



NATIONAL HEALTH  
LABORATORY SERVICE



## Reference standards for NAAT

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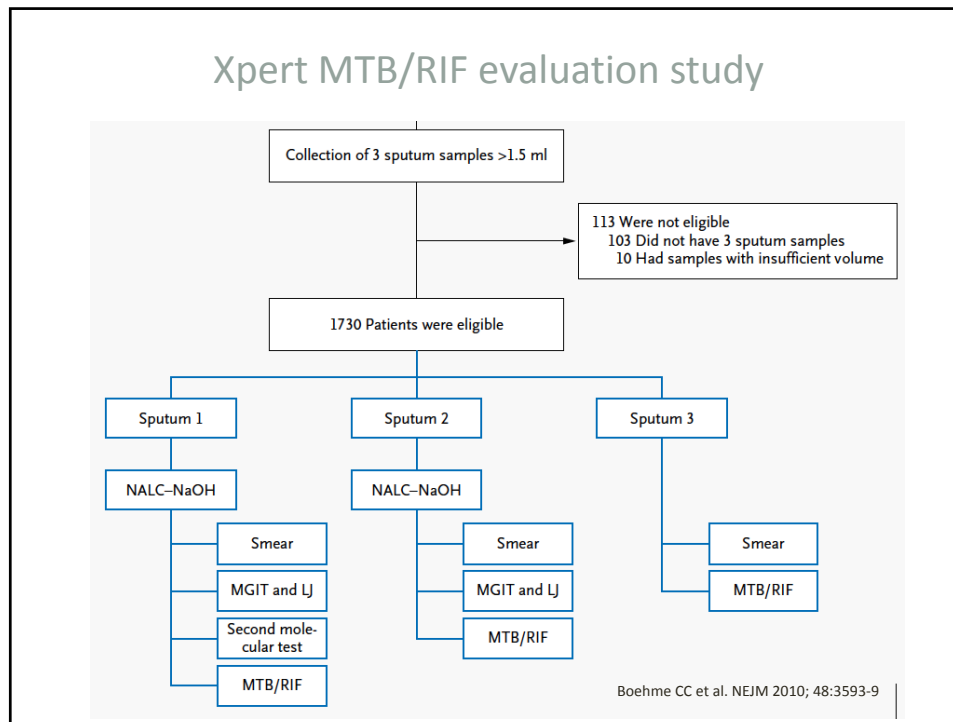
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## Issues to consider

- Culture as a reference standard
  - Number of cultures
  - Solid and liquid cultures
  - Same sample or different sample
  - Pellet vs. raw sputum
- False positive cultures
  - Cross-contamination
- False-negative cultures
  - Index test may perform better than reference standard
  - Very low bacillary loads
  - Clinical diagnosis / response to treatment as a reference standard

## Xpert MTB/RIF evaluation study



## Xpert MTB/RIF evaluation study

- Reference standard 3 cultures vs. 1, 2 or 3 Xpert tests
- However, for patients with positive Xpert and negative cultures
  - Independent clinical review (masked) of clinical data (very limited) and CXR response to treatment (combined reference standard)
  - Equivalently sized group of randomly selected controls
- Problem: differential verification bias
  - When patients receive different reference standard depending on the index test result
  - Ameliorated by control group, however, statistically skewed to improvement of results

## Need to compare like with like (# of samples)

	Sensitivity	Specificity
<b>All children with complete results from at least one induced sputum specimen (n=452)</b>		
MTB/RIF		
All	52/70, 74.3% (63.8-84.8)	376/382, 98.4% (97.2-99.7)
HIV-infected	17/17, 100% (80.5-100)	91/91, 100% (96.0-100)
HIV-uninfected	35/53, 66.0% (52.9-79.2)	285/291, 97.9% (96.3-99.6)
Smear microscopy	27/70, 38.6% (26.9-50.3)	382/382, 100% (99.0-100)
<b>Children with complete results from two induced sputum specimens (n=385)*</b>		
MTB/RIF (first induced sputum specimen)		
MTB/RIF (both induced sputum specimens)	34/58, 58.7% (45.6-71.1)	325/327, 99.4% (98.5-100)
MTB/RIF (both induced sputum specimens)		
All	44/58, 75.9% (64.5-87.2)	323/327, 98.8% (97.6-99.9)
HIV-infected	14/14, 100% (76.8-100)	80/80, 100% (95.5-100)
HIV-uninfected	30/44, 68.2% (53.9-82.5)	241/245, 98.4% (96.8-99.9)
Smear microscopy (two smears)		
All	22/58, 37.9% (25.1-50.8)	327/327, 100% (98.9-100)

Nicol MP et al. Lancet ID 2011; 11:819-24