

 **K N C V**



TUBERCULOSISFOUNDATION

Tuberculin skin test and interferon-gamma assays in ARI surveys

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Annual risk of TB infection

= average annual risk in a population of getting (re-)infected with *M. tuberculosis*

- Estimated from age-specific prevalence of TB infection measured by tuberculin skin testing
- Usually among school-age children
 - recent transmission
 - low HIV prevalence
- Point estimate (derive prevalence/incidence)
- Trend over time

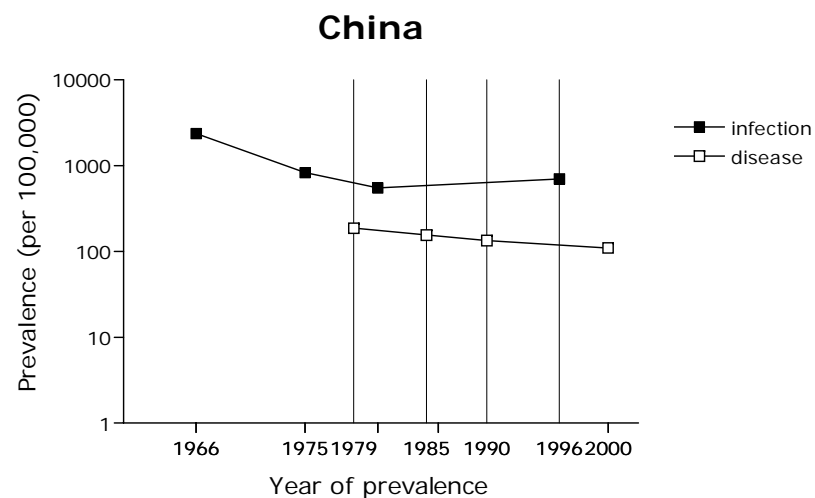
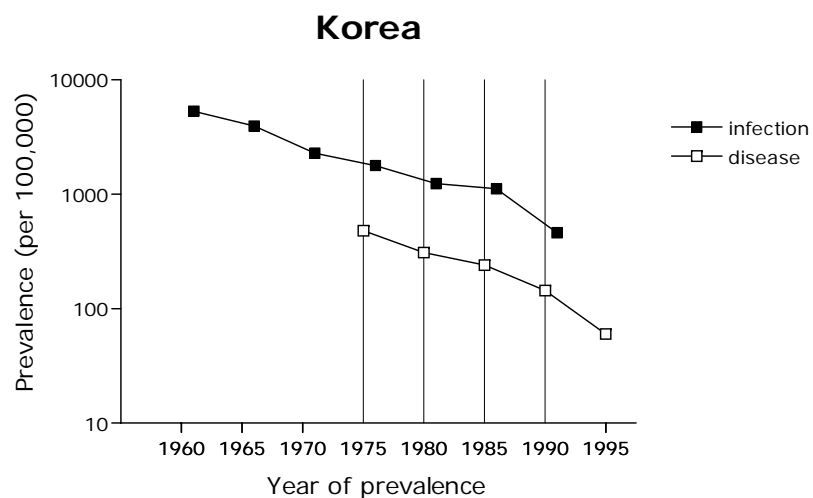


ARI surveys

- Nationwide or regional
- Representative study population
- Generally school-based (ages 6-14)
- Cluster design
 - Select districts
 - In districts select schools
 - In school test all children of eligible age
- Primary analysis based on unvaccinated children



Prevalence of disease and infection



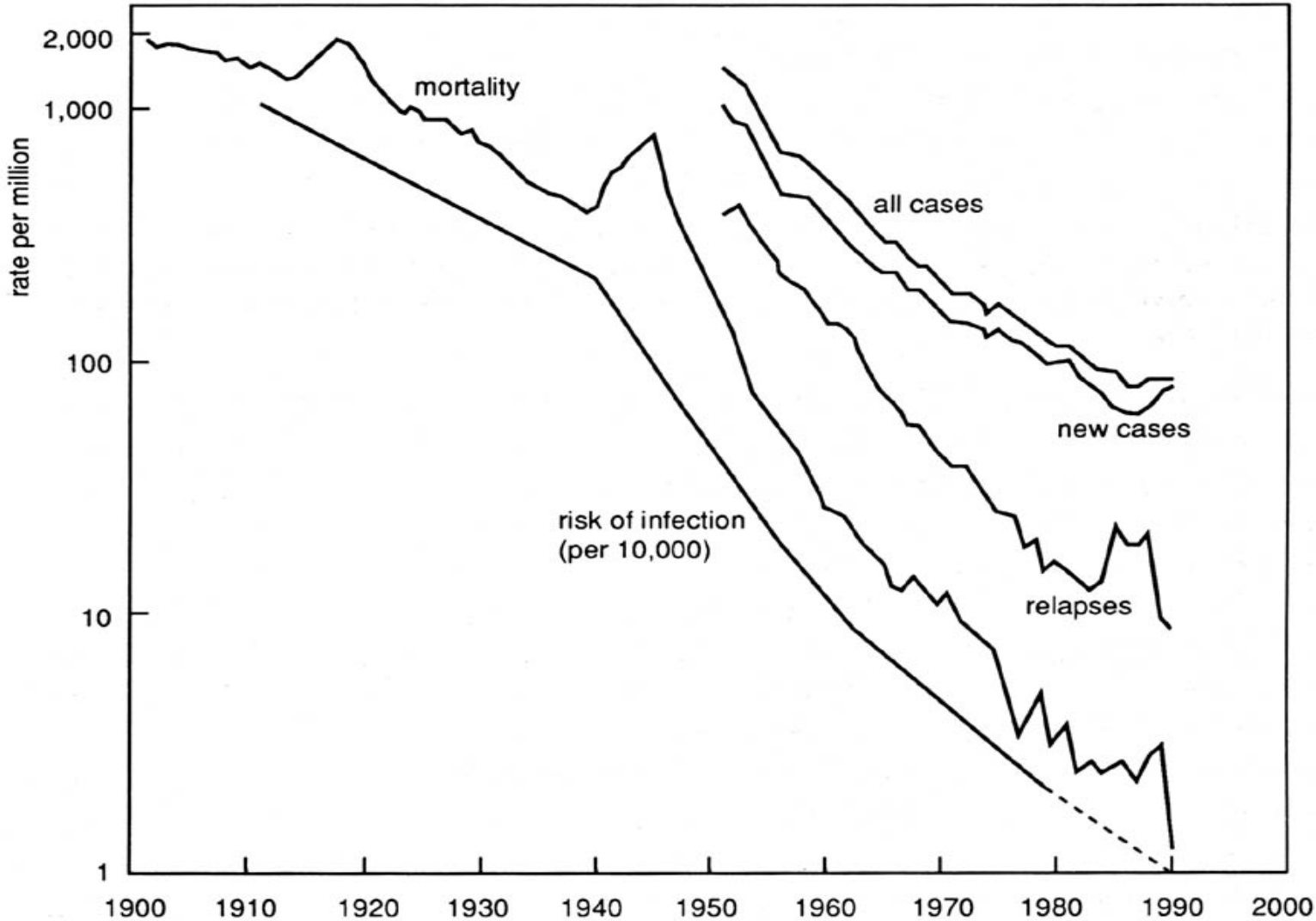
References:

Korea - Hong et al. Tuber Lung Dis 1993 and Int J Tuberc Lung Dis 1998

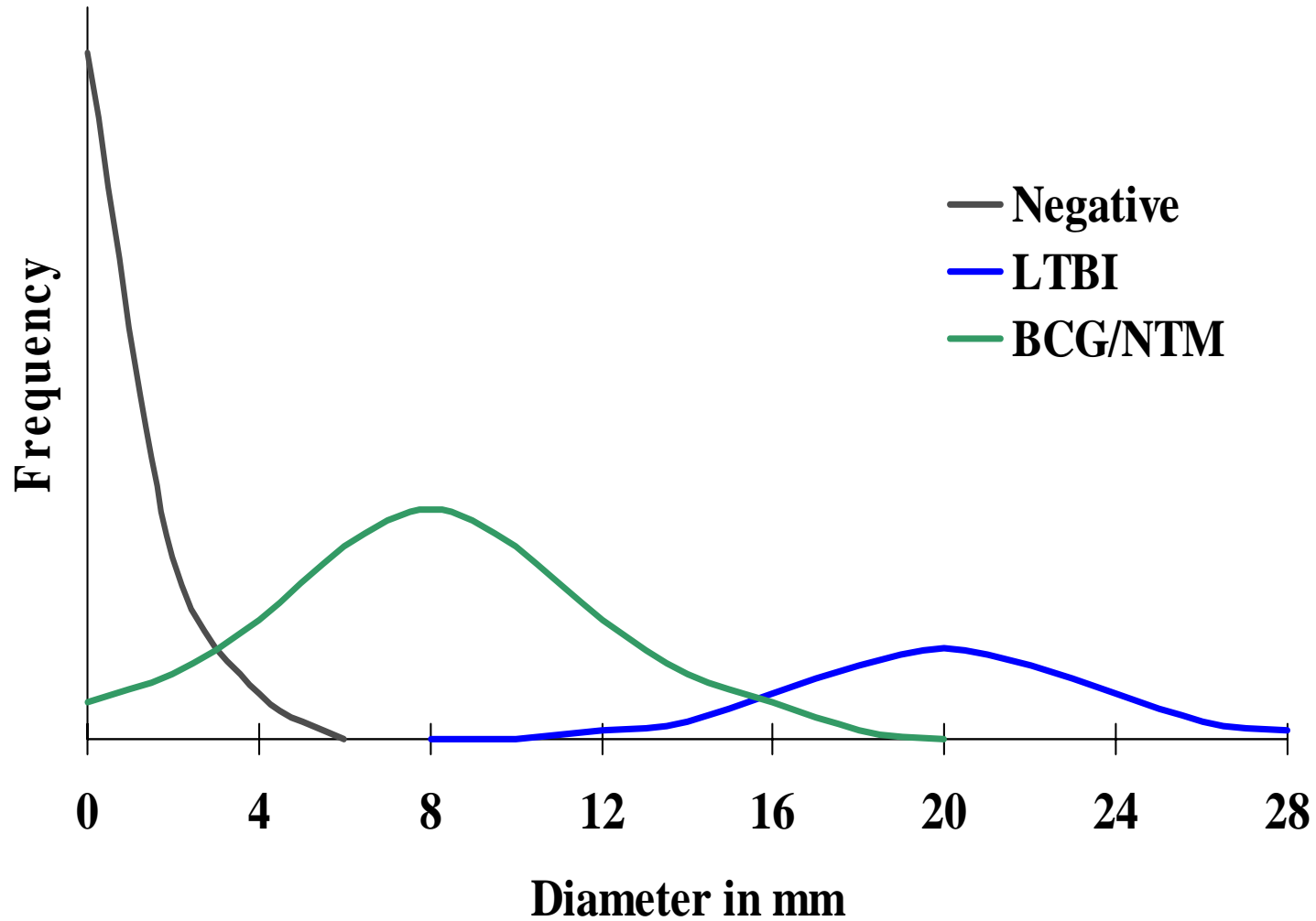
China - China Tuberculosis Control Collaboration. Lancet 2004



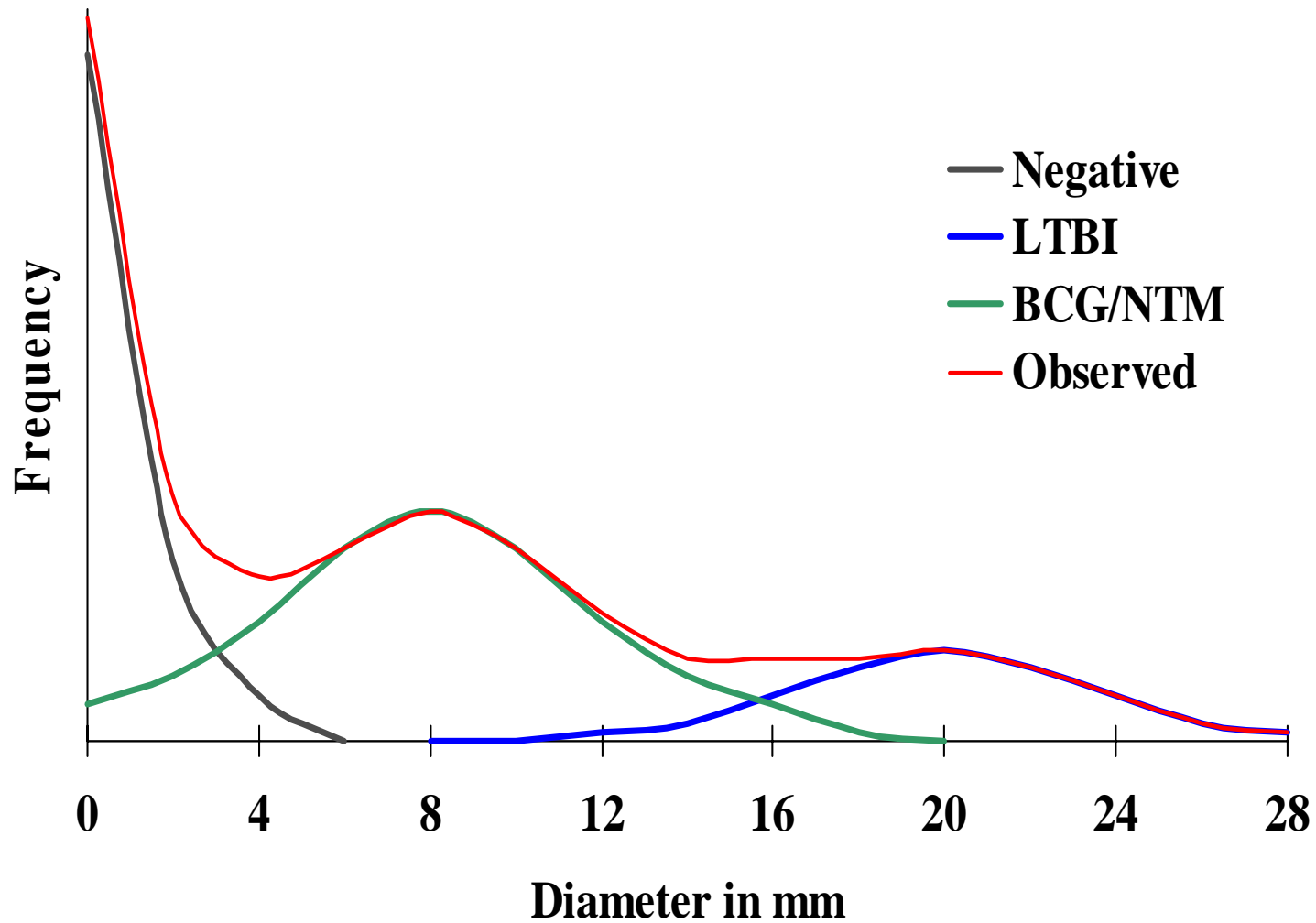
TB trends in The Netherlands, 1900-1990

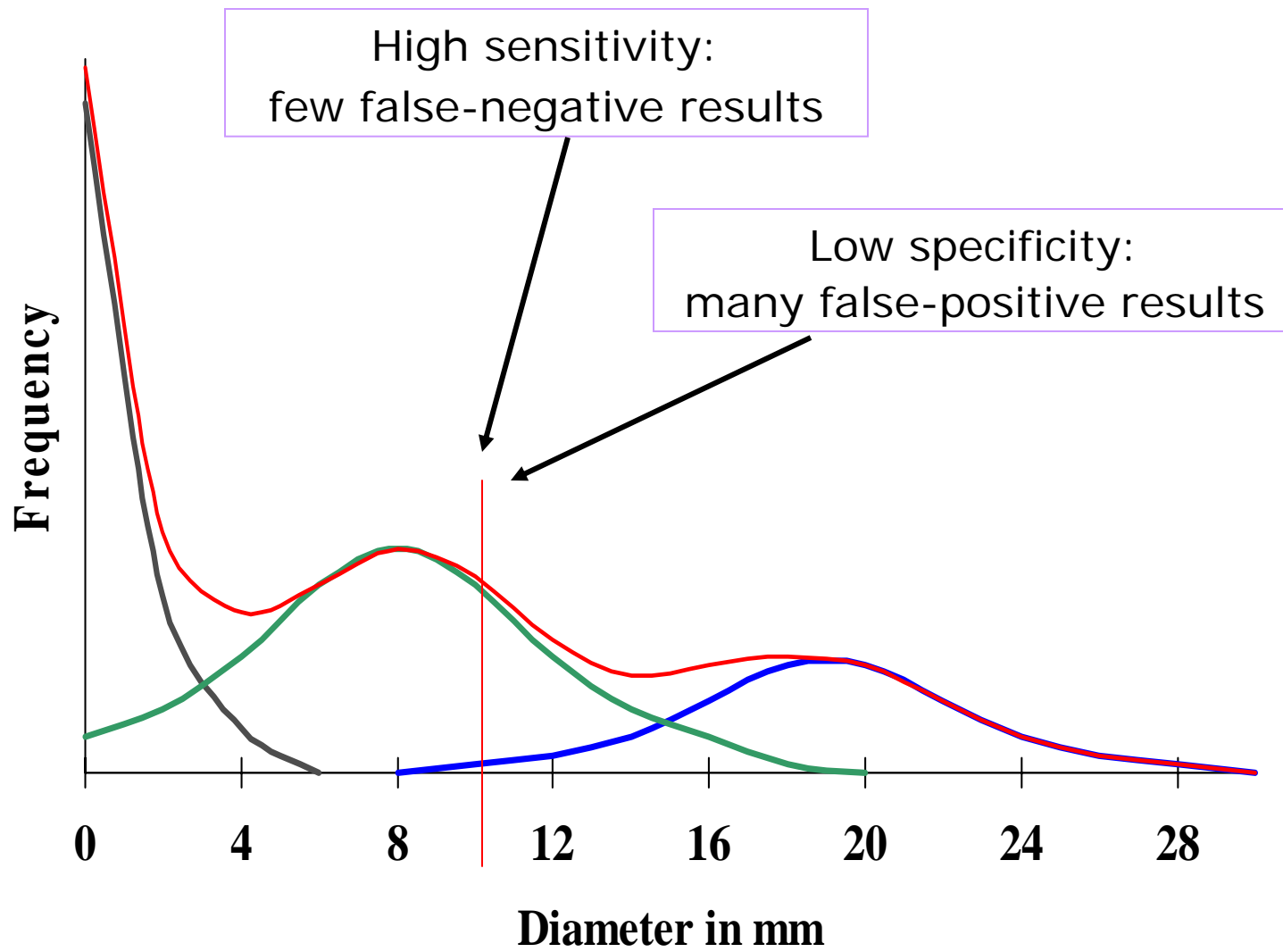


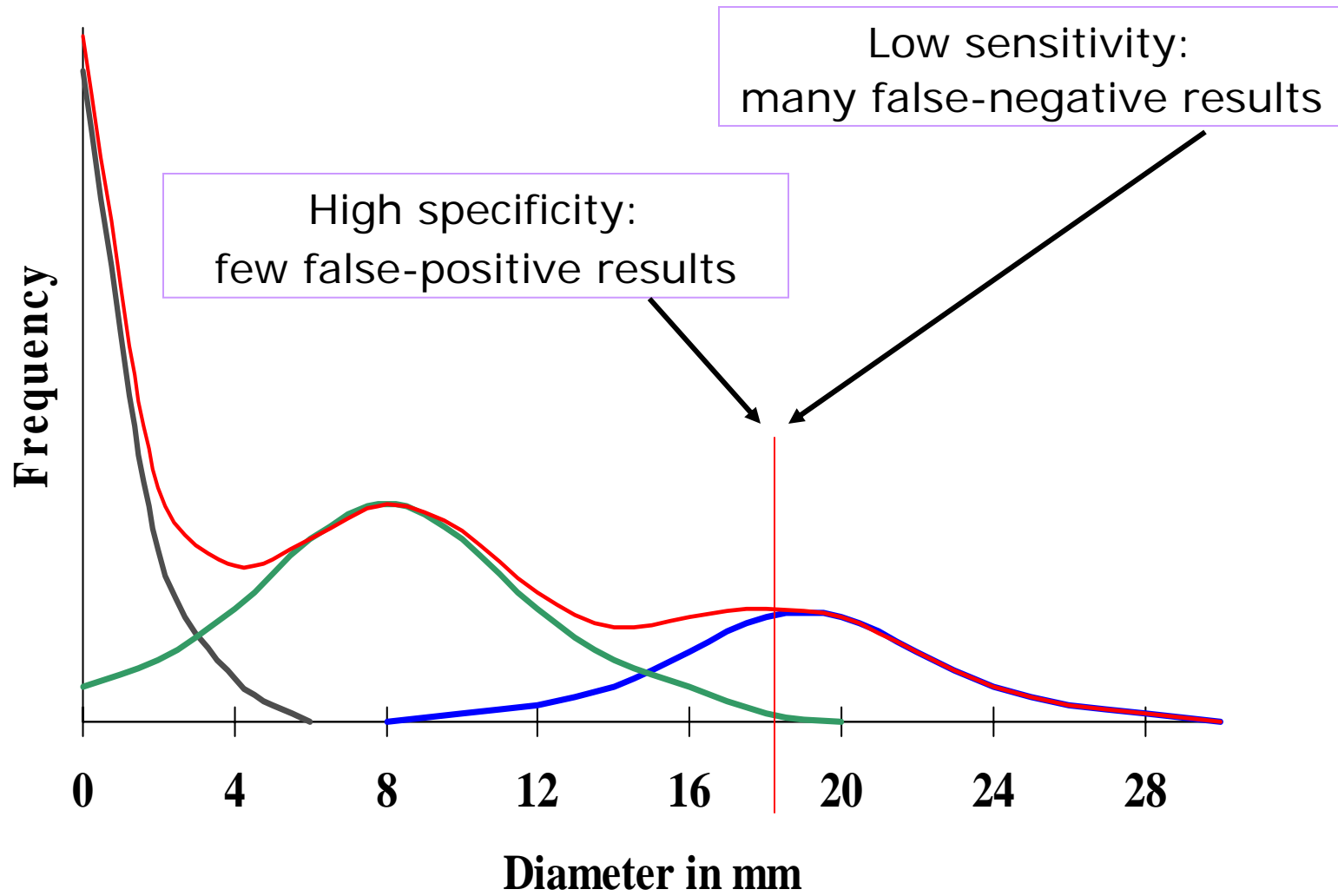
When is the TST positive?

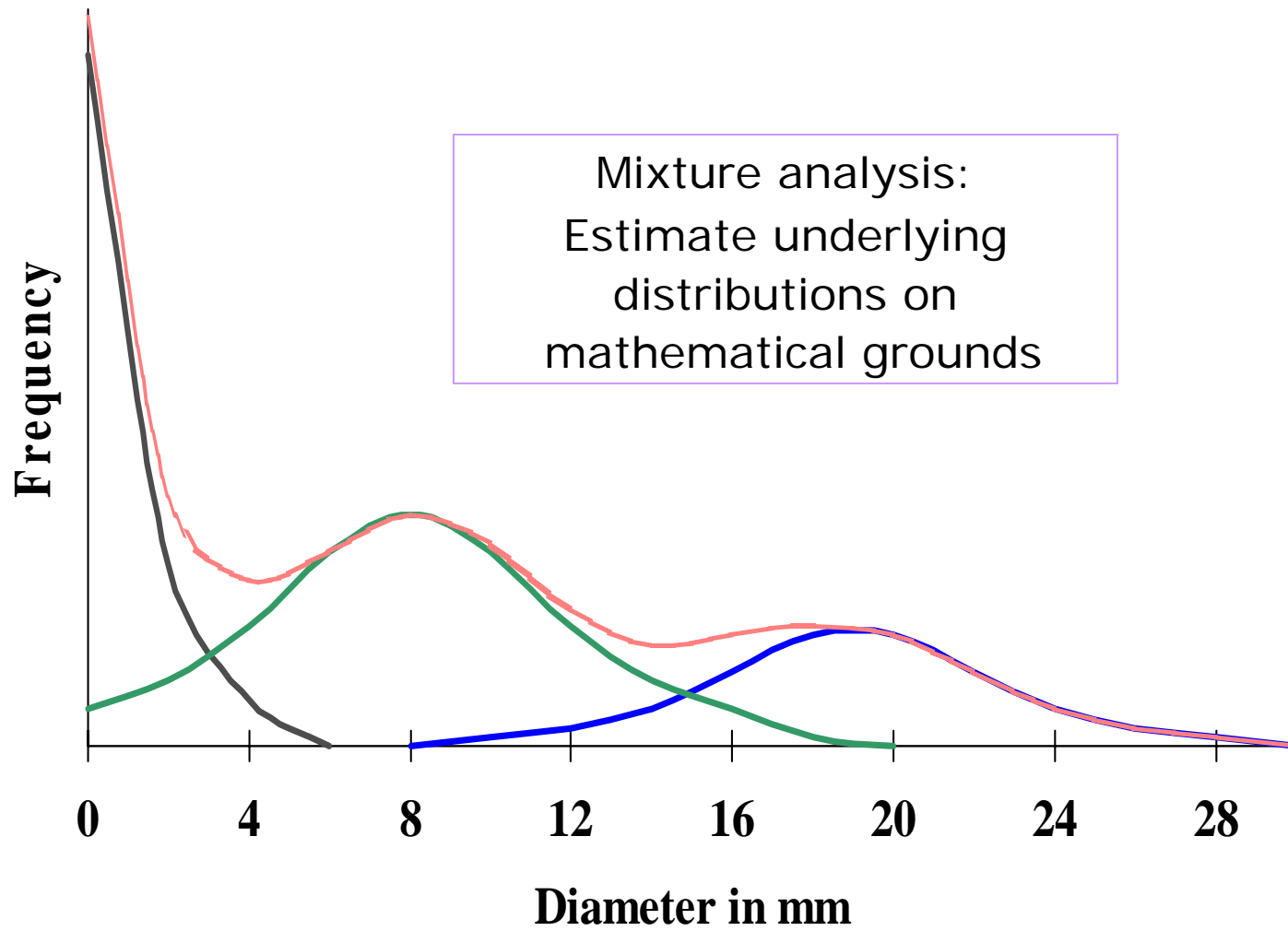


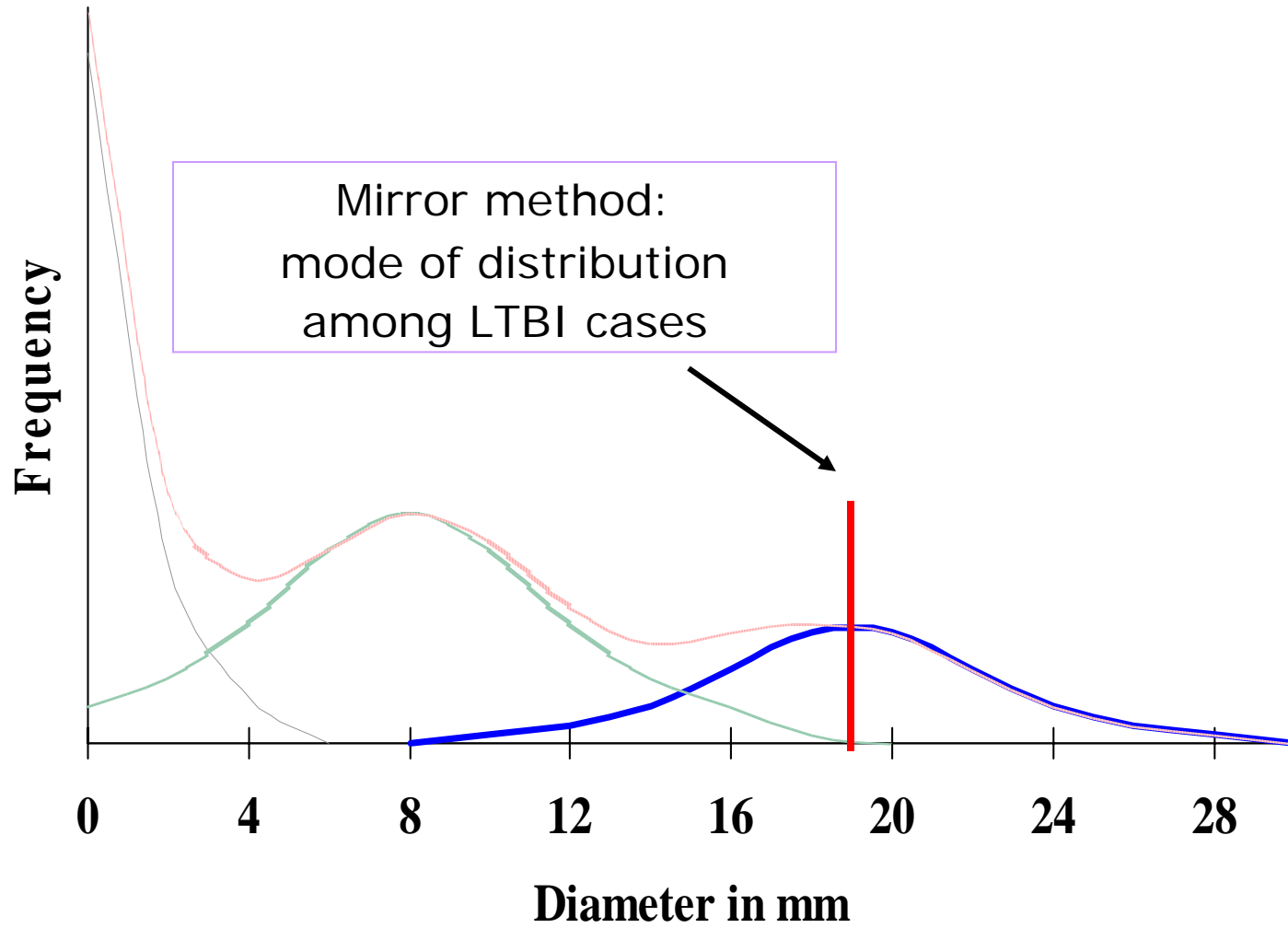
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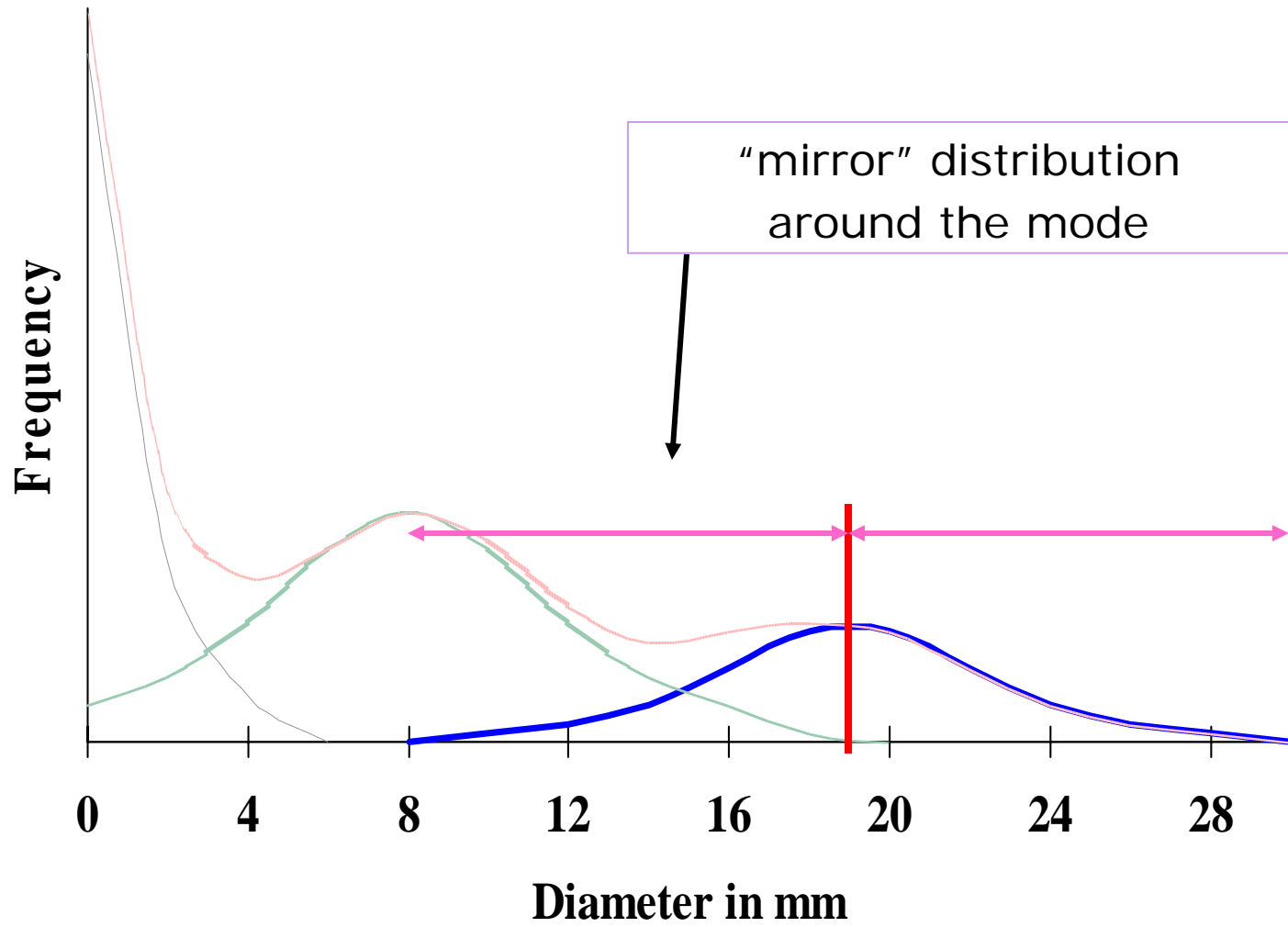


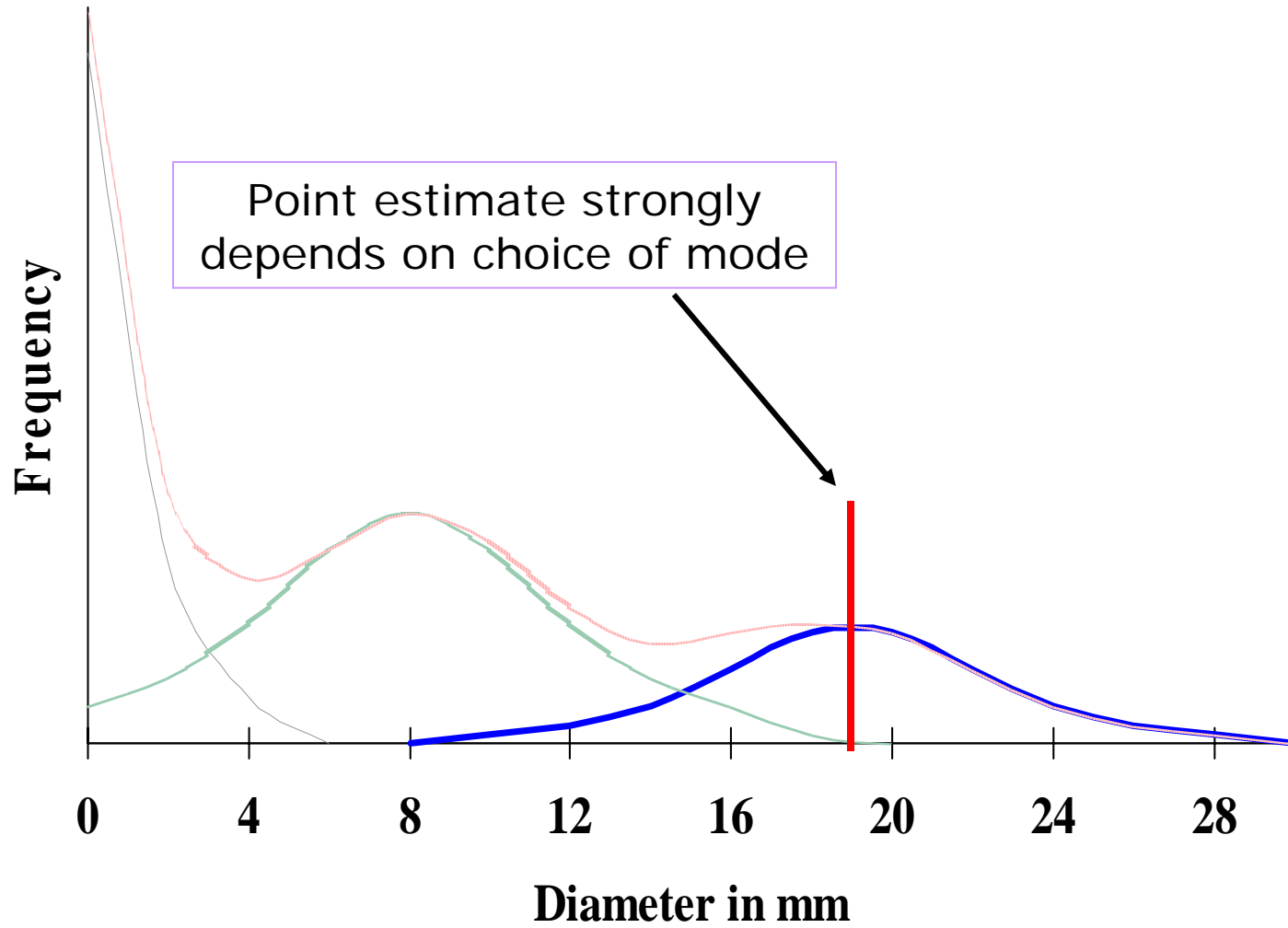








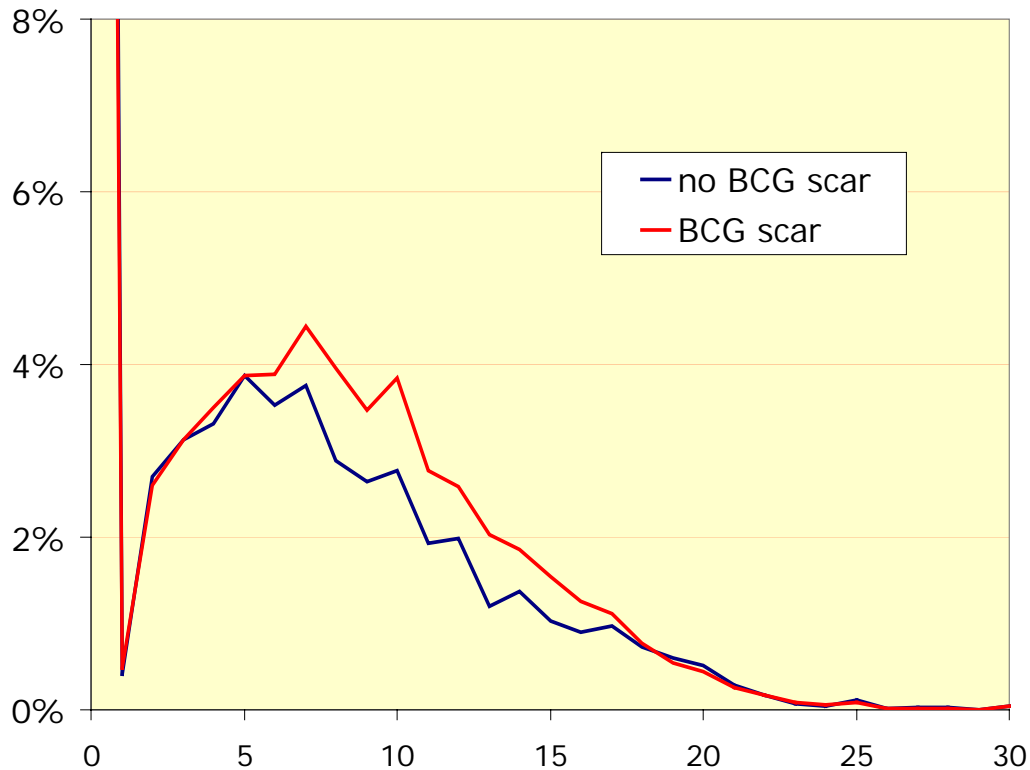




Tanzania tuberculin survey

4th round (1999-2003)

BCG = 10,239 No BCG = 85,287

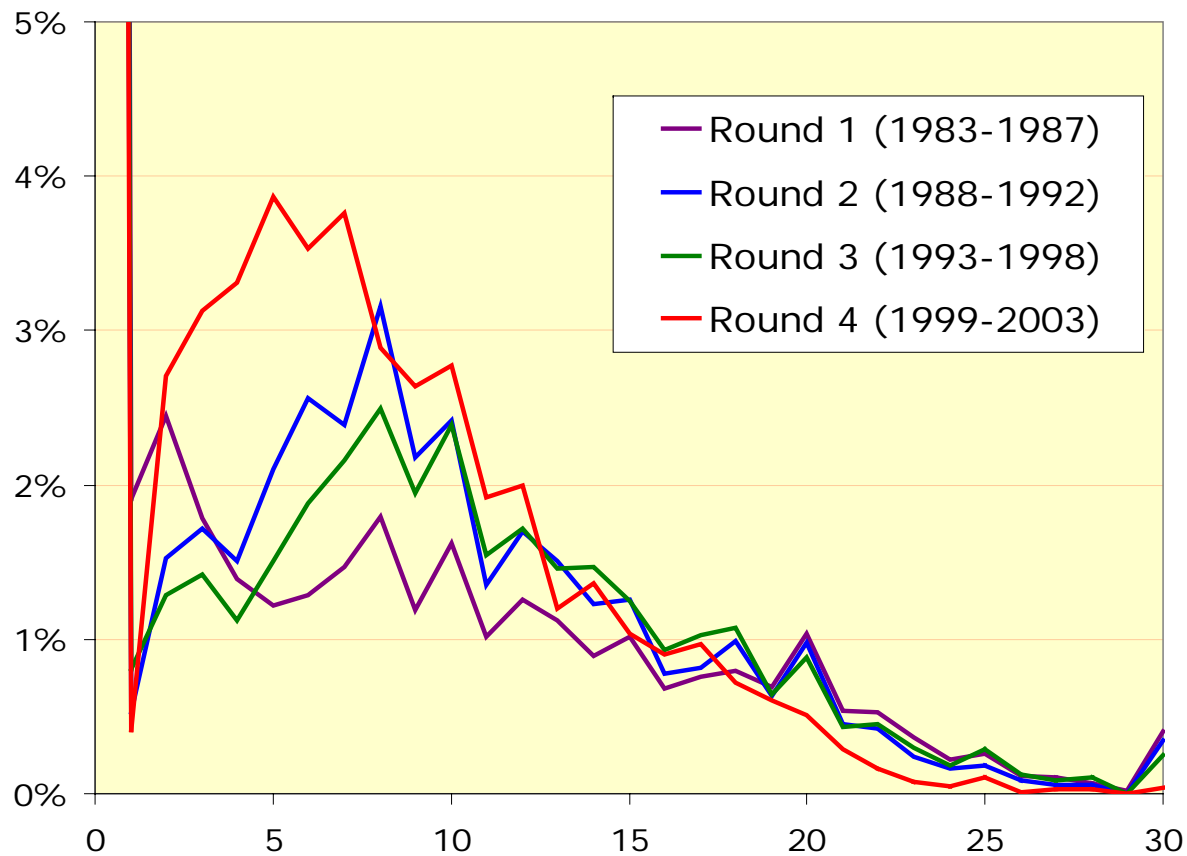


- Strongly overlapping distributions
- no BCG effect ≥ 17 mm
- only 11% has no BCG scar (large sample size)
- how representative are these children?



Tanzania tuberculin survey, 1983-2003

Reaction size distributions in children with no BCG scar

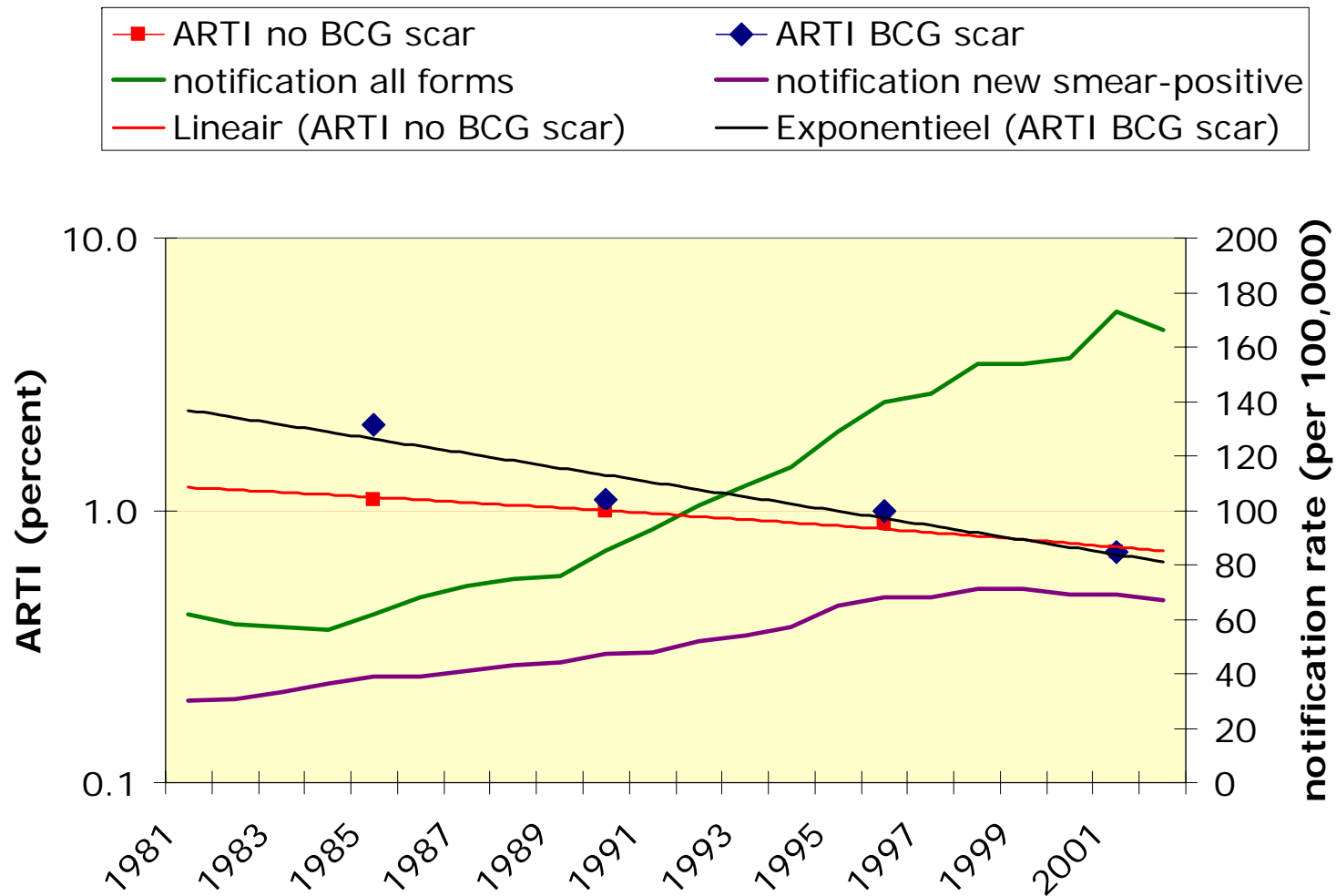


Egwaga et al. AIDS *in press*



Tanzania tuberculin survey, 1983-2003

Trends in case notification rates and ARTI

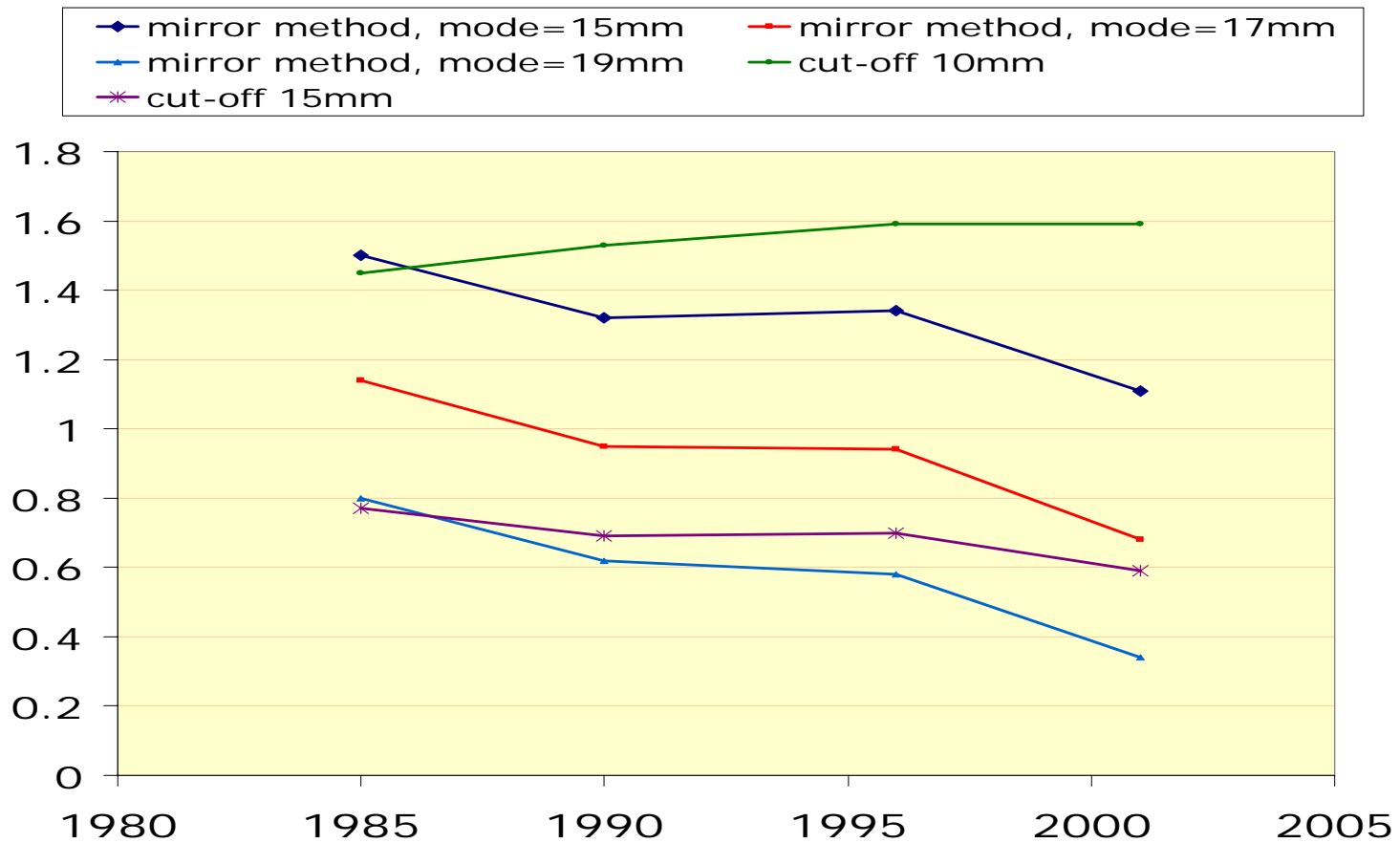


Egwaga et al. AIDS *in press*



Tanzania tuberculin survey, 1983-2003

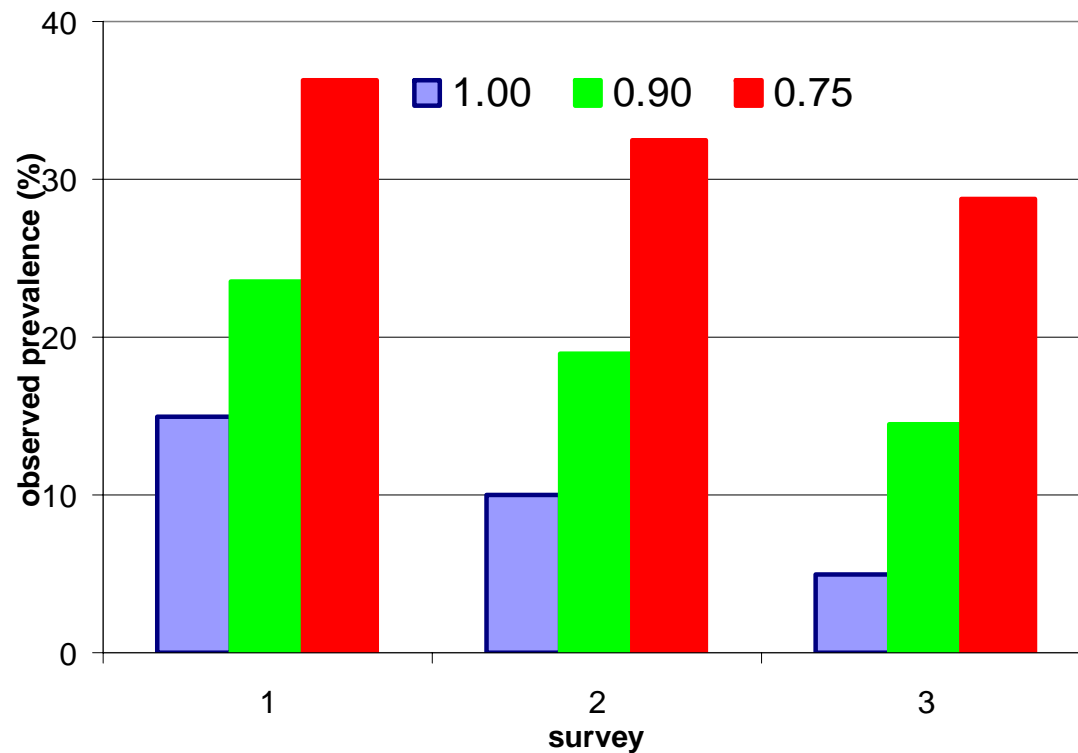
Trend in ARTI using various definitions of latent TB infection



Egwaga et al. AIDS *in press*



Incomplete specificity produces biased trend estimates



Average OR:

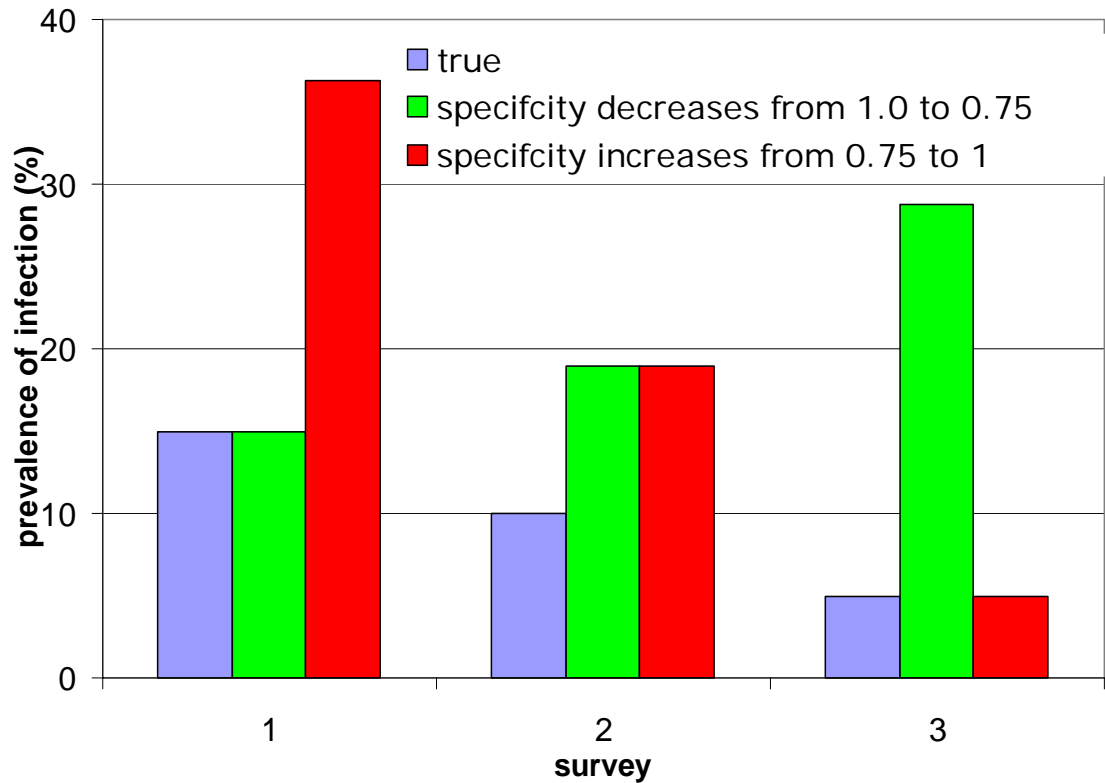
Spec=1.00 0.55

Spec=0.90 0.74

Spec=0.75 0.84



Changing specificity produces biased trend estimates



Average OR:

Spec true 0.55

Decreases 1.52

Increases 0.32



Reading variability



- Inter-observer variability
- Intra-observer variability
- Terminal digit preference
- Administration errors
- Recording errors
- Conservation errors
tuberculin (cold chain)



ARTI surveys

issues in using TST: strengths

Advantages

- No lab required
- No blood taken



ARTI surveys

IGRA: potential strengths

- No effect of BCG
 - Total sample sizes can be smaller
 - No BCG-related selection bias or misclassification
- Less effect of environmental infections
 - More valid trend estimates
 - Less likely to change over time
- Standardized method
 - Limited inter/intra-observer variability
 - No administration errors or digit preference
- Single contact



ARTI surveys

I GRA: potential limitations - 1

- Need venous blood
 - Acceptability: volume, venapuncture/finger
 - Technical requirements
- Transit restrictions of specimens
 - Time allowed (where can processing be done?)
 - Conditions
- Need lab
 - Equipment (e.g. ELISA)
 - Capacity (cell separation needed?)
- Cost
 - Test kits & supplies
 - Equipment (e.g. ELISA)



ARTI surveys

IGRA: potential limitations - 2

- Specificity unclear in some populations
 - High prevalence of *kansasii*, *szulgai* or *marinum* infections
 - Effect of *M. leprae* infections?
- Sensitivity may be less than TST
 - no biased trend estimates but will affect study power
 - may reflect recent rather than lifetime infection risk



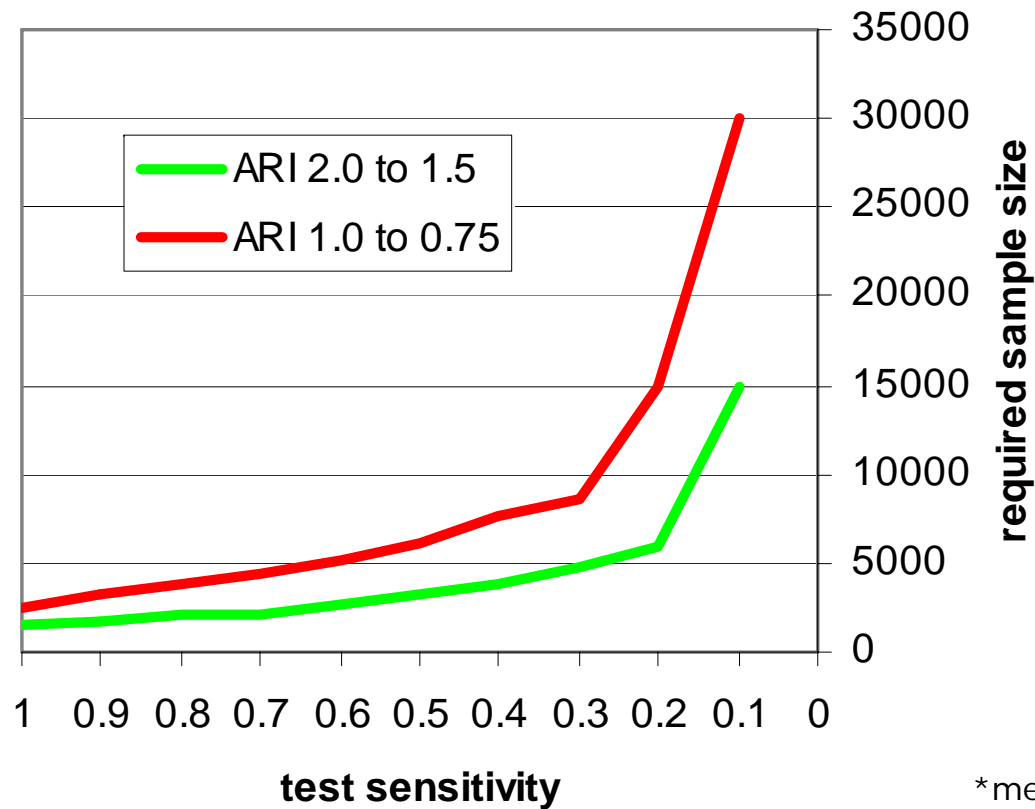
What if IGRA are less sensitive for detecting remote infections?

- “Classical” ARI cannot be estimated from cross-sectional designs
 - ARI estimated from observed prevalence and mean age
 - Assume constant ARI & test sensitivity over time
- “Sensitivity-corrected” ARI
 - Don’t need to know sensitivity as long as it is constant over time and with age
 - Point-estimates of this ARI meaningless
 - Time trends can be estimated
 - May reflect more recent situation than classical ARI
 - Will affect study power and sample size



Incomplete sensitivity affects power for determining trends

Required sample size for 2 surveys among children* to detect a 25% decrease in ARI ($n_1=n_2$, $deff=1$)



*mean age 10 years

Alternative uses of IGRAs for estimation of ARI

1. Cross-sectional surveys in adults
 - acceptability
 - sentinel populations, e.g. recruits, workers
 - No/limited non-response in HIV infection
 - Useful if IGRAs primarily reflect recent infection
 - Trade-off with study power
2. For determining cut-off for TST
 - estimate population-specific sensitivity and specificity using IGRAs as standard
 - Small scale studies in children



Issues for research - 1

1. Sensitivity IGRA (remote infections!)
 - IGRA-based infection prevalence in randomly selected adults in high-prevalence countries
 - Compare TST and IGRA in subjects with history of documented TST conversion following TB exposure, after various time intervals
2. Specificity IGRA in populations with high prevalence of EM or *M. leprae* infections
 - Test randomly selected subjects in areas with low LTBI but high EM prevalence?
 - e.g. southern USA, northern Australia
 - Compare IGRA in subjects with and without household leprosy exposure



Issues for research - 2

- Field feasibility and robustness
 - Longer transit times
 - Processing close to the field
 - Smaller blood volumes
 - Test validity under survey conditions
- Cost-effectiveness
 - Compare current strategies with strategies using IGRA
- Develop and validate skin test reagents based on RD1 antigens



Conclusions

- Replacing TST by IGRA in ARI surveys may improve validity and reduce sample sizes
- Sample size reduction may be offset by lower sensitivity and require “corrected” ARI (trends)
- Specificity not entirely established
- Logistics problematic (QFN IT more suitable)
- Cost may be prohibitive





THANK YOU

