Diagnostic Meta-Analysis of Nucleic Acid Amplification Tests for TB pleuritis

(work in progress)

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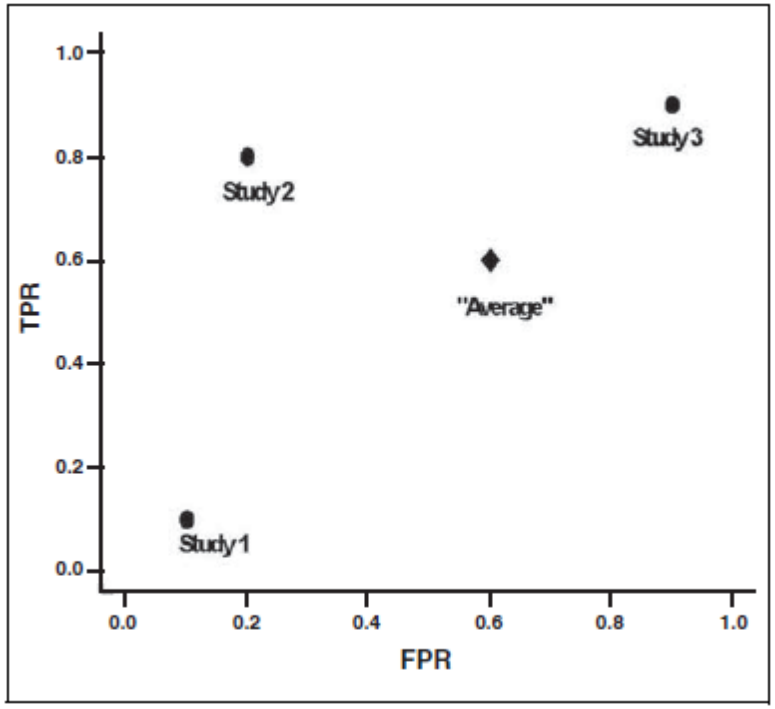
Diagnostic Meta-Analysis

- A meta-analysis is carried out to pool information across studies.
  - Individual studies may be small, report conflicting results
- Diagnostic meta-analyses involve pooling of both sensitivity and specificity
  - Sensitivity and specificity may be correlated across studies:
    - e.g. due to use of different thresholds, or due to differences in population parameters
  - Therefore, a bivariate model is needed for meta-analysis

Separate pooling may lead to bias*

- Separate pooling ignores correlation between sensitivity and specificity
- Results in an (Average Sensitivity, Average Specificity) combination that may be impossible



Gatsonis and Paliwal, Am J Roentgen, 2006

Models for joint meta-analysis of sensitivity and specificity

- Three widely used candidates:
  - Univariate model of the log diagnostic odds ratio
  - Bivariate models of the sensitivity and specificity
    - 'HSROC Model' proposed by Rutter and Gatsonis[1] relates sensitivity and specificity to the positivity threshold and the 'diagnostic accuracy'
    - 'Bivariate Model' proposed by Reitsma et al.[2] models sensitivity and specificity directly

- The two bivariate models are algebraically equivalent in the absence of covariates[3]
  - But if covariates enter the picture they may yield different results. Thus one model may be preferred over the other depending on the context.

1: Rutter and Gatsonis, Stats in Med, 2001; 2: Reitsma et al, J Clin Epi, 2005; 3: Harbord et al, Biostatistics, 2007

Models for joint meta-analysis of sensitivity and specificity

- Bayesian and Frequentist estimation available for all three models

- All models are also now available in numerous software packages (R, STATA, WinBUGS, SAS...)

Reference standard bias in TB diagnostic meta-analyses

- As previously discussed, reference standard bias may arise in individual studies due to an imperfect reference test

- In a meta-analysis setting, the problem is worsened because each study may use a different reference standard
  - Thus the diagnostic meta-analyses may not be pooling the same quantity across studies!

In-house NAATs (IS6110) for TB pleuritis†

Study	NAAT, Reference				Reference Test	Sensitivity of Reference*
	++	+,-	-,+	-,-		
1	11	1	14	75	Culture	20-60%
2	1	1	3	25	Culture	20-60%
3	8	0	1	16	Culture/Clinical data	20-70%
4	16	6	0	43	Culture/Clinical data	20-70%
5	30	6	0	14	Culture/Microscopy	60-80%
6	16	0	1	56	Culture/Biopsy	70-90%
7	9	0	6	10	Culture/Biopsy	70-90%
8	13	0	4	25	Culture/Biopsy	70-90%
9	17	2	4	84	Culture/Biopsy	70-90%
10	7	0	3	13	Culture/Biopsy	70-90%
11	14	1	19	97	Culture/Biopsy	70-90%
12	31	7	11	63	Culture/Biopsy	70-90%

† Pai et al, BMC Inf Dis, 2004; * Specificity of Ref assumed to lie from 90-100%

Adjusting for heterogeneity in reference in a diagnostic meta-analysis

- Standard approach:
  - Pool studies within strata defined by each standard or use ‘reference type’ as a covariate in a meta-regression model

- Problems with standard approach:
  - May not have sufficient studies in a ‘pure’ strata where the same reference is used
  - Even if possible, sens/spec may be underestimated

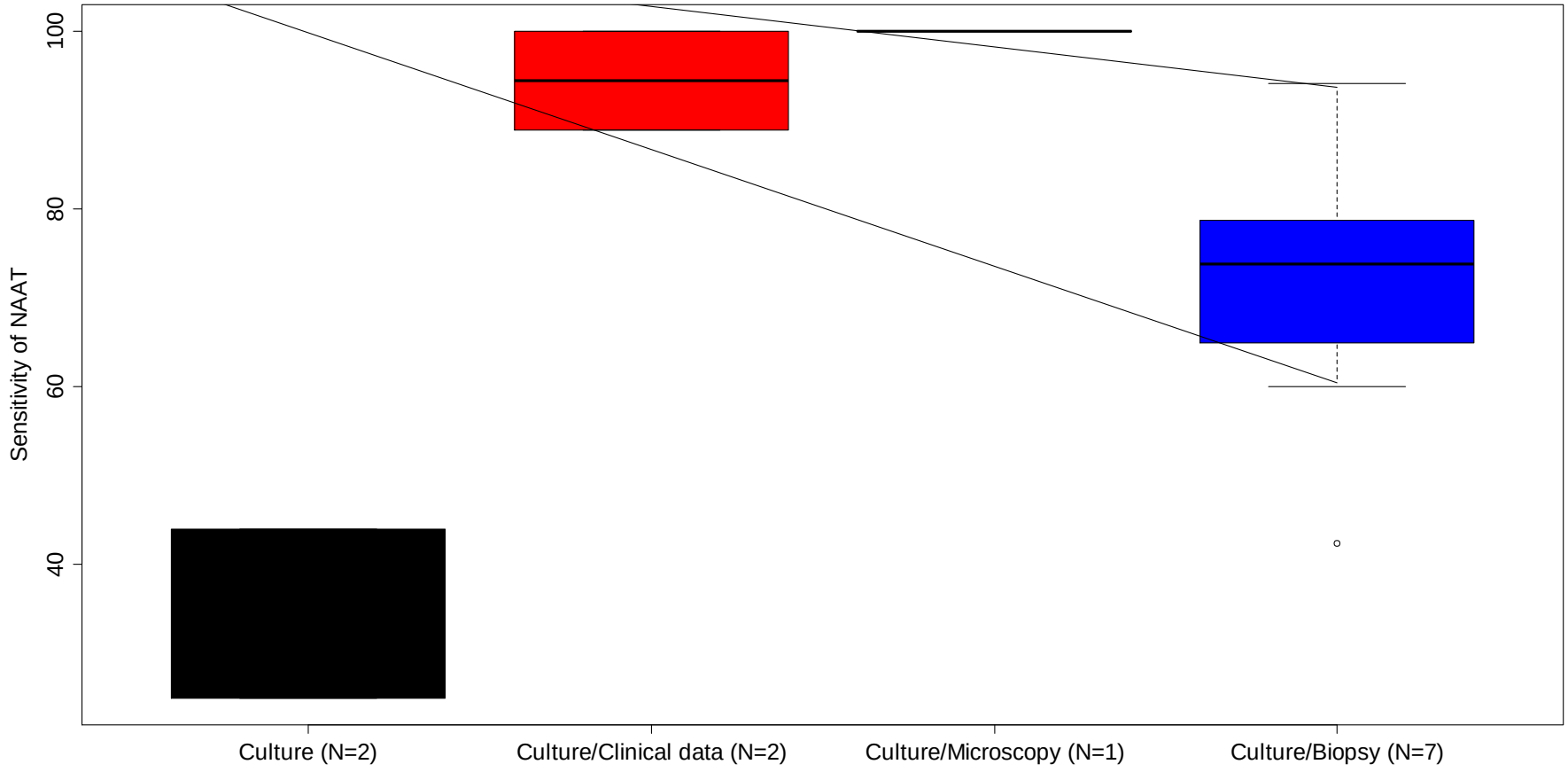
Apparent variability in threshold appears to be due to the reference standard

Traditional Analysis

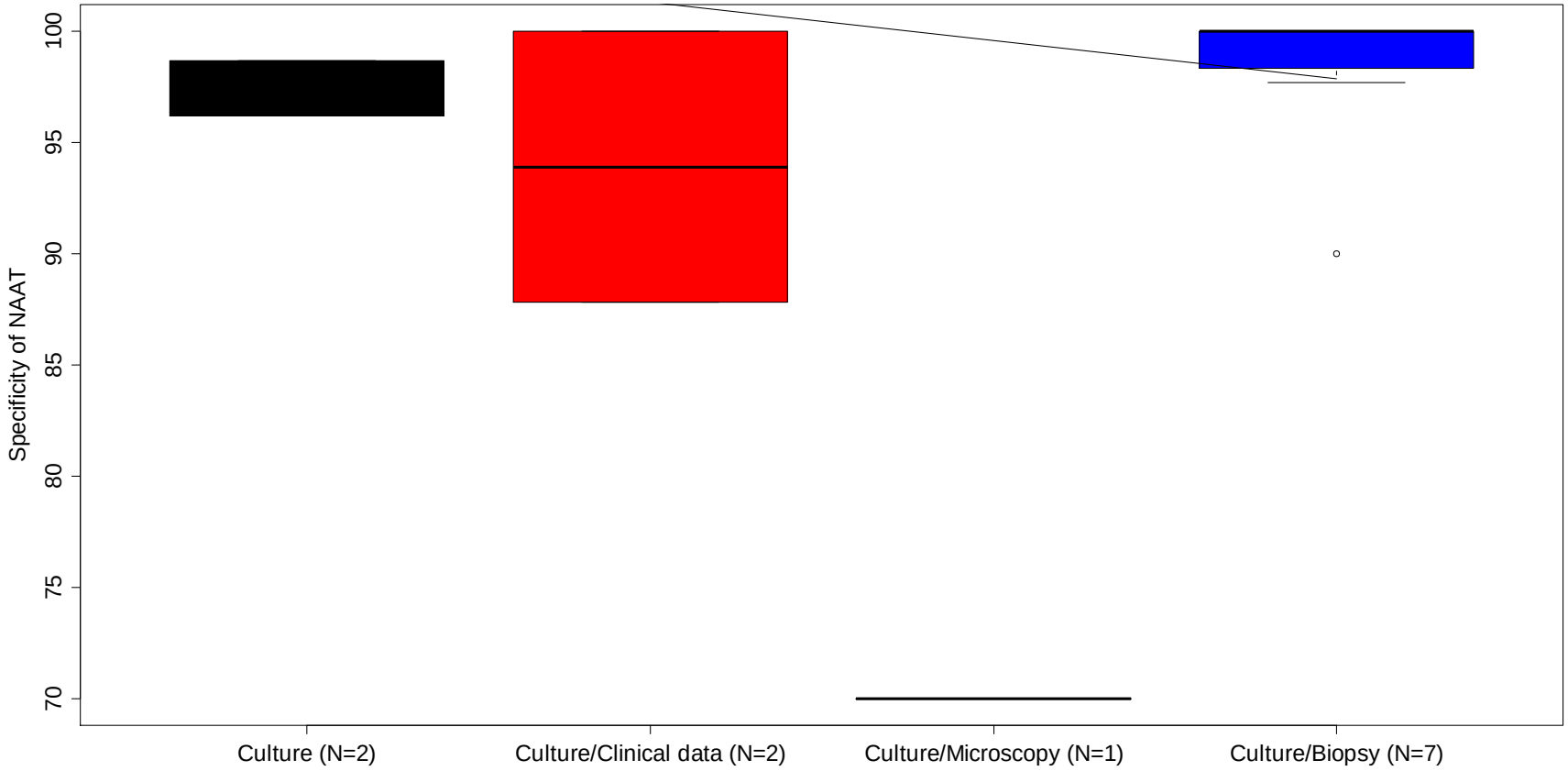
Study	Reference Test	Sensitivity of NAAT (%)	Specificity of NAAT
1	Culture	44	99
2	Culture	25	96
3	Culture/Clinical data	89	100
4	Culture/Clinical data	100	87
5	Culture/Microscopy	100	70
6	Culture/Biopsy	94	100
7	Culture/Biopsy	60	100
8	Culture/Biopsy	77	100
9	Culture/Biopsy	81	98
10	Culture/Biopsy	70	100
11	Culture/Biopsy	42	99
12	Culture/Biopsy	74	90

Apparent variability in threshold appears to be due to the reference standard

Heterogeneity in traditional estimates of sensitivity



Heterogeneity in traditional estimates of specificity



Diagnostic meta-analysis in the absence of a gold-standard

- 3 articles have appeared so far[1,2,3]:
  - All have assumed a common imperfect reference used in all studies
  - The article by Chu et al.[3] is an extension of the Reitsma model

- We have developed an extension of the model by Rutter and Gatsonis
  - Allows for threshold and 'diagnostic accuracy' to vary across studies
  - Allows for reference standards to be different
  - R package (HSROC) to implement this model

1: Walter et al, J Clin Epi, 1999; 2: Sadatsafavi et al, J Clin Epi, 2010; 3: Chu et al, JASA, 2009

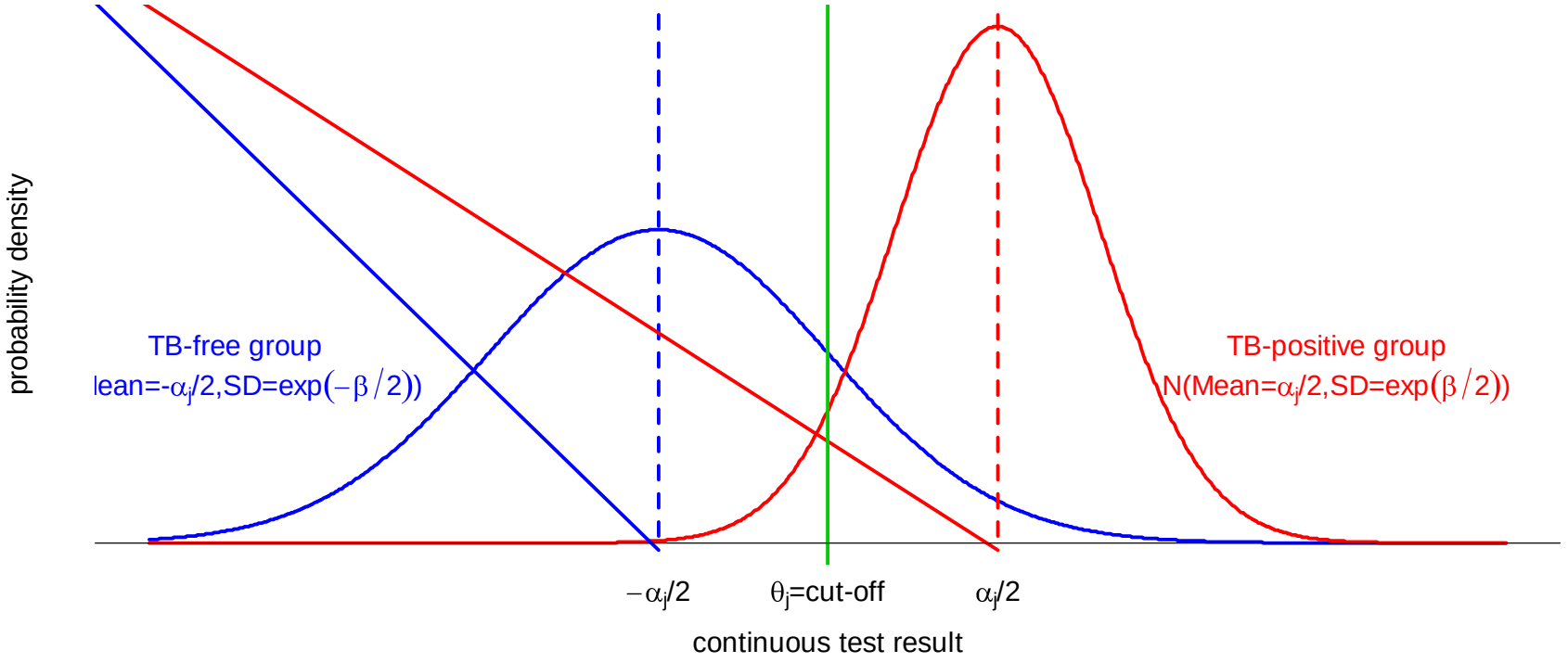
HSROC model adjusted for imperfect reference standard

- Observed data in each study:

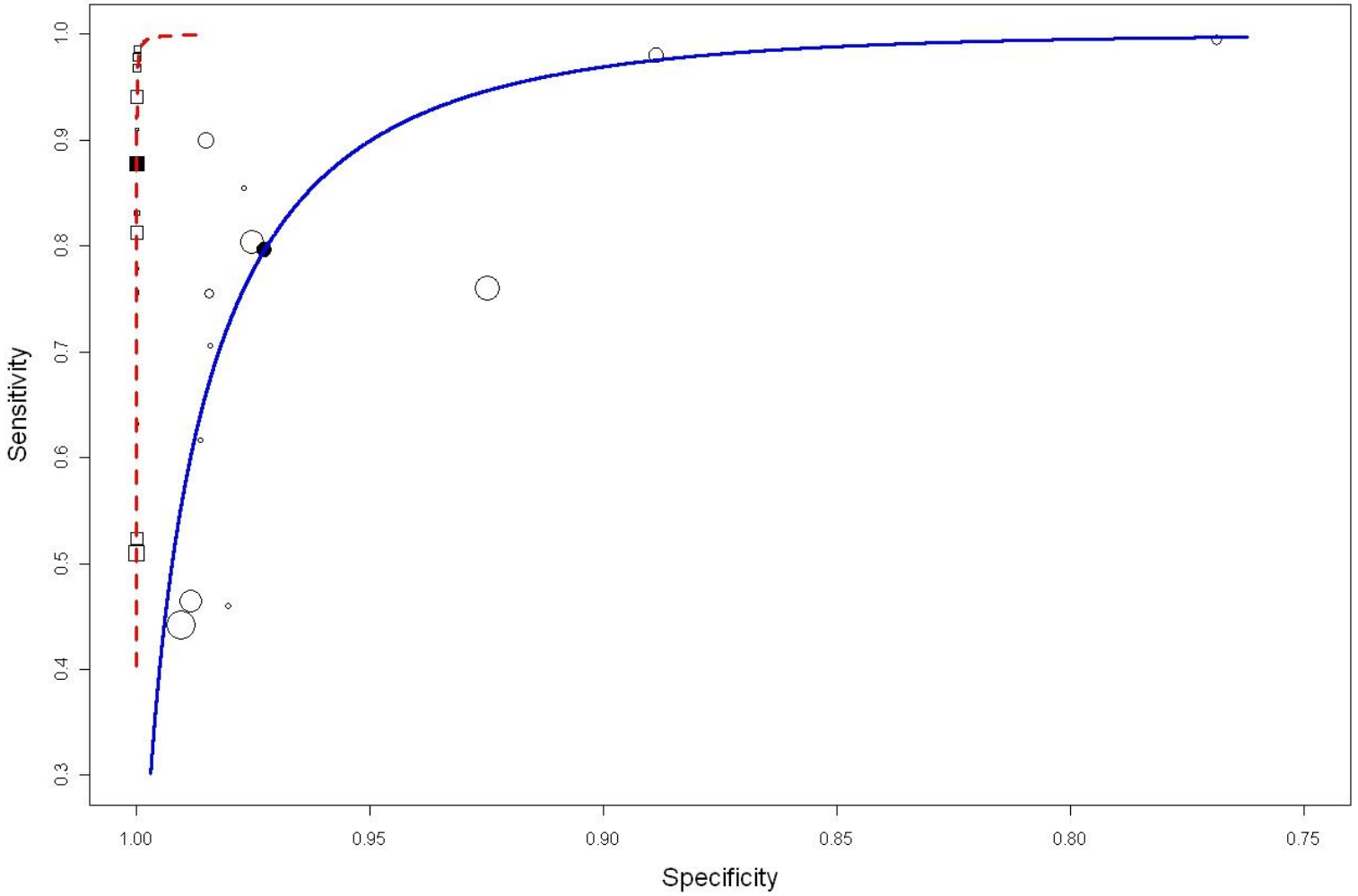
NAAT+, Ref-	NAAT+, Ref-	NAAT+, Ref-	NAAT+, Ref-
n11	n10	n01	n00

- Assume
  - observed data arise from a mixture of true TB pleuritis+ and TB pleuritis- subjects
  - positivity threshold (θ) varies across studies
  - diagnostic accuracy (α) varies across studies

Dichotomous data in each study assumed to arise from an underlying continuous variable

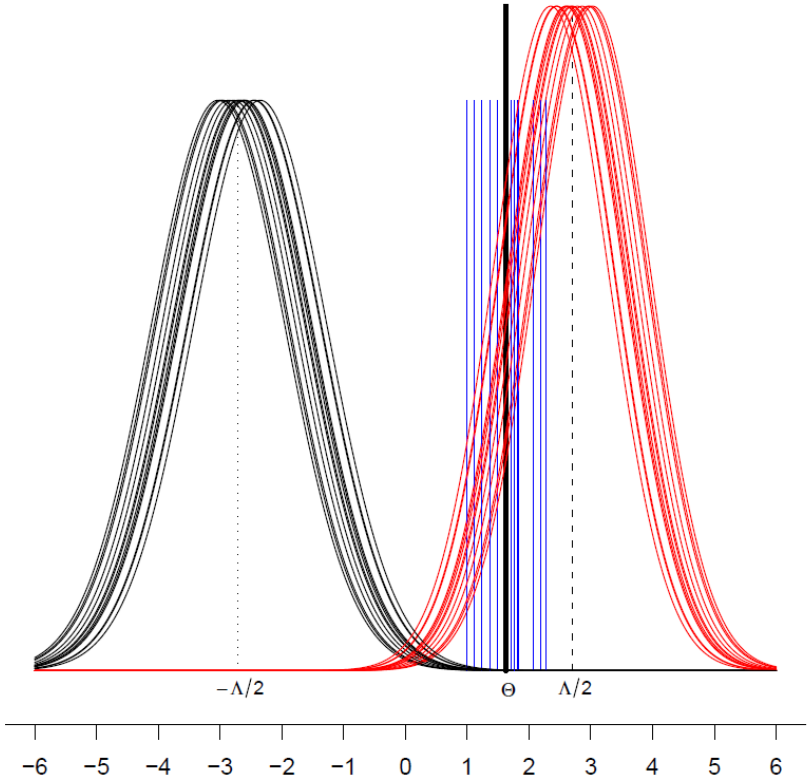


Results from HSROC model: SROC Curves

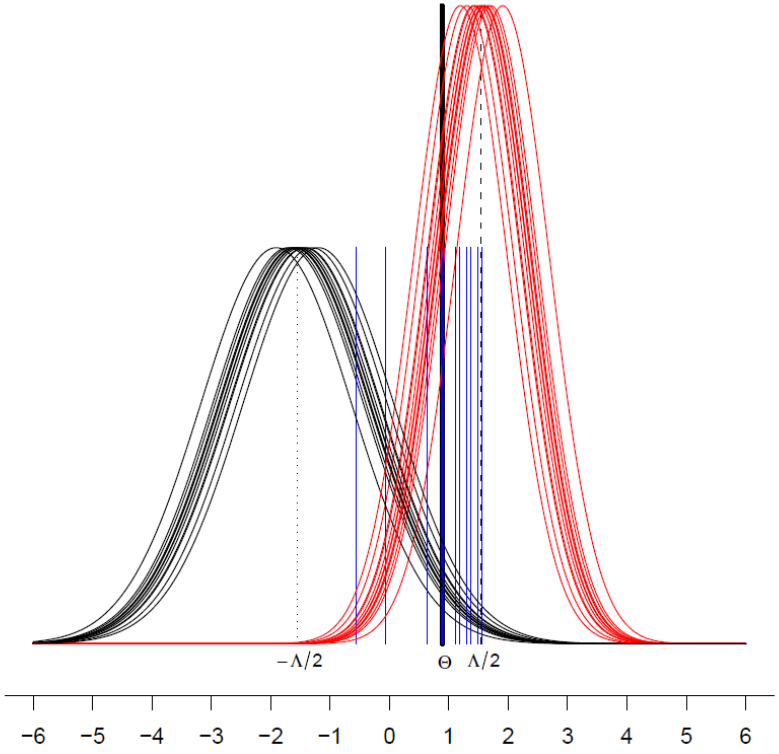


Impact of adjustment on heterogeneity due to threshold

Adjusting for imperfect Ref



Assuming Ref perfect



Variability in threshold diminished when adjusting for reference standard accuracy.