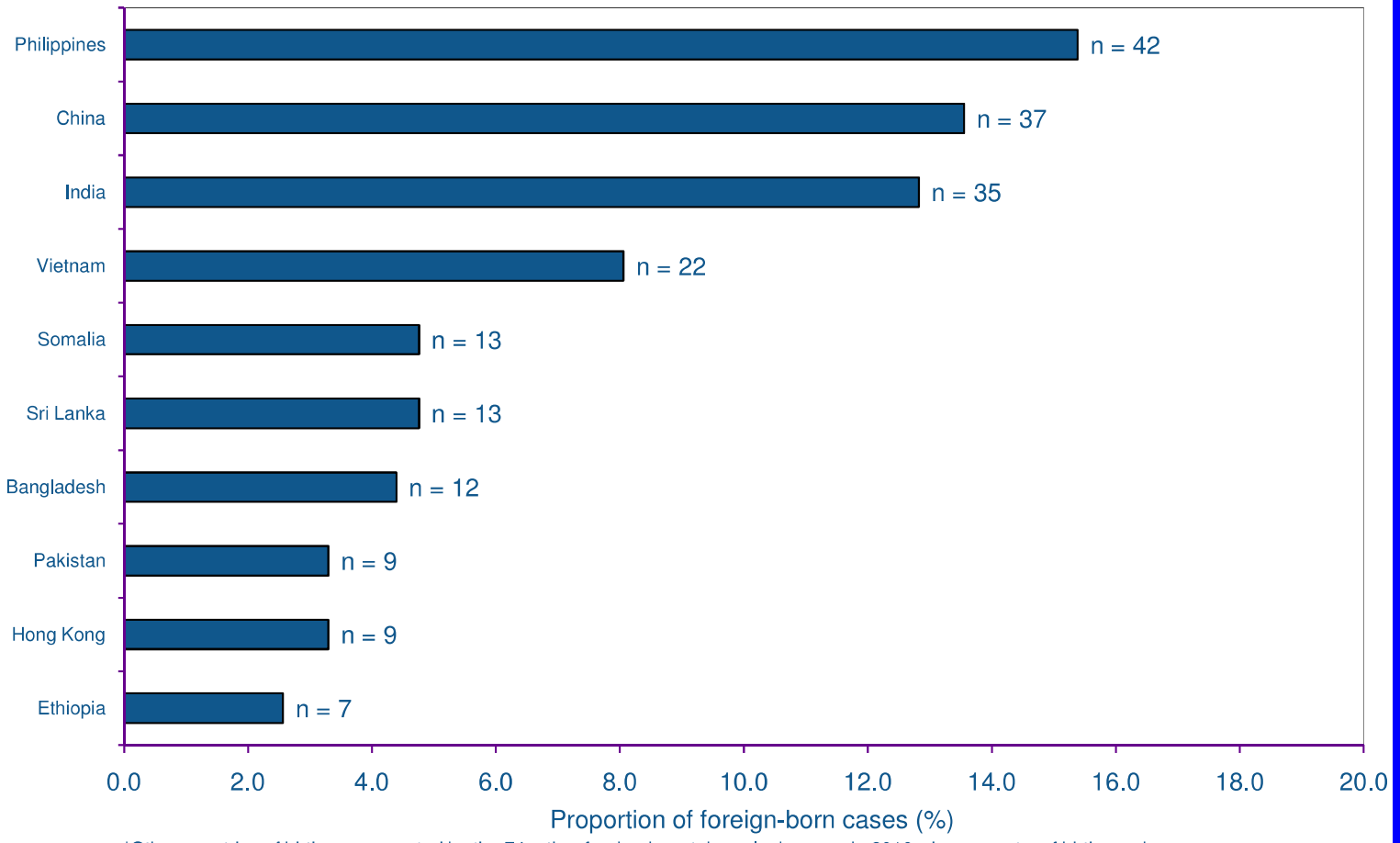
TB in Toronto reflects Global TB incidence (WHO 2010)



TB in Toronto

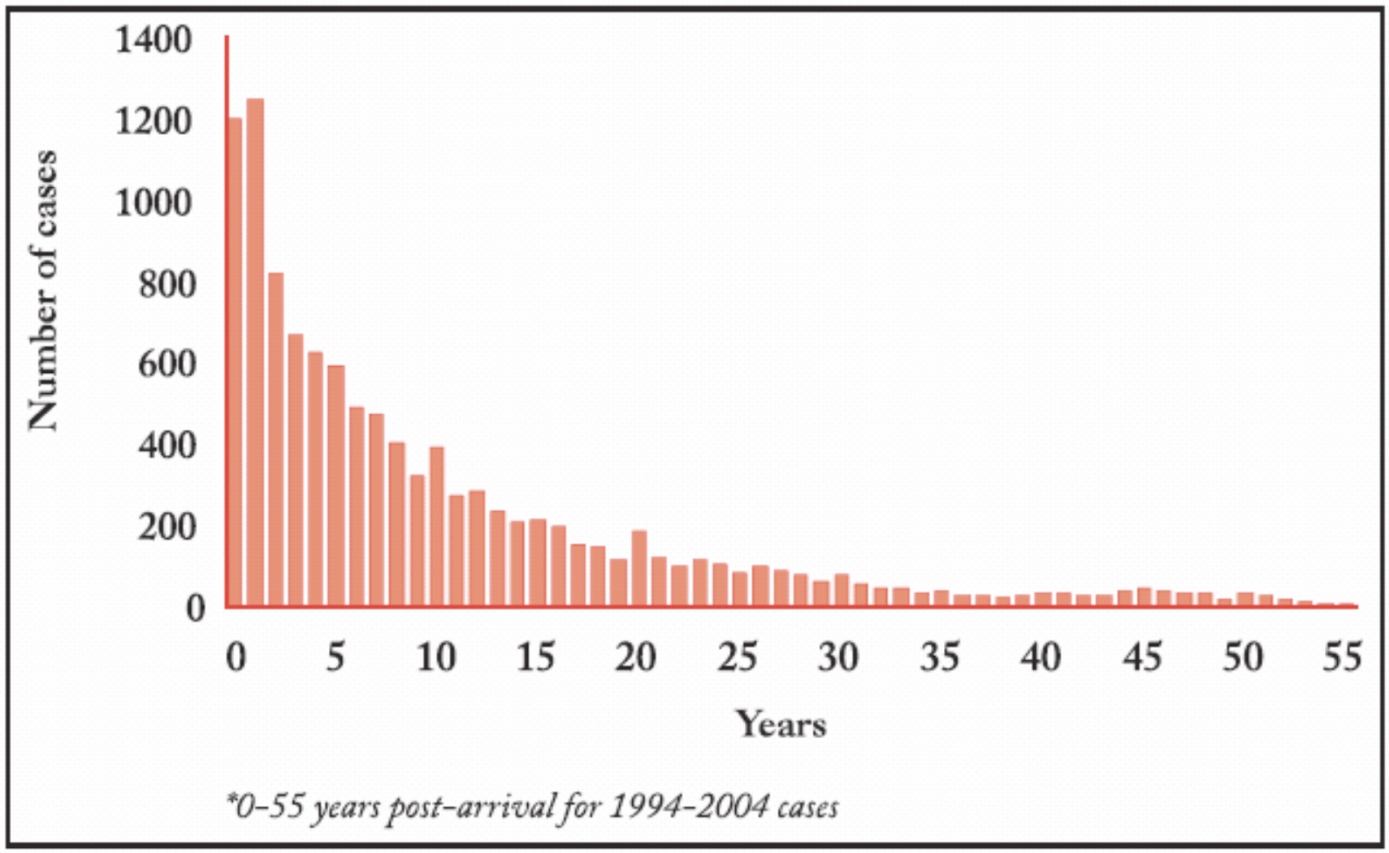
- 450 active cases annually in GTA
  = 1/3 of cases in Canada
- Annual Toronto incidence rate 9.8/100,000
- 93% of cases foreign-born
- 5% known HIV co-infection
- 5-10 homeless cases / year
- 8% fatality rate (all causes among TB patients)
- 1/6 drug-resistant
- 5 XDR-TB cases ever

Figure 4.20: Proportion of foreign-born tuberculosis cases by top countries* of birth. Toronto, 2010



*Other countries of birth were reported by the 74 other foreign-born tuberculosis cases in 2010 where country of birth was known .

Foreign-born tuberculosis cases in Canada: time from arrival in Canada to diagnosis in years*



Thinking about TB: High-risk groups

High risk of exposure (infection):

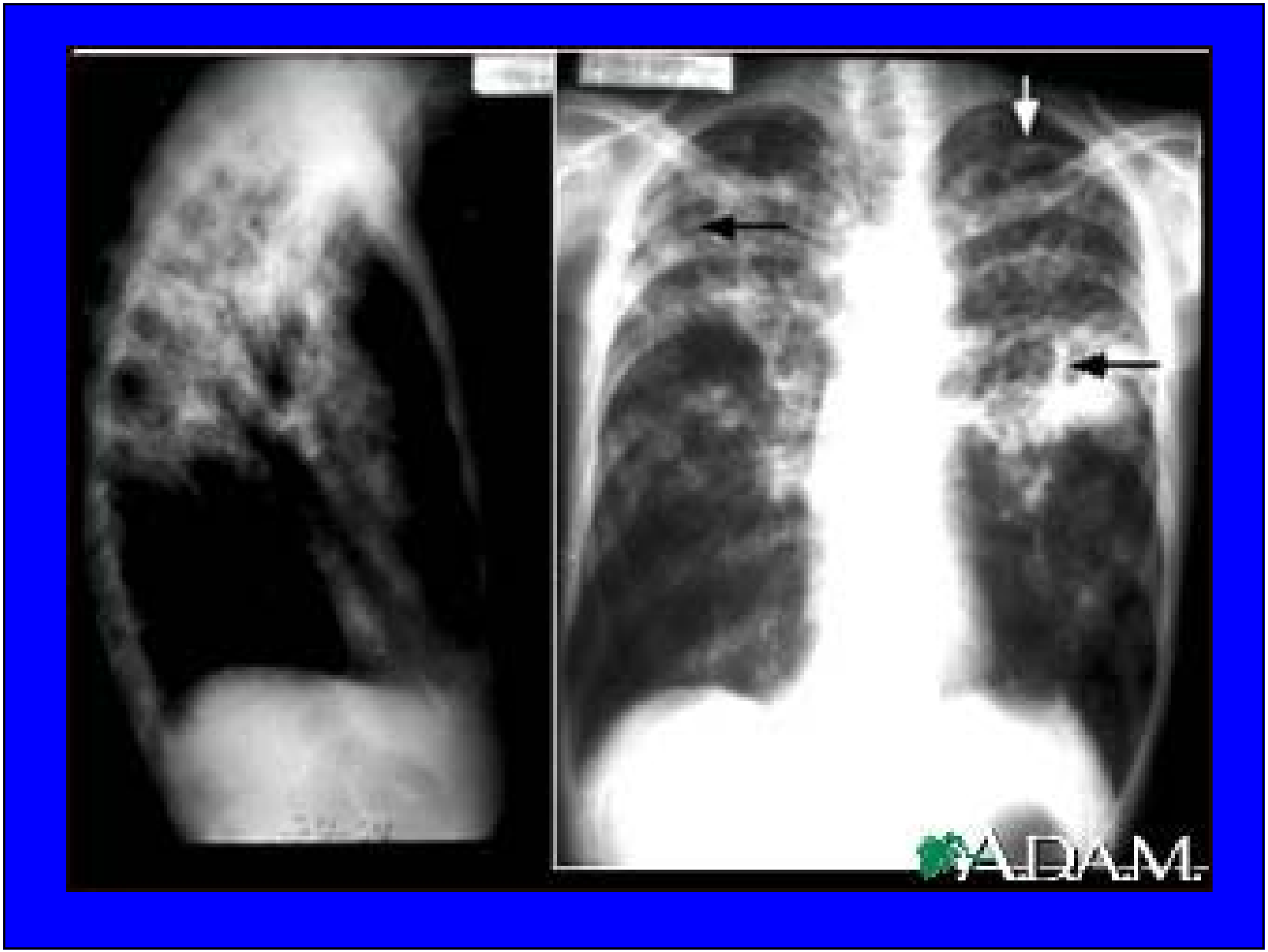
- born in endemic country
- Refugee camps
- native Canadians on / from northern reserve or Arctic
- shelter system; jail?

High risk of progression to active disease:

- contact of active TB in last 2 years
- recent immigration (2-5 years)
- immunocompromised (HIV, ca, IDU, diabetes, pregnancy, babies, malnutrition, alcoholic…)
- homeless

Symptoms of Active TB

- New or worsened cough >3 weeks
- fever
- night sweats
- fatigue
- anorexia, weight loss
- hemoptysis
- extra-pulmonary site in about 30%
  - lymph nodes 20%; bone, meninges, kidney…


A.D.A.M.

As immigrant communities get older…

- Dialysis clinics
- Oncology clinics
- Rheumatology, GI clinics (TNF alpha inhibitors)
- Other medical settings

→ screening implications, early prophylaxis

TB in Toronto: Case #2

- 31 yr woman from Cameroon – refugee claimant along with 6yr old daughter, arrived 6wks ago
- Intermittent fever, cough, SOB – not that ill
- IME in Toronto – CXR miliary TB pattern
- Smear negative, culture positive for TB
- HIV positive
- Daughter is well, TST negative despite BCG at birth in Cameroon

Suspect TB in the office

- TB risk factors + CAP → TB on ddx
- Recurrent CAP → think TB!
- TB longer duration sx, slower onset
- Physical examination usually normal for pulmonary TB
- If TB possible – avoid use of fluoroquinolones (eg moxifloxacin, levofloxacin)

If active TB possible

- If ?respiratory TB – isolate immediately
  - Triage → single room (negative pressure not necessary) and close door
  - surgical mask on patient
  - N95 mask on staff
  - Wait 2 hours before using room again
- CXR (sent patient with mask)
- Sputum for TB (at home / outside)
- If extrapulmonary TB – CXR and sputum too

Laboratory testing for TB

- Sputum x3 (or biopsy x1) for:
  - AFB
  - Nucleic acid amplification tests to confirm MTB (if AFB+ve): AMTD (1-2 days)
  - TB Culture (1-4 weeks)
- Sputum can be collected same day, at least one hour apart – at least one first-morning specimen
- CXR
- HIV

When to call public health

- If you think you have a TB case
  - Investigation / treatment advice
  - Office infection control advice
- If you know you have a TB case
  - Getting urgent specialist assessment
  - Compliance issues (resp isolation, travel, meds)
- LTBI, including contacts
  - Investigation/treatment advice
  - Free meds

Screening for TB: test = treat

- Why do we screen?
  - Younger: LTBI and proph
  - High risk of exposure / progression
  - Older: active TB disease
  - Contact follow-up (individual + determining scope of transmission)
- TST – not for ruling out active disease!
- What's the intervention – proph? Sx counselling?

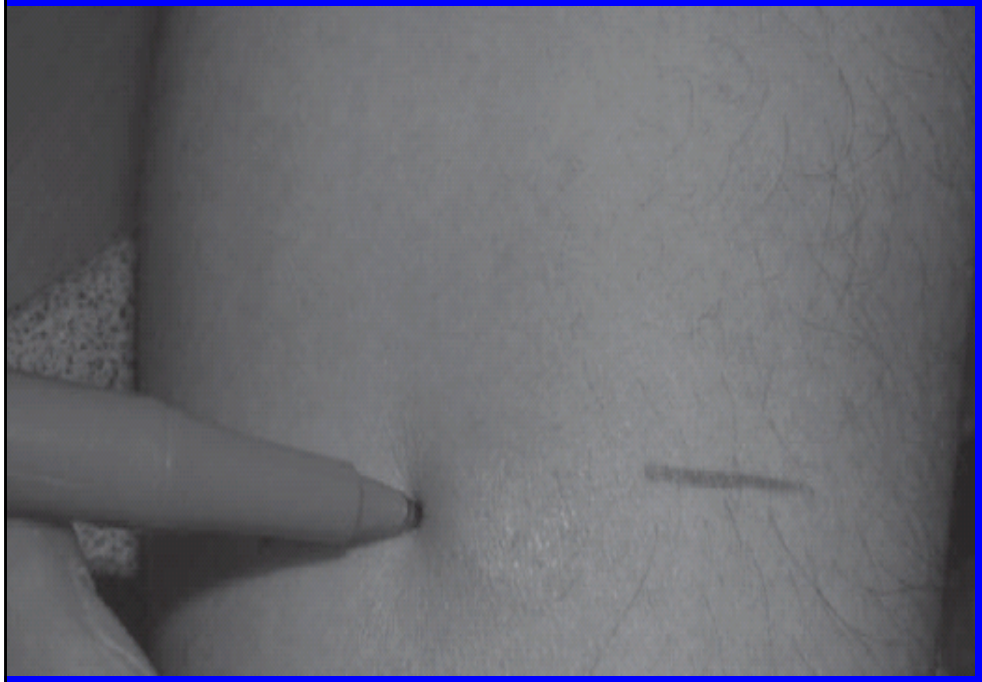
Who to screen for LTBI?

- Contacts of active case
- Foreign-born <20 years old or arrived in the last two years
- Refugees to 50 yrs from high incidence countries
- other adult immigrants with risk factors progression to active TB disease
- radiographic evidence of old, healed TB and no history of treatment

Who else to screen for LTBI?

- Health care workers at risk for occupational exposure to TB
- Staff and residents in communal care:
  - long-term care,
  - correctional facilities, and
  - shelters/services for homeless/underhoused

Interpreting TSTs



- Size of reaction
- Positive predictive value – chance of real TB exposure vs false positive
- Likelihood of progression if true positive

FIGURE 6 The First Dimension of Interpretation of the TST – Size	
TST Reaction Size (mm induration)	**Situation in Which Reaction is Considered Positive**
0-4	HIV infection with immune suppression AND the expected likelihood of TB infection is high (e.g. patient is from a population with a high prevalence of TB infection, is a close contact of an active contagious case, or has an abnormal x-ray)
5-9	HIV infection Close contact of active contagious case Children suspected of having tuberculosis disease Abnormal chest x-ray with fibronodular disease Other immune suppression: TNF-alpha inhibitors, chemotherapy
≥ 10	All others

- 10+mm → 90% sensitivity, 95% specificity

False positive TST

- BCG
- Non-tuberculous mycobacteria – generally <10mm

False negative TST

- Active TB! 25% of cases
- Window period – TB exposure <8 weeks ago
- Anergy (dialysis, ca, end-stage HIV, very elderly, etc)

Positive predictive value: BCG

Age at BCG	% with TST >10mm
0-12 months	1% (after 2-3 years old)
1-5 years	10-15% (up to 25 years later)
6+ years	up to 40%

- Ignore BCG if high risk for progression to active TB! includes contacts

Risk Factor	Estimated Risk of TB Relative to Persons with No Known Risk Factor
HIGH RISK	
Acquired immunodeficiency syndrome (AIDS)	110-170
Human immunodeficiency virus (HIV) infection	50-110
Transplantation (related to immunosuppressant therapy)	20-74
Silicosis	30
Chronic renal failure requiring hemodialysis	10-25
Carcinoma of head and neck	16
Recent TB infection (≤ 2 years)	15
Abnormal chest x-ray – fibronodular disease	6-19
INCREASED RISK	
Treatment with glucocorticoids	4.9
Tumor necrosis factor (TNF)-alpha inhibitors	1.5-4
Diabetes mellitus (all types)	2.0-3.6
Underweight (< 90% ideal body weight; for most persons this is a body mass index ≤ 20)	2-3
Young age when infected (0-4 years)	2.2-5.0
Cigarette smoker (1 pack/day)	2-3
Abnormal chest x-ray – granuloma	2
LOW RISK	
Infected person, no known risk factor, normal chest x-ray ("low risk reactor")	1

TB in Toronto: case #3

- Healthy 32 year old woman
- Arrived from Viet Nam 1 year ago
- Strong family history of diabetes
- TST 23mm
- CXR clear
- BCG as infant

TB in Toronto: case #4

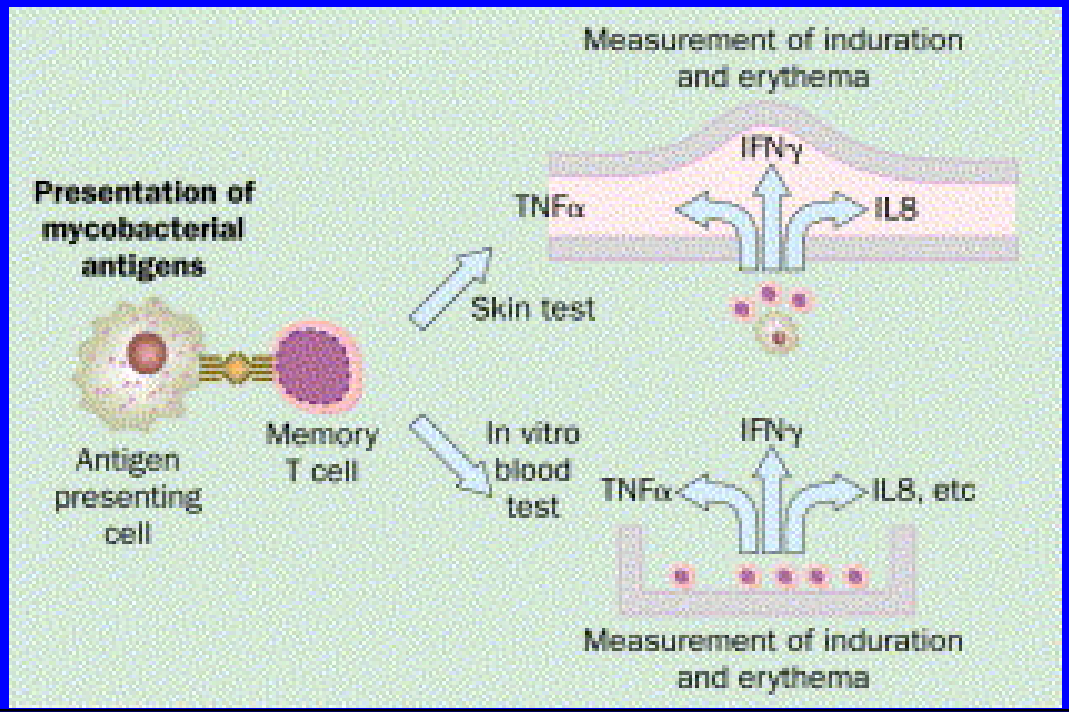
- 68 year old man from China
- Arrived 27 years ago
- TST 12mm
- CXR – small granulomas
- Basically well – smoker, ?early COPD

TB in Toronto: case #5

- 50 year old woman from Jamaica
- Diabetes
- BCG as infant
- CXR unremarkable
- TST 15mm

QuantiFERON (QFT)

- Contains TB specific antigens – will not react to BCG
- Incubate whole blood 16 hours, then measure IFN-γ released from sensitized lymphocytes.
- NOT covered by OHIP - $90



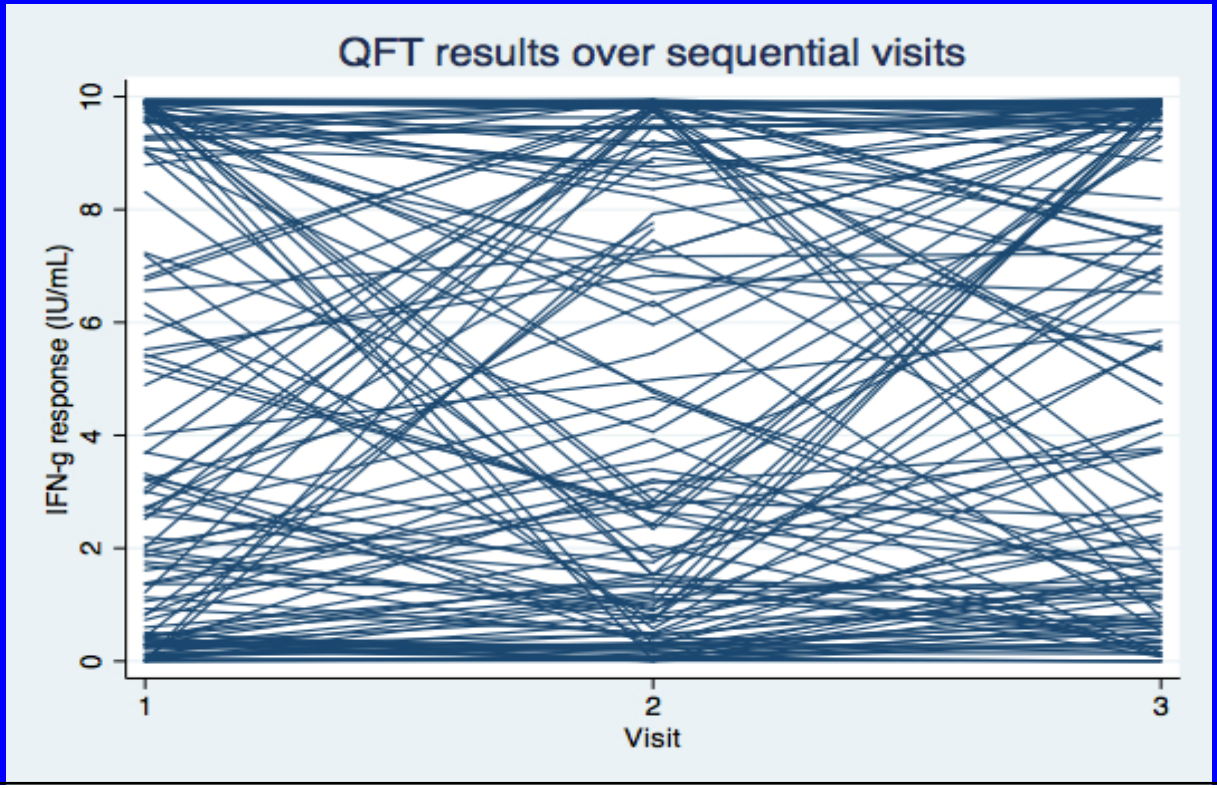
From: Pai M, et al., *Lancet Infect Dis* 2004

From 2013 Canadian TB Standards

- Both TST and IGRA are acceptable alternatives for LTBI diagnosis.
- Can be used together to increase sensitivity when risk of progression to active TB is very high (pediatric contact, immunosupressed from endemic country, etc)
- IGRA preferred when
  - BCG over 1 yr old
  - TST positive but low risk of infection (to increase specificity)

TST is recommended (IGRA is NOT acceptable)

For any serial testing - eg healthcare workers



Fun and useful!

- On-line TST interpreter (Dick Menzes)

http://www.tstin3d.com/index.html

- International TB rates

http://www.phac-aspc.gc.ca/tbpc-latb/itir-eng.php

- BCG Atlas

http://www.bcgatlas.org/

32 yr from Vietnam…

- The likelihood that this is a true positive test (PPV) is: 84.03%
- The annual risk of development of active tuberculosis disease is estimated to be 0.08%.
- The cumulative risk of active tuberculosis disease, up to the age of 80, is: 4.03%

68 yr old from China…

- The cumulative risk of active tuberculosis disease, up to the age of 80, is: 2.46%
- If treated with INH, the probability of clinically significant drug-induced hepatitis is 5%, and the associated probability of hospitalization related to drug-induced hepatitis is 2.4%.

Pros and cons of prophylaxis

- Pro: if widespread, eliminate pool of "future TB" from community
- proph while younger (healthy, liver in good shape, diabetes nil or not complicated yet)
- Con: adherence is critical – and tough
- If older/alcoholic may not tolerate
- At very high medical risk of progression to active TB – consult! **induced sputum

2013 Canadian Standards: LTBI treatment recommendations

- 9 months INH remains standard
- 3-4 months INH & Rif daily acceptable
  - Strong evidence (5 RCTs with a systematic review)
  - Equivalent to 6INH in most RCTs
- 6 months daily INH acceptable (but less efficacy)
- 3-4 months INH&RIF twice weekly – alternative – (1 RCT)
- 4 months RIF alone - alternative (3RIF = 6INH in one RCT, Better safety)
- 2 months RIF-PZA – NOT recommended

Adverse drug reactions

- Incidence of hepatitis on INH is lower than previously thought (0.1 to 0.15%)
- Hepatitis risk increases with age
  - Uncommon in persons < 20 years old
  - Nearly 2% in persons 50 to 64 years old
- Risk increased with underlying liver disease or heavy alcohol consumption

Smoking and TB: not a good idea

- Interferes with innate lung immune systems
- Linked to higher rate of TST conversion for contacts
- Linked to higher rate of LTBI → active TB
- Linked to longer time to smear conversion for cases, ?worse case outcomes

→ Include "stop or decrease smoking" in all TB education for LTBI and cases

Initiating Treatment for LTBI

- Rule out TB disease prior to starting prophylaxis!!
  - Physical (including lymph nodes), symptoms
  - CXR
  - add sputum for TB smear & culture if either positive
- Baseline liver function tests (AST, ALT) for adult patients
- Order free TB meds through public health

Standard Treatment for LTBI

- Isoniazid x 9 months
  (270 doses within 12 months)
- Adults: 300 mg daily
- Children: 10-15 mg/kg/day (max 300mg)
- Add pyridoxine (vitamin B6 25mg) if pregnant, diabetes, alcoholism, malnutrition
- 90% efficacy (if >80% compliance)
- "Reduces lifetime risk from 10% → 1%"

Clinical Monitoring

- Brief monthly assessment
  - Symptoms of adverse drug reactions
  - Reinforce rationale for treatment
  - Adherence with therapy
  - Plans to continue treatment

Adverse INH reactions

- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Dark urine
- Fatigue or weakness
- Numbness in hands or feet (add B6 25mg/day)
- Rash

Laboratory Monitoring

Repeat LFTs monthly only if patient has

- Abnormal baseline results
- Higher risk for adverse reactions (>35 years, liver disease, alcoholism, other hepatotoxic meds)
- Pregnancy / within 3m post-partum
- Symptoms of hepatotoxicity

Hepatotoxicity on INH

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
- hold INH if transaminase level > 3 times the upper limit of normal if hepatotoxicity, OR 5 times the upper limit of normal if asymptomatic

Alternate: INH + RIF

- 4 months – so completion may be better
- INH 300mg + Rifampin 600mg daily
- RIF has many significant drug interactions! Check first! Nb oral contraceptives
- Be especially careful to rule out active TB – RIF is critical TB drug

3 months once weekly INH & Rifapentine –**Incidence of active TB**

Sterling et al, NEJM, 2011; 365: 2155-66

	9INH	3HP
Randomized	**3649**	**3895**
Completed	**2536 (69%)**	**3190 (82%)**
TB Disease - All patients	**12 (0.4%)**	**7 (0.2%)**
- Completed	**5 (0.2%)**	**4 (0.1%)**

3 months once weekly INH & Rifapentine – **Adverse events**

Sterling et al, NEJM, 2011; 365: 2155-66

	9INH	3HP
Randomized	**3649**	**3895**
Total- Grade 3-4 AE	**7.4%**	**6.0%**
Drugs stopped for AE	**3.6%**	**5.0%**
Hepatotoxicity	**2.8%**	**0.5%**
Hypersensitivity	**0.8%**	**4.0%**

Getting back-up

- Clinical advice on diagnosis / management, review of CXR / CT
- TB Clinics in Toronto, Brampton
- Toronto Public Health / local public health
- Provincial Lab (PHO)
- Others with TB experience!