SMARTube™ as a Test for Recent Infection

Reshma Kassanjee[1,2], Alex Welte[1,2], Tamar Jehuda-Cohen[3]

[1] University of the Witwatersrand, South Africa

[2] South African DST/ NRF Centre for Epidemiological Modelling and Analysis, South Africa

[3] Smart Biotech Ltd, Israel

Tests for Recent Infection (TRI's)

- What?

  Classify infections as recently or non-recently acquired

- Why?

  Incidence estimation

  Using cross-sectional surveys rather than prospective follow-up

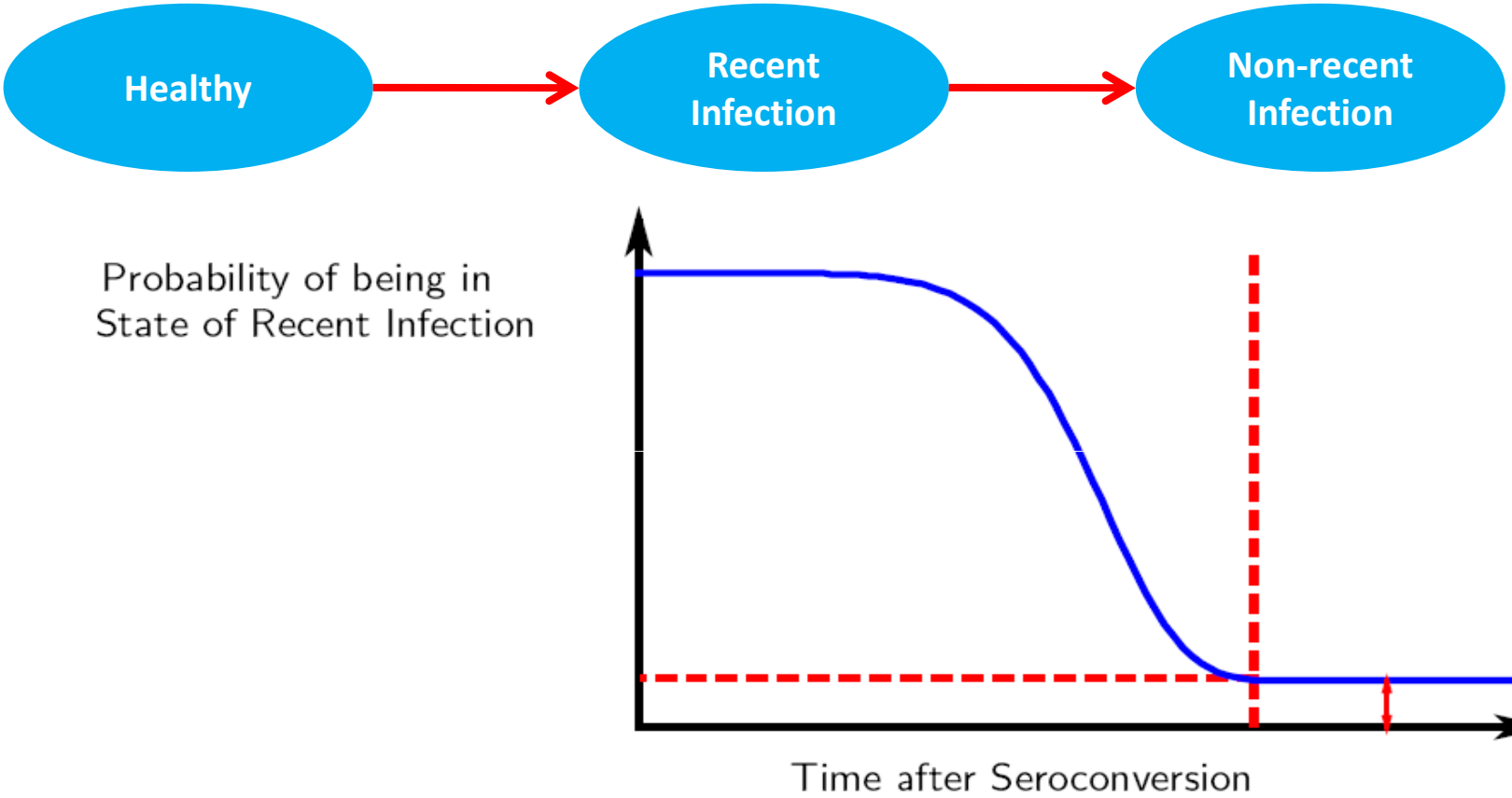
- Challenges?

  Achieve certain performance characteristics (**not** specificity / sensitivity)

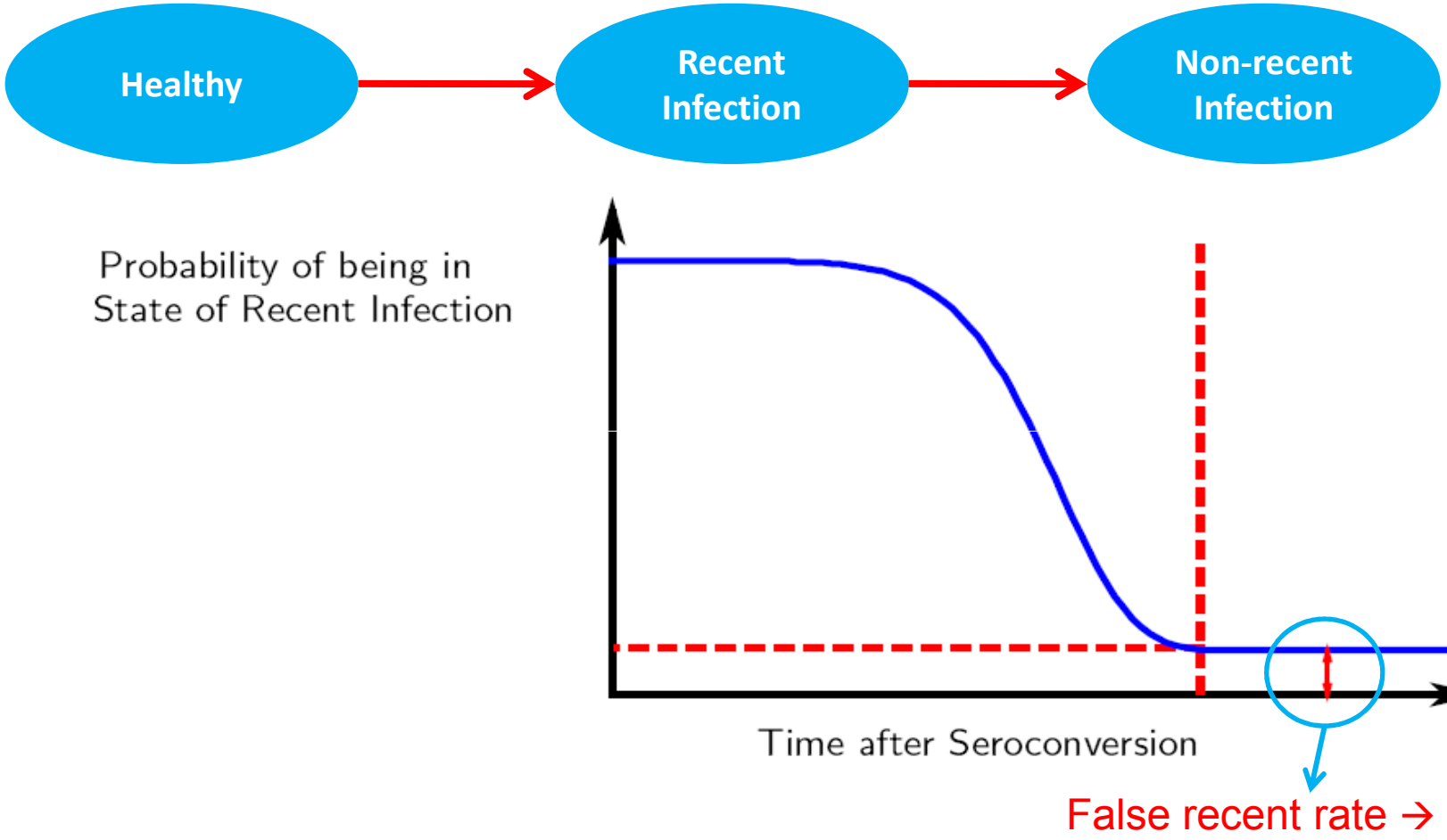
  Surveillance, not **diagnostics**

Performance Requirements

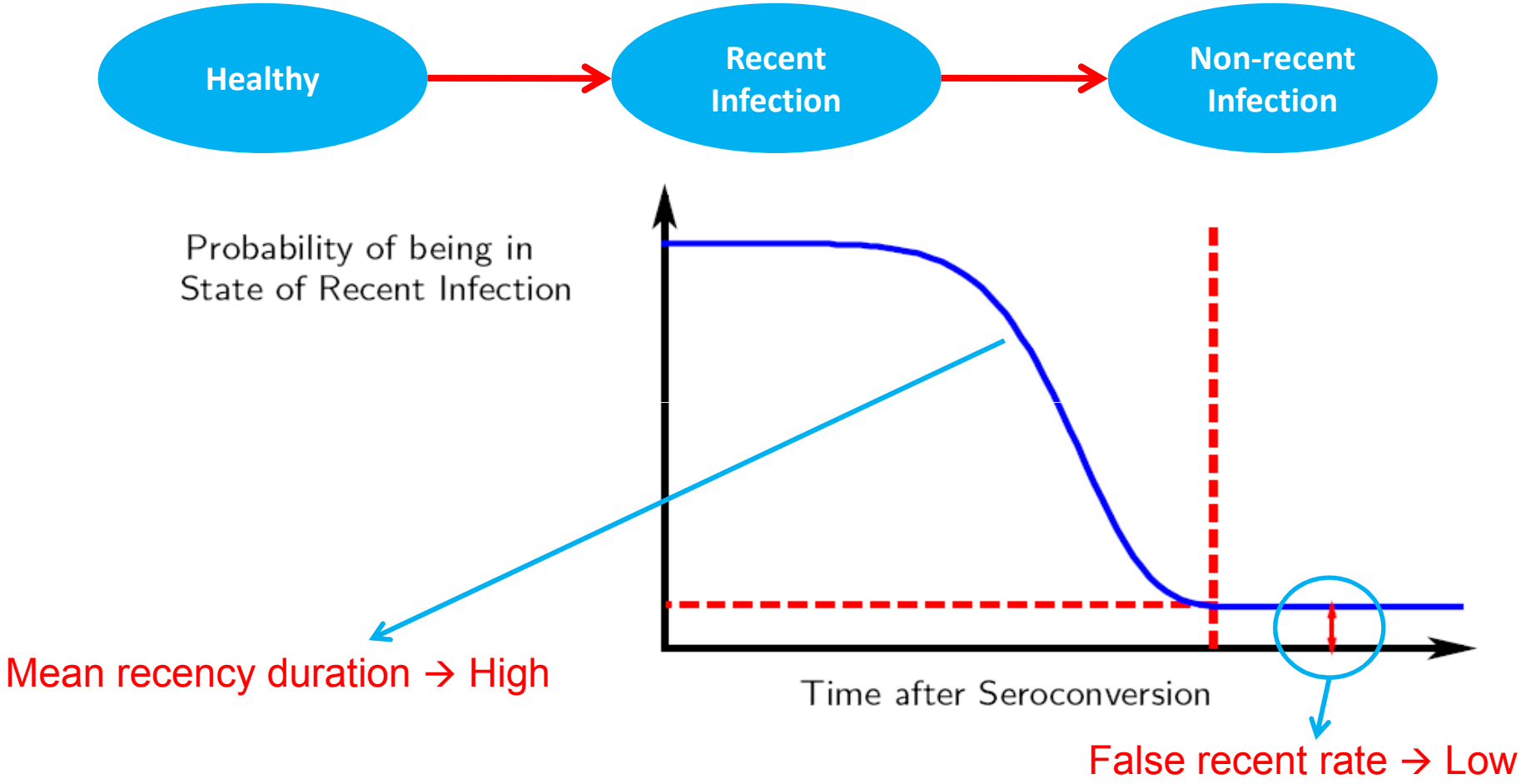
Performance Requirements



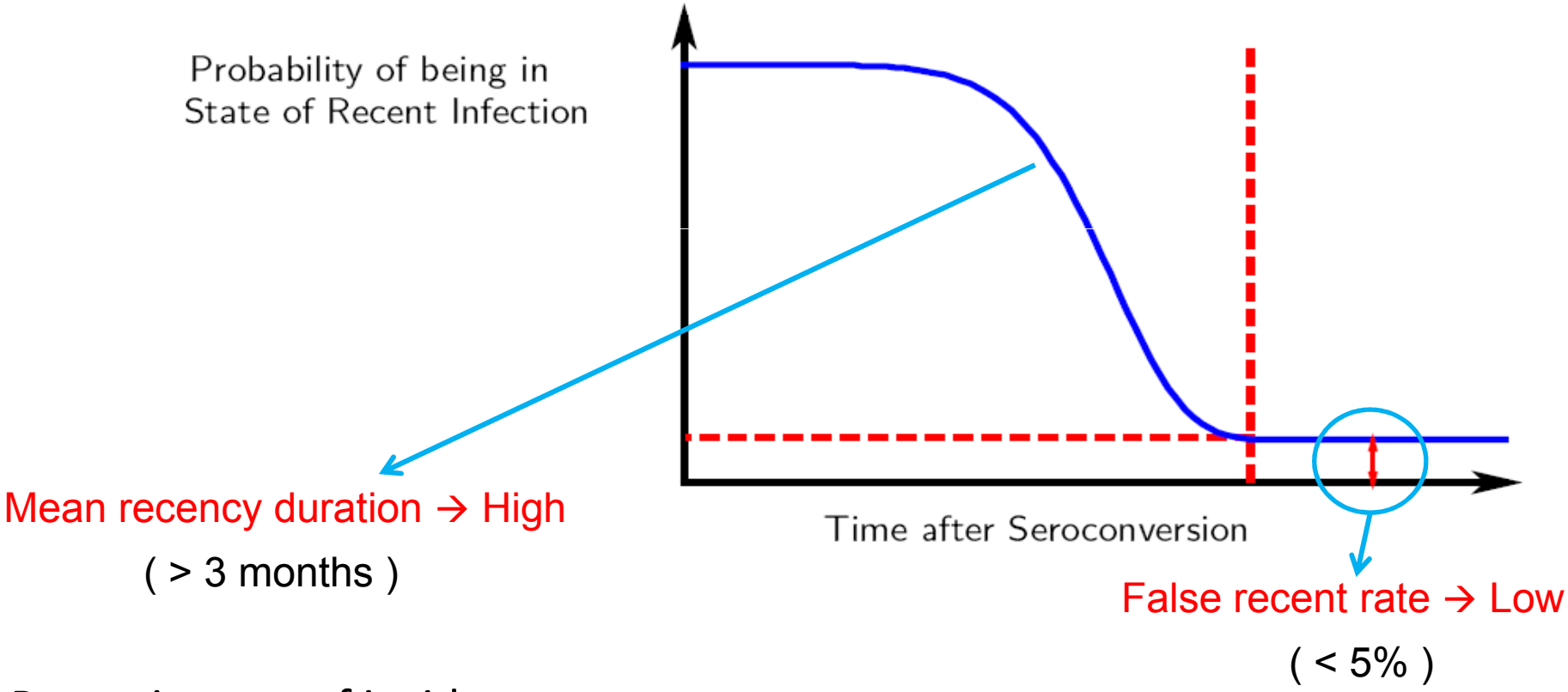
Performance Requirements



Performance Requirements



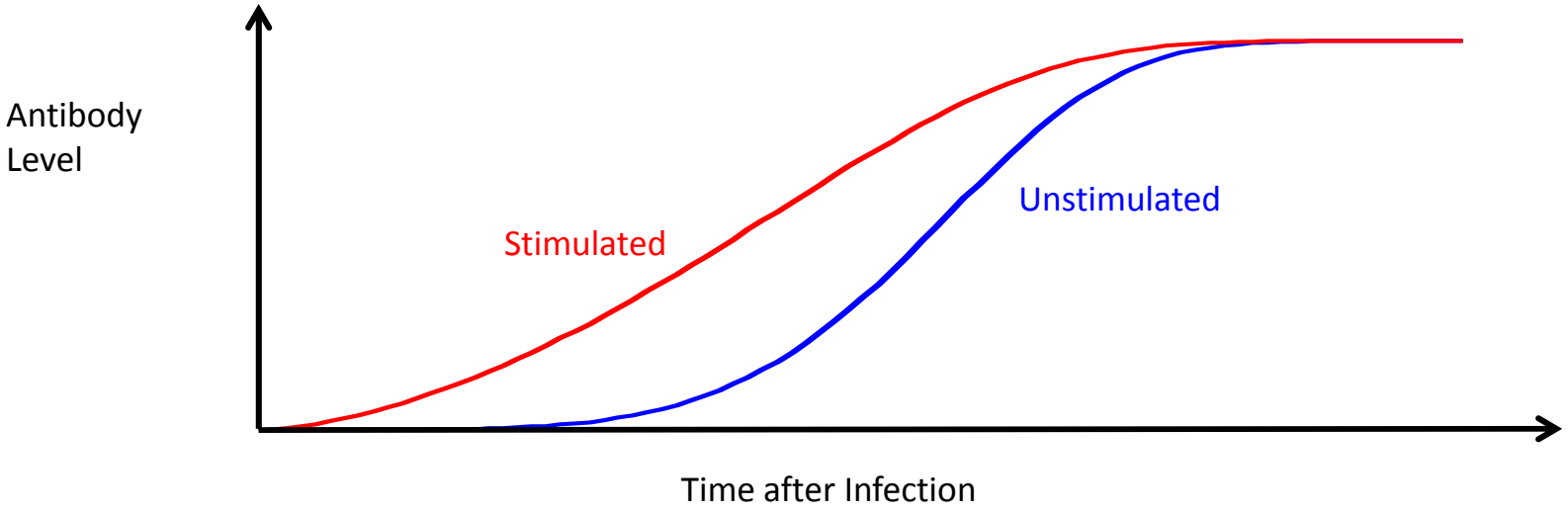
Performance Requirements



Power in tests of incidence:
http://www0.sun.ac.za/sacema/collaboration/abie/

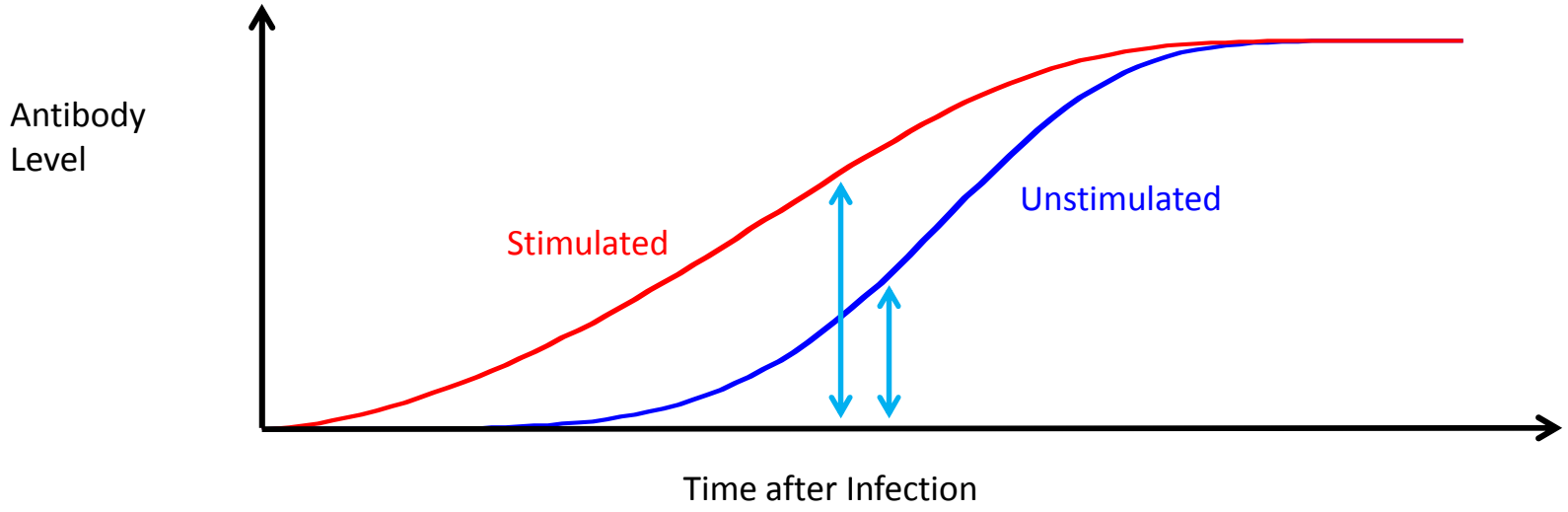
SMARTube™ Technology

- Stimulating Maximal Antibody Response Tube
  - In-vitro stimulation of antibody producing B cells
  - Allows for earlier detection of HIV infection



SMARTube™ Technology

- Stimulating Maximal Antibody Response Tube
  - In-vitro stimulation of antibody producing B cells
  - Allows for earlier detection of HIV infection



→ Novel biomarker for a test for recent infection

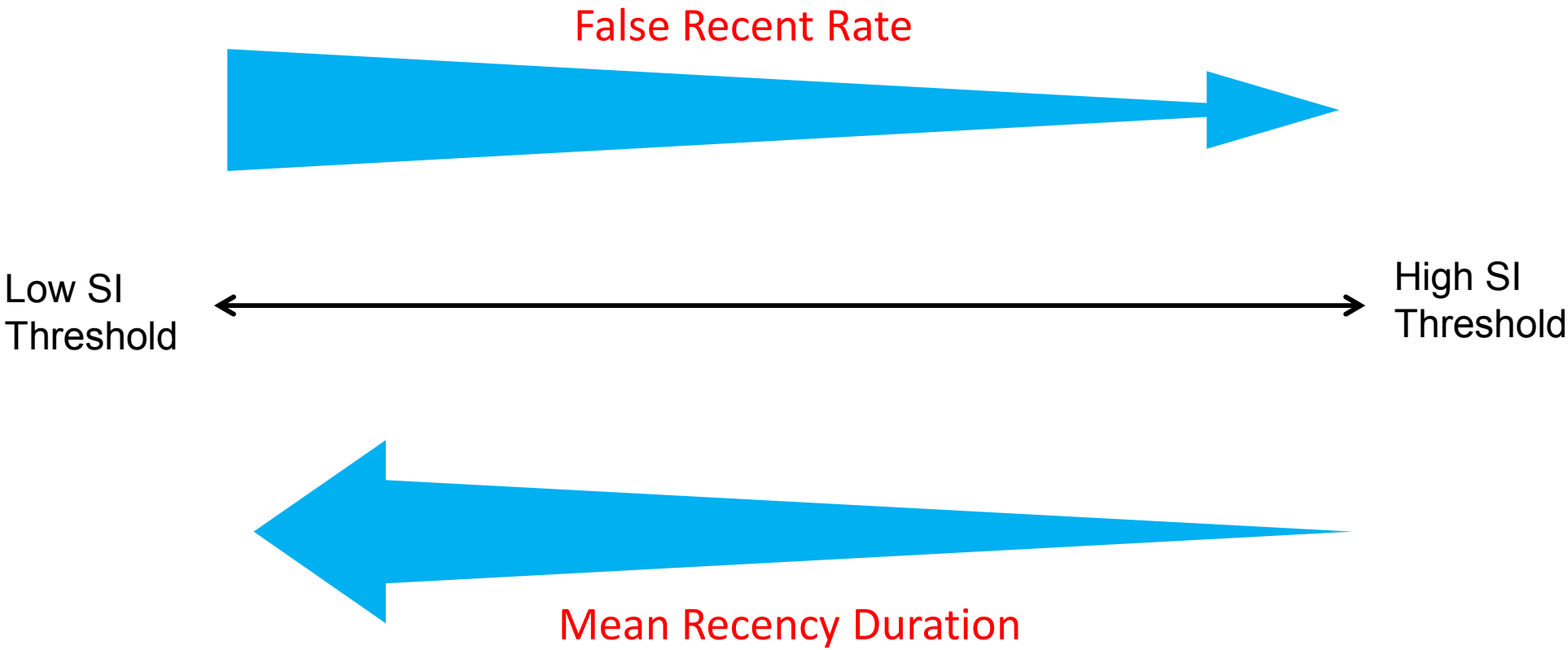
- Stimulation Index: $SI = \frac{\text{Stimulated Antibody Level}}{\text{Unstimulated Antibody Level}}$
- Recent infection ↔ SI > SI Threshold

Performance of a Recency Test Using SMARTube™

Convenience sample of seropositive individuals in China, method of maximum likelihood

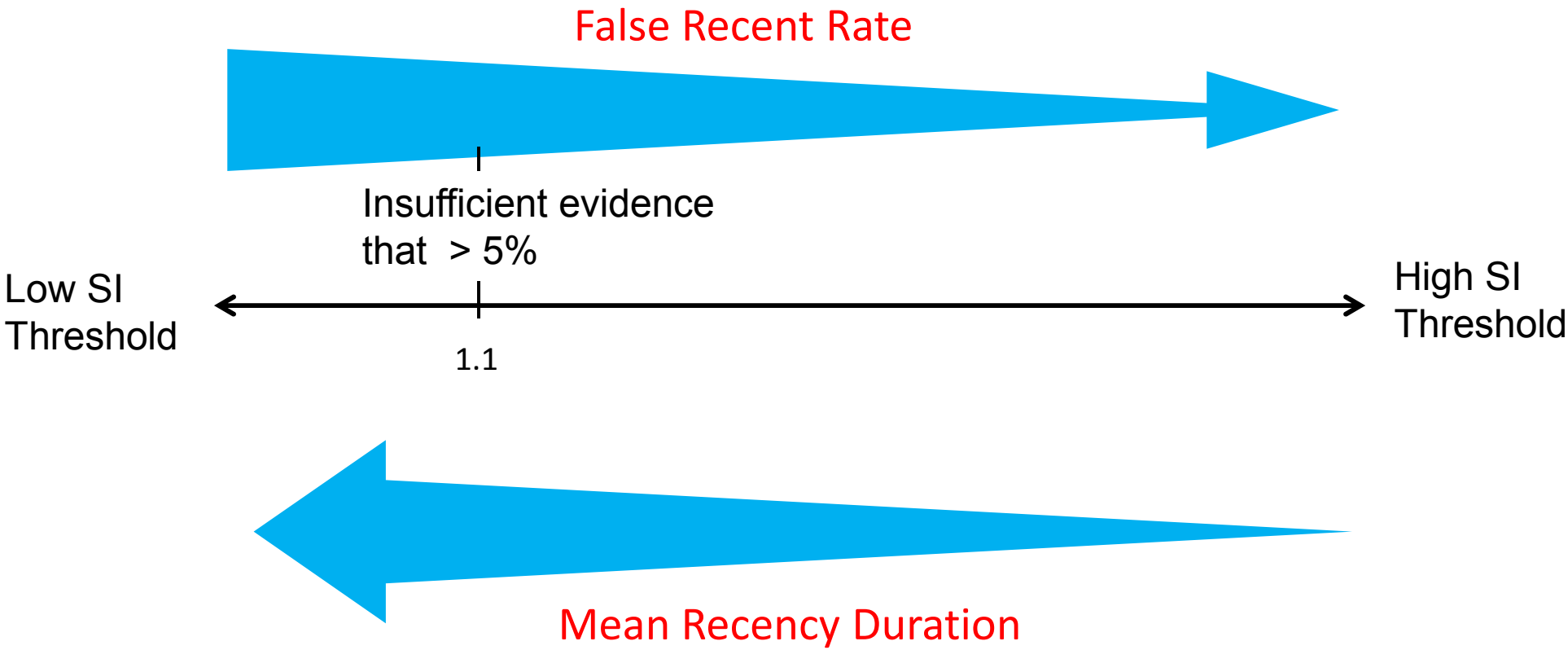
Performance of a Recency Test Using SMARTube™

Convenience sample of seropositive individuals in China, method of maximum likelihood



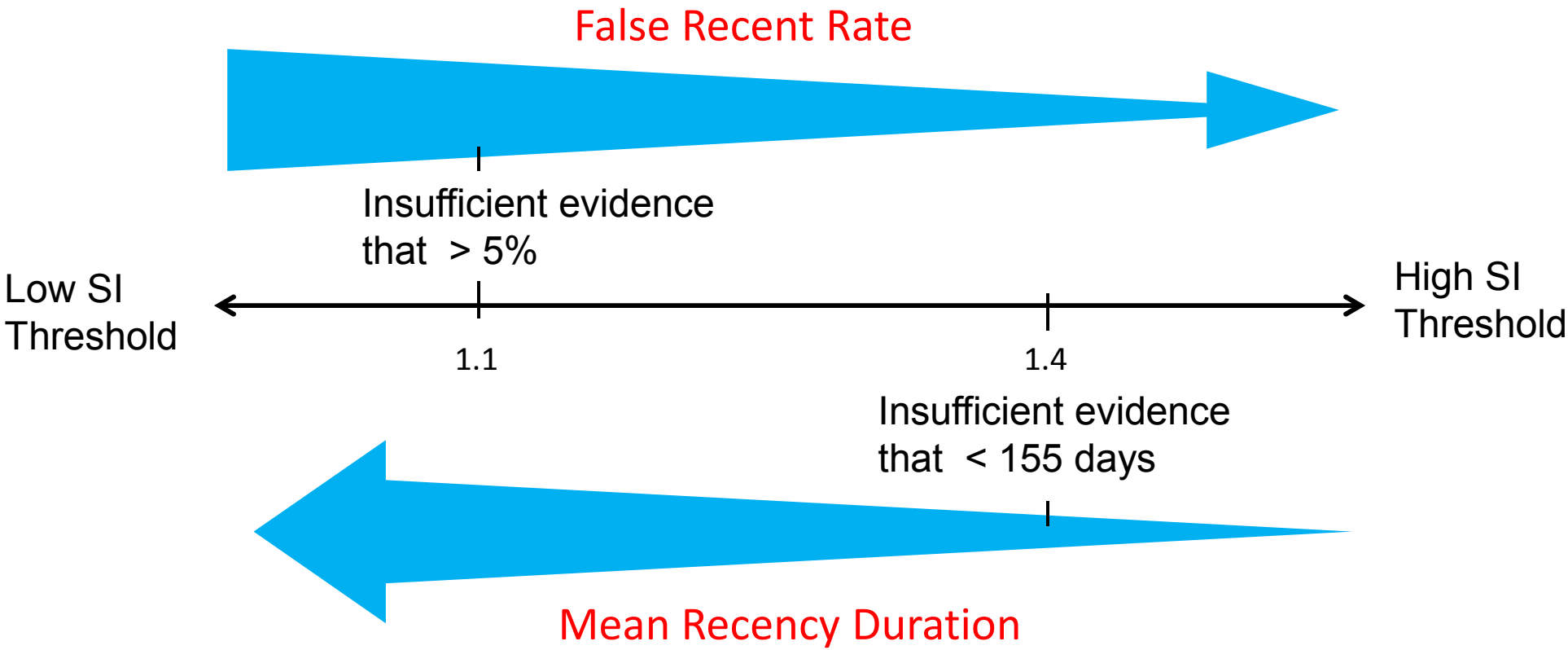
Performance of a Recency Test Using SMARTube™

Convenience sample of seropositive individuals in China, method of maximum likelihood



Performance of a Recency Test Using SMARTube™

Convenience sample of seropositive individuals in China, method of maximum likelihood



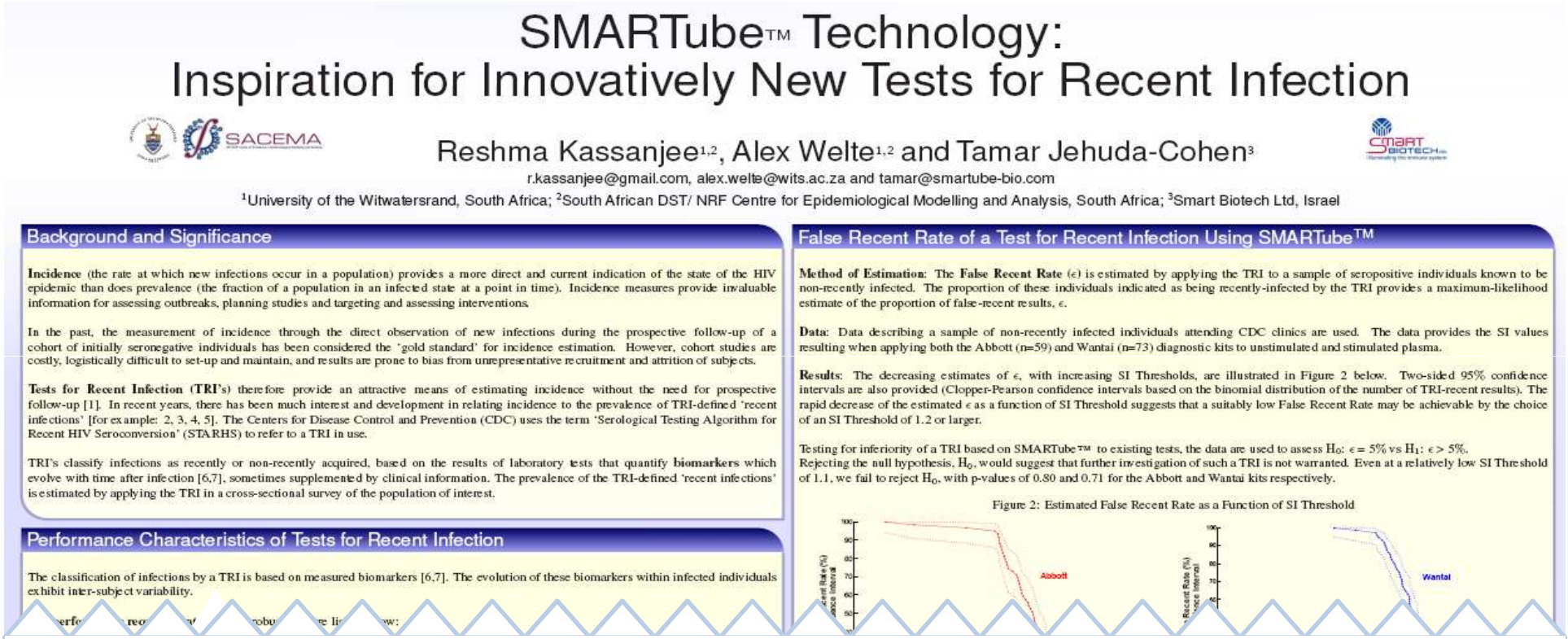
Conclusion

- Preliminary analysis provides promising results
- Test for recent infection using SMARTube™
  - Low false recent rate

    AND
  - High mean recency duration
- Recommend a larger dataset of better characterised specimens is analysed
- There is scope for non-traditional approaches for constructing tests for recent infection

To find out more ...

Poster,



SMARTube™ Technology:
Inspiration for Innovatively New Tests for Recent Infection

Reshma Kassanjee[1,2], Alex Welte[1,2] and Tamar Jehuda-Cohen[3]
r.kassanjee@gmail.com, alex.welte@wits.ac.za and tamar@smartube-bio.com
[1]University of the Witwatersrand, South Africa; [2]South African DST/ NRF Centre for Epidemiological Modelling and Analysis, South Africa; [3]Smart Biotech Ltd, Israel

Background and Significance

Incidence (the rate at which new infections occur in a population) provides a more direct and current indication of the state of the HIV epidemic than does prevalence (the fraction of a population in an infected state at a point in time). Incidence measures provide invaluable information for assessing outbreaks, planning studies and targeting and assessing interventions.

In the past, the measurement of incidence through the direct observation of new infections during the prospective follow-up of a cohort of initially seronegative individuals has been considered the 'gold standard' for incidence estimation. However, cohort studies are costly, logistically difficult to set-up and maintain, and results are prone to bias from unrepresentative recruitment and attrition of subjects.

Tests for Recent Infection (TRI's) therefore provide an attractive means of estimating incidence without the need for prospective follow-up [1]. In recent years, there has been much interest and development in relating incidence to the prevalence of TRI-defined 'recent infections' [for example: 2, 3, 4, 5]. The Centers for Disease Control and Prevention (CDC) uses the term 'Serological Testing Algorithm for Recent HIV Seroconversion' (STARHS) to refer to a TRI in use.

TRI's classify infections as recently or non-recently acquired, based on the results of laboratory tests that quantify **biomarkers** which evolve with time after infection [6,7], sometimes supplemented by clinical information. The prevalence of the TRI-defined 'recent infections' is estimated by applying the TRI in a cross-sectional survey of the population of interest.

Performance Characteristics of Tests for Recent Infection

The classification of infections by a TRI is based on measured biomarkers [6,7]. The evolution of these biomarkers within infected individuals exhibit inter-subject variability.

False Recent Rate of a Test for Recent Infection Using SMARTube™

Method of Estimation: The **False Recent Rate** (ϵ) is estimated by applying the TRI to a sample of seropositive individuals known to be non-recently infected. The proportion of these individuals indicated as being recently-infected by the TRI provides a maximum-likelihood estimate of the proportion of false-recent results, ϵ.

Data: Data describing a sample of non-recently infected individuals attending CDC clinics are used. The data provides the SI values resulting when applying both the Abbott (n=59) and Wantai (n=73) diagnostic kits to unstimulated and stimulated plasma.

Results: The decreasing estimates of ϵ, with increasing SI Thresholds, are illustrated in Figure 2 below. Two-sided 95% confidence intervals are also provided (Clopper-Pearson confidence intervals based on the binomial distribution of the number of TRI-recent results). The rapid decrease of the estimated ϵ as a function of SI Threshold suggests that a suitably low False Recent Rate may be achievable by the choice of an SI Threshold of 1.2 or larger.

Testing for inferiority of a TRI based on SMARTube™ to existing tests, the data are used to assess H_0: $\epsilon = 5\%$ vs H_1: $\epsilon > 5\%$. Rejecting the null hypothesis, H_0, would suggest that further investigation of such a TRI is not warranted. Even at a relatively low SI Threshold of 1.1, we fail to reject H_0, with p-values of 0.80 and 0.71 for the Abbott and Wantai kits respectively.

Figure 2: Estimated False Recent Rate as a Function of SI Threshold

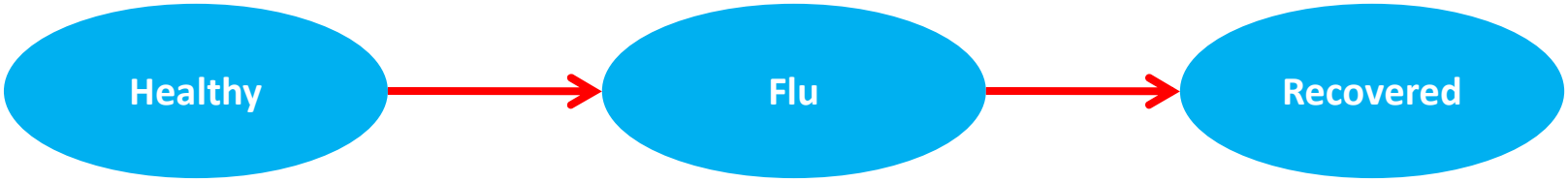
http://www0.sun.ac.za/sacema/collaboration/abie/,

and Questions

Surveillance NOT Diagnostics

Why Specificity and Sensitivity are not of concern...

Example: Estimating the incidence of Flu



- Individuals remain infected for 3-7 days, average of 5 days
- Incidence ≈ ‘Prevalence’ ÷ (5/365)
- Whether a particular person is still infected 4 days after infections is not of concern for incidence estimation