Diagnosis of TB in Vaccine Trials

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Overview

- Background / Declarations
- Previous work, inferences
- Current interpretations
- Future considerations

Background: Clinician-Scientist

- **Clinician:**
  - **Head of McGill University Health Centre Mycobacteriology lab**
    - **This is not strictly a TB lab**
    - **2.5 NTM: 1 *M. tuberculosis* in 2010**
- **Scientist:**
  - **Molecular epidemiology of TB**
  - **Mycobacterial genomics**

Background: Limitation

- Diagnostic research:
  - Collaborator of Madhu Pai on his TB Dx grants/projects
  - *de facto* student of Madhu Pai on TB Dx research
- This talk is not based on a systematic review of the literature
  - There will be no Forest plots, pooled estimates, landscape reports, etc.
  - Mostly personal perspective

Background: Influences

- **Financial:**
  - **Molecular differences between species of the *Mycobacterium tuberculosis* complex. US Patent filed May 25, 1999.**
  - **TB7.7 in Quantiferon test**
- **Consultancy:**
  - **Aeras Global TB Vaccine Foundation:**
    - **Clinical & Epidemiological Technical Advisory Board**

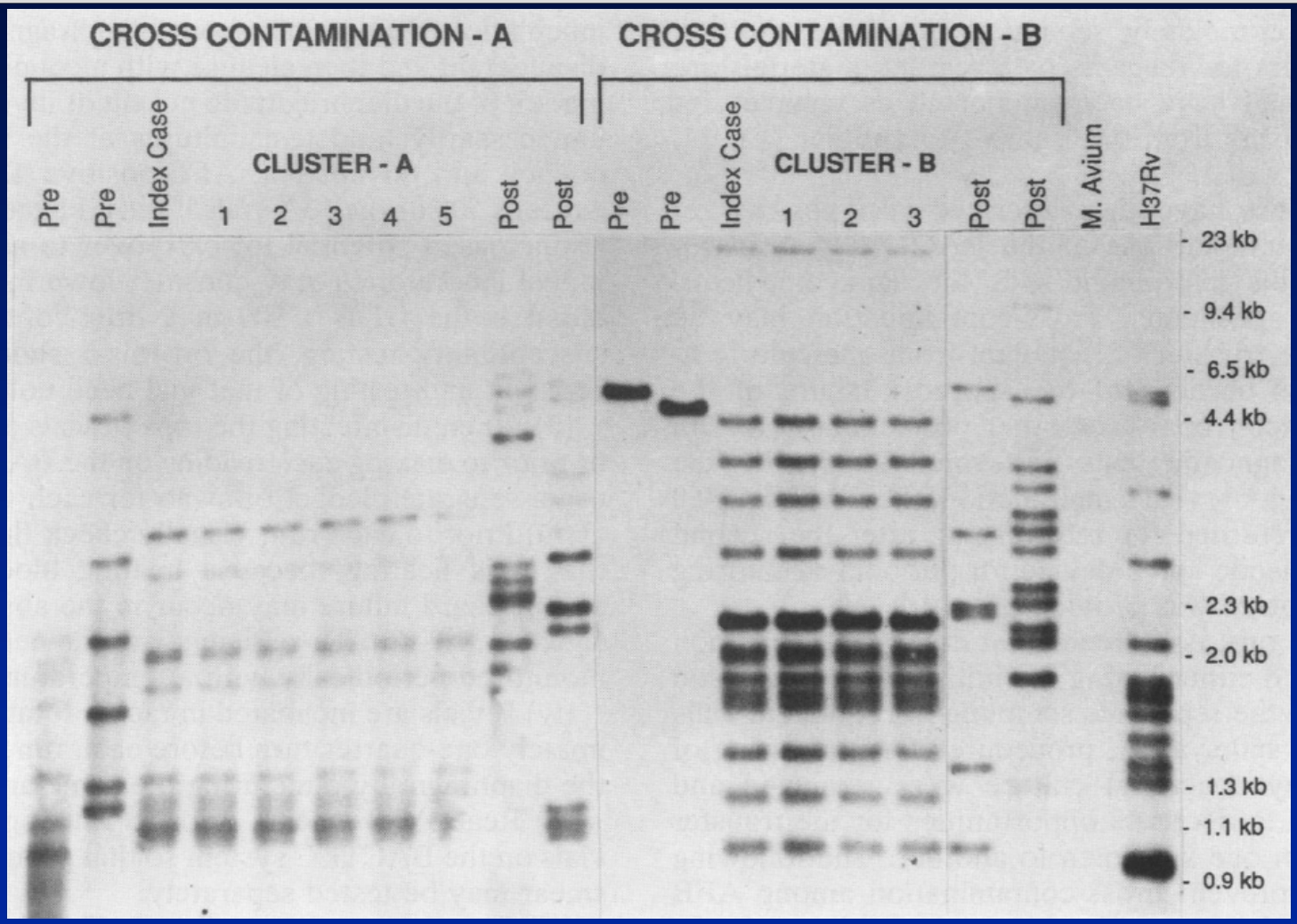
How did I become interested in TB Dx in Vaccine trial?

- Sequella sponsors vaccine trial in South Africa, circa 2000
- I am asked to lead molecular epidemiology effort there
- Previous reports:
  - High rates of clustering, exogenous reinfection, etc.
  - No data on lab x-contamination as potential source of pseudo-clusters

Exploring lab x-contamination: 1. Molecular epidemiology

- Collect sequential isolates from lab
- Subject to genotyping
- If organisms from different patients processed on the same day return the same genotype, despite patients being epidemiologically distinct, suspect lab contamination

Exploring lab x-contamination: 1. Molecular epidemiology



Small PM, JCM, 1993

Exploring lab x-contamination: 1. Molecular epidemiology

- NHLS Lab Greenpoint
- 250,000 samples per year from all communities around Capetown
- Samples from 2 patients in same community might be separated by 100 samples from other sites
  - Can assess lab contamination by RFLP
  - Hard to determine whether it is contributing to clustering within e.g. Ravesmead, Gugulethu

Exploring lab x-contamination: 2. Simulated sputum

- Emulsified egg in 1% aqueous methylcellulose, autoclaved, dispensed into sputum containers
- Samples introduced at clinic with phony names
- Determine proportion of dummy samples that have positive result:

  1 – specificity

Exploring lab x-contamination: 2. Simulated sputum: findings

A Results for all simulated specimens

	Simulated culture result*			
	Mycobacterium tuberculosis	Other	Negative	Total
Simulated smear result				

B Results for simulated specimens after excluding scanty smears and other cultures

		Simulated culture result		
		+	−	Total
Simulated smear result	+	0	6	6
	−	2	182	184
	Total	2	188	190

Demers, IJTLD, 2010

Exploring lab x-contamination: 2. Simulated sputum: findings

- Culture specificity = 99%
- Smear specificity = 97%

- N.B.1: this is the diagnostic lab, for patient care
- N.B.2: this is also the lab used for clinical trial, RFLP studies, etc.

- What are the implications?

99% specificity in Montreal

- 5000 samples per year
- 99% specificity → 50 false+ per year
- 2010: 42 new patients with TB
- Inference: ~ 1 false-positive for each true-positive
- Interpretation: Unacceptable

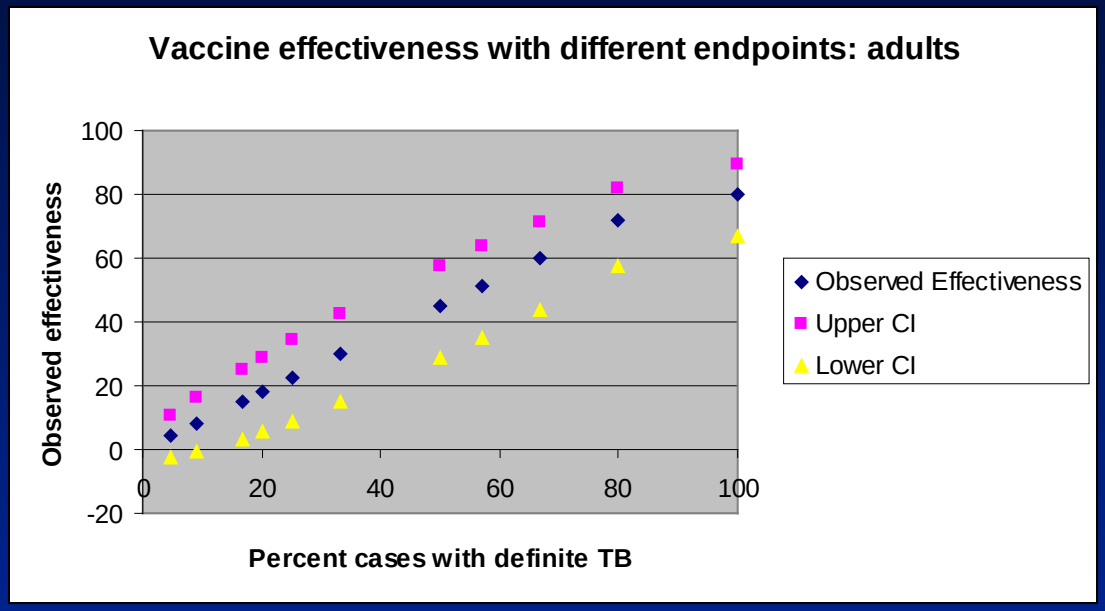
99% specificity in Gugulethu

- 6093 samples
- 99% specificity -> 45 false-positive
- Study: 1862 positive cultures
- Inference: ~ 1 false-positive for every 40 true-positive
- Interpretation: 2.4% of + cultures were false-positive (acceptable)

99% specificity in vaccine trial

- 11680 infants, BCG s.c. vs. i.d.
- 1576 admitted for suspected TB:
  - 2 sputum induction + 2 gastric lavage
  - ~6000 samples
- 99% specificity → 60 false-positive
- Study: 172 definite TB (i.e. + cultures)
- Inference: ~ 1 false+ per 2 true+?
- Interpretation: 1/3 of ‘definite TB’ may have been false+: Is this acceptable?

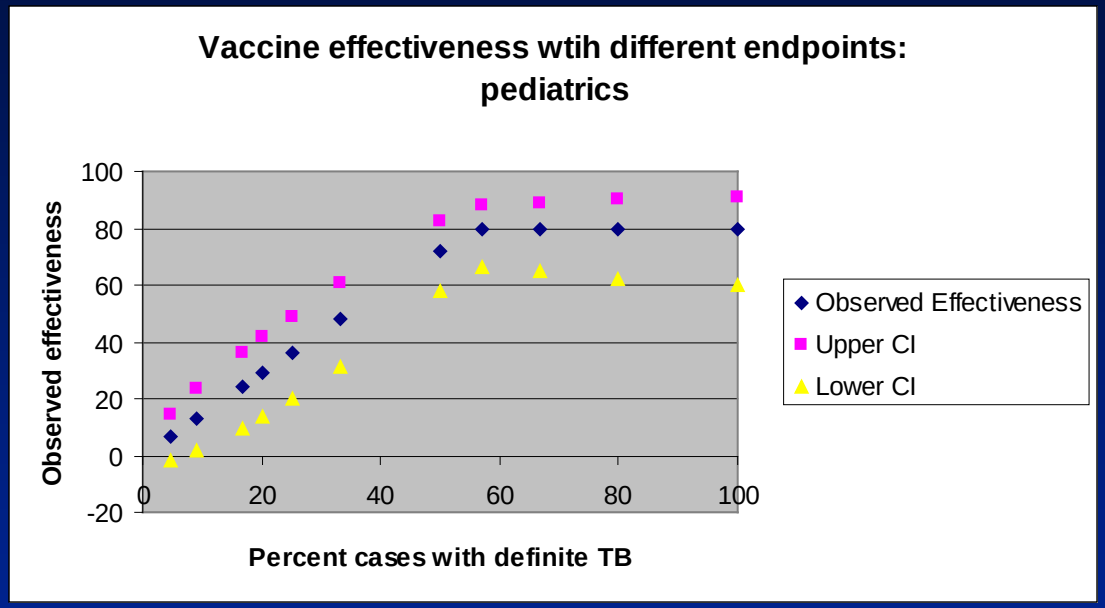
What are effects of endpoint dilution?: Simulations - 1



Adult study
Microbiology has high sensitivity
Vaccine has 80% efficacy

Behr, Schwartzman, Pai, unpublished simulations

What are effects of endpoint dilution?: Simulations - 2



Peds study
Microbiology has lower sensitivity
Vaccine has 80% efficacy

Behr, Schwartzman, Pai, unpublished simulations

My interpretation

- In a trial, you must do two things:
  - Ensure patient care
  - Obtain scientific data
- Good Dx is good enough for patient care
  - Especially in high incidence settings
- For efficacy of vaccine, aim for perfect
  - Dilution of cases reduces observed efficacy

Beyond microbiology

- Efforts underway to increase numbers
  - Inclusion of probable and possible cases
- Criteria suggested include:
  - Physical exam, IGRA / TST, Radiology
- Can these, alone or in combination, help find more ‘cases’?

Beyond microbiology: RCT of active case finding

Variable	TB suspects				TB cases			
	Group 1* (*n* = 527) *n* (%)	Group 2† (*n* = 353) *n* (%)	OR (95%CI)‡	*P* value	Group 1* (*n* = 89) *n* (%)	Group 2† (*n* = 36) *n* (%)	OR (95%CI)‡	*P* value
Cough >2/52								
Yes	204 (39)	119 (34)	1.24 (0.94–1.65)	0.13	33 (37)	15 (42)	0.83 (0.38–1.80)	0.63
No	323 (61)	234 (66)			56 (63)	21 (58)		
Failure to thrive§								
Yes	189 (36)	124 (35)	1.02 (0.77–1.36)	0.86	36 (40)	18 (50)	0.72 (0.33–1.56)	0.41
No	330 (63)	222 (63)			50 (56)	18 (50)		
Unknown/missing	8 (2)	7 (2)	NA		3 (3)	0	NA	
TB contact								
Yes	339 (64)	230 (65)	0.96 (0.73–1.28)	0.80	64 (72)	29 (81)	0.62 (0.25–1.56)	0.32
No	188 (36)	123 (35)			25 (28)	7 (19)		
TST-positive (≥10 mm)								
Yes	120 (23)	87 (25)	0.90 (0.66–1.24)	0.52	43 (48)	18 (50)	0.93 (0.43–2.01)	0.86
No	407 (77)	266 (75)			46 (52)	18 (50)		
CXR abnormalities								
Yes	87 (17)¶	35 (10)	1.77 (1.17–2.69)#	0.01§	83 (93)	29 (81)	2.29 (0.62–8.48)	0.23
No	431 (82)	308 (87)			5 (6)	4 (11)		
Unknown/missing	9 (2)	10 (3)	NA		1 (1)	3 (8)	NA	
Bacteriology**								
Positive	10 (2)¶	8 (2)	0.84 (0.34–2.08)	0.71	10 (11)¶	8 (22)	0.46 (0.17–1.25)	0.13
Negative	514 (98)	345 (98)			76 (85)	28 (78)		
Unknown/missing	3 (1)	0	NA		3 (3)	0	NA	

Authors: Active case finding led to more cases

My concern: risk of dilution – note 22% culture-confirmed to 11% culture-confirmed

Moyo, IJTLJ, 2012

Beyond microbiology: my view

- Attempts to ↑ cases need assays with > 99% specificity to be useful
  - If less specificity, stronger effects of dilution than we saw with 1% of cultures false+
- Increasing ‘cases’ with probables and possibles will gain a few true cases, plus a larger number of false cases
- I submit you should calculate sample size based on ‘definite TB’ only

Special considerations - 1

- If candidate vaccine prevents infection, then IRGA might be an endpoint of vaccine study
- Active TB: patient care
- LTBI: scientific question

- Until we know, both types of tests should be done (for exploratory analysis)
- Try not to confuse reason for test being done
  - E.g. + IGRA or + culture as evidence of TB

Special considerations - 2

- To optimize vaccine trial, need to go where incidence high
- Settings with highest incidence often have few resources for laboratory quality control program
  - Consider contract with private lab, or setting up designated vaccine Dx lab
  - Ask whether there is capacity to Dx the different diagnoses?

Questions

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