Treatment of Latent TB and T2DM

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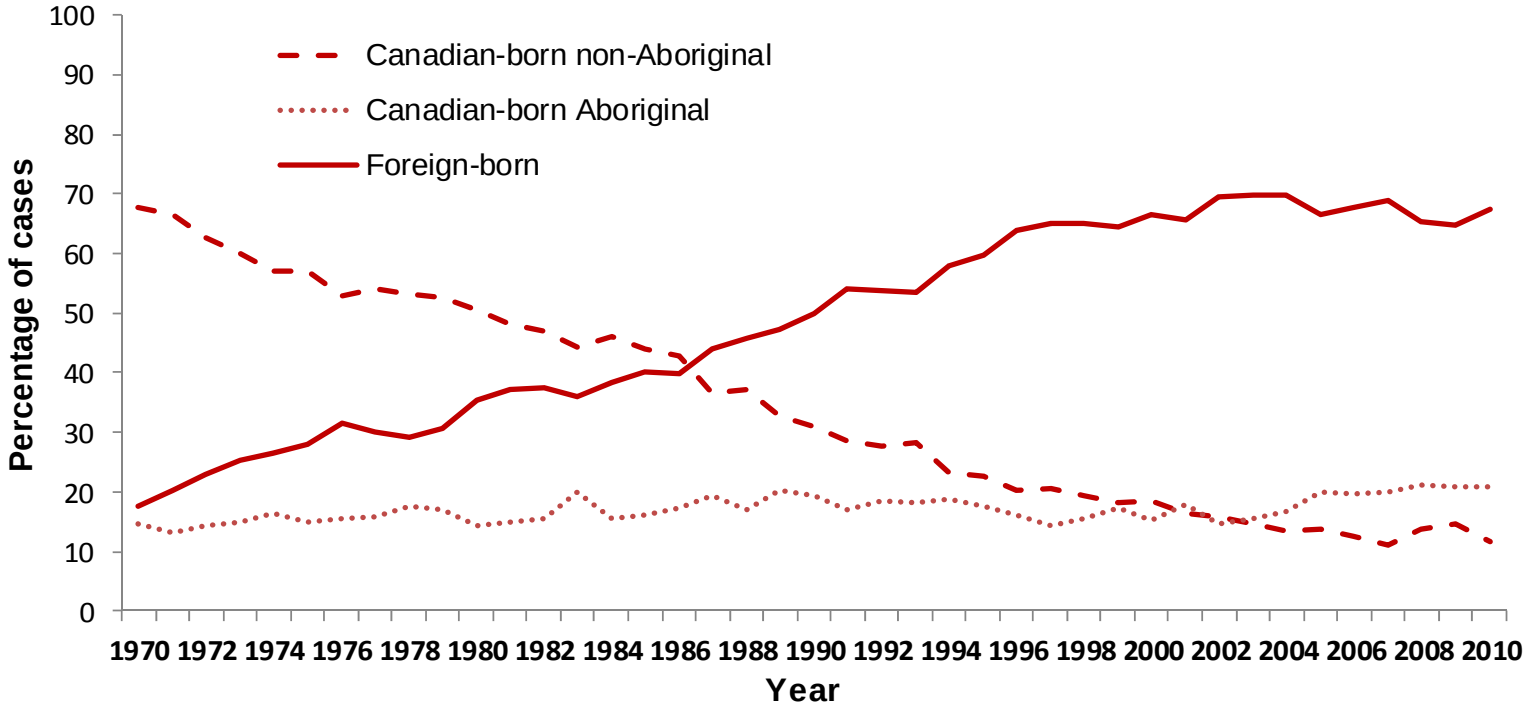
Conflict of interest statement

- **Still nothing, after 25 years of work in the field!**
- **Although, I do hold research operating grants from Canadian Institutes of Health Research, and have received research grants from the World Health Organization, the International Union against TB, and Health Canada**

In Canada, TB is increasingly a disease of the Foreign-born, and the Indigenous populations

Percentage of Reported TB Cases by Population Group in Canada, 1970-2010



Epidemiology – TB & DM

- Well known rise in DM in many countries
- PAF of TB due to DM - rising
- Associated with TB risk among migrants from those countries to low TB incidence countries (Walker 2010; 20% of TB in Asian male immigrants in UK)
- But, overall – what is the evidence of a new epidemic of TB driven by DM?

Impact of DM on TB epidemiology - Summary

- DM increasing in many populations. But is TB also increasing in those populations?
  - Simplistically – Obesity ⇧ DM risk
  - But Obesity ⇩ TB risk, Malnutrition ⇧ TB risk
  - At a population level – which effect predominates?
  - What about other SES factors? Housing? Crowding?
- Can increased DM be considered a marker of generally improved socio-economic conditions?

Diagnosis of Latent TB

TST or IGRA? Or the new QFTplus?

What is the impact of DM on Diagnostic tests for Latent TB?

The sensitivity of interferon-gamma release assays is not compromised in tuberculosis patients with diabetes.

Walsh MC, Int J Tuberc Lung Dis. 2011;15(2):179-84,

- Small study – 70 patients. All newly Dx active TB
- 70% positive QFT. Diabetics MORE likely positive

Reduced sensitivity of the QuantiFERON(®) test in diabetic patients with smear-negative tuberculosis.

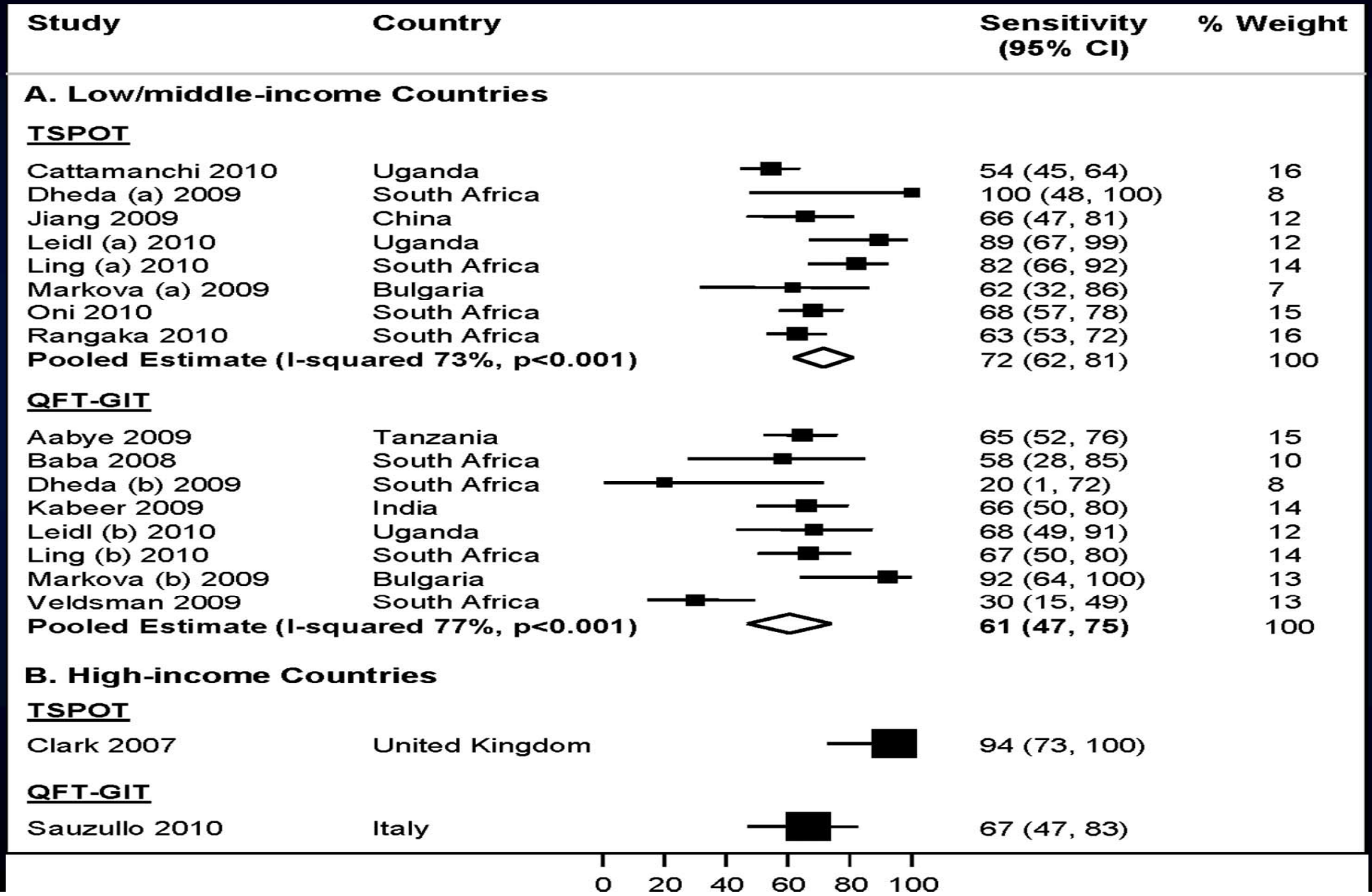
Choi JC, Int J Tuberc Lung Dis. 2015; 19(5):582-8.

- 300 patients with newly diagnosed active TB in SF, USA
- Diabetes a risk factor for negative QFT
- But TST appararently unaffected – Diabetes not a risk factor for false negative TST

Effect of Immune suppressive Treatment on IGRA results *(Wong Thorax 2016)*

	On IST N	Not on IST N	Odds of Pos. IGRA OR (95% CI)
All 17 studies	**2215**	**982**	**0.66 (0.5, 0.8)**
Test			
TST	**nr**	**nr**	**0.72 (0.6, 0.9)**
Quantiferon	**1728**	**764**	**0.65 (0.5, 0.8)**
T-Spot-TB	**924**	**448**	**0.81 (0.6, 1.1)**
Treatment			
Steroids	**988**	**788**	**0.75 (0.6, 1.0)**
Other oral imm. Supp.	**1189**	**737**	**0.68 (0.5, 0.9)**
Anti-TNFa	**249**	**334**	**0.50 (0.3, 0.9)**

Sensitivity of IGRA in HIV infected *(Cattamanchi et al, J AIDS, 2011*



Impact of DM on Dx of LTBI - Summary

- Unclear as evidence scanty and inconsistent
- If DM causes immune suppression, then it should reduce LTBI test sensitivity
  - As HIV does
  - As Immune suppressing drugs do
- The biggest problem with these tests:
  - Poor prediction of disease = 90% of Test positive do NOT develop disease
  - No evidence that Tests in diabetics are much better or worse

Treatment of LTBI

Is there direct evidence that LTBI treatment is effective in Diabetics

- No RCT of LTBI ttx in DM
- Cochrane review (2011) of RCT in HIV (-)
  - DM not mentioned
- Some recent major RCT – DM not mentioned
  - Sterling (NEJM 2011) 3HP vs 9INH
  - Many in HIV infected (Martinson NEJM 2011, Rangaka Lancet 2014, Samandari Lancet 2011)

Serious hepato-toxicity from INH treatment

(Smith; CMAJ: 2011)

Unadjusted risks of hospitalization for hepatic illnesses per 100 patients

	LTBI therapy no. of events/patients / 100 patients (95% CI)		Risk difference Treated vs. Untreated / 100 patients (95% CI)
	All patients	Patients without comorbidity	All patients
Age group, yr			
Total	45/9145 (0.5)	15/6532 (0.2)	0.4 (0.3 to 0.6)
≤ 35	5/4523 (0.1)	5/3765 (0.1)	0.1 (0.0 to 0.2)
36-50	8/2533 (0.3)	4/1898 (0.2)	0.2 (-0.1 to 0.4)
51-65	10/1232 (0.8)	2/668 (0.3)	0.6 (0.1 to 1.2)
> 65	22/857 (2.6)	4/205 (2.0)	2.4 (1.3 to 3.5)

Therapeutic drug monitoring in anti-tuberculosis treatment: a systematic review and meta-analysis.

Mota L; Int J Tuberc Lung Dis. 2016 20(6):819-26

- Systematic Review of 41 studies
- Peak (2 Hr) concentrations of INH & RIF were low in approx. 50% of all patients
- Diabetics somewhat more likely to have low drug levels – for all 4 drugs

Cost-effectiveness

- Campbell 2015: SR of 8 Cost-utility studies of LTBI screening/treatment
- Only one study (Linas 2011) examined screening in diabetics (within USA)
  - Screening with TST or IGR was **not** cost-effective
  - Incremental cost with TST: $240,000 per QALY

Population level impact - of LTBI treatment

- Recent studies:
- Churchyard (NEJM 2014). SA mines. Short-term benefits, long term no impact.
- ZAMSTAR (Lancet 2013). Community based, TB-HIC interventions including IPT – non-significant reduction
- THRio (CID 2015): Prolonged individual benefit, but not able to identify population level impact

LTBI therapy in DM - Summary

- No direct evidence of efficacy of current regimens in DM
- Indirect: More likely INH hepato-toxicity – older and co-morbid
  - Lower drug levels – may reduce efficacy
- Little evidence of cost-effectiveness
  - Again – usually ignored
- Population level impact:
  - Modern studies – no impact of INH – but poor uptake
  - Older studies – Rapid decline in TB, but multiple interventions

Thank you

- Merci
- Gracias
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