Modeling TB Diagnostics: Challenges and Future Directions

Advanced TB Diagnostic Research Course
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Objectives

- To describe limitations of TB diagnostics models
  - Uncertain parameters
  - Uncertain assumptions
- To characterize future directions for models of TB diagnostics
  - Meaningful parameters
  - Appropriate assumptions
- Without delaying a key component
  - Lunch

Presentation Outline

- Brief recap of last session
- Modeling limitations & examples of "failures"
  - Parameters: "Styblo rule"
  - Assumptions: Impact of DOTS
- Current/future directions of TB diagnostics models
  - User-defined parameters
  - Diagnostic-specific assumptions
- Summary & Conclusions

Session 3: Recap

- Modeling of TB diagnostics is a new field.
- 2006 as a turning point
  - Nature & AIDS papers, plus external forces
- Specific refinements since 2006
  - Expansion of existing diagnostics
  - Introduction of novel diagnostics
  - Diagnostics as part of integrated TB control strategy
  - Diagnostics for managing MDR-/XDR-TB

Session 3: Modeling Goals

- Craft Policy
  - 2006: Enhance awareness of diagnostics
  - Post-2006: Target specific audiences
- Conceptualize
  - 2006: Access to diagnostic services
  - Post-2006: Repeat attempts, relation to smear, speed vs. accuracy, nosocomial vs. community
- Project
  - 20% realistic mortality reduction
- Operationalize
  - Target areas with poor infrastructure
  - Diagnostics as part of an integrated package

Models don't always achieve their goals.

Prevalence of tuberculous infection and incidence of tuberculosis; a re-assessment of the Styblo rule

F van Leth,[a] MJ van der Werf[a] & MW Borgdorff[a]

Bulletin of the World Health Organization 2008;86:20–26.

The "Styblo Rule"

- Each case of smear-positive TB generates, on average, 8-12 secondary infections.

Table 1. **Original data as reported by Styblo[5]**

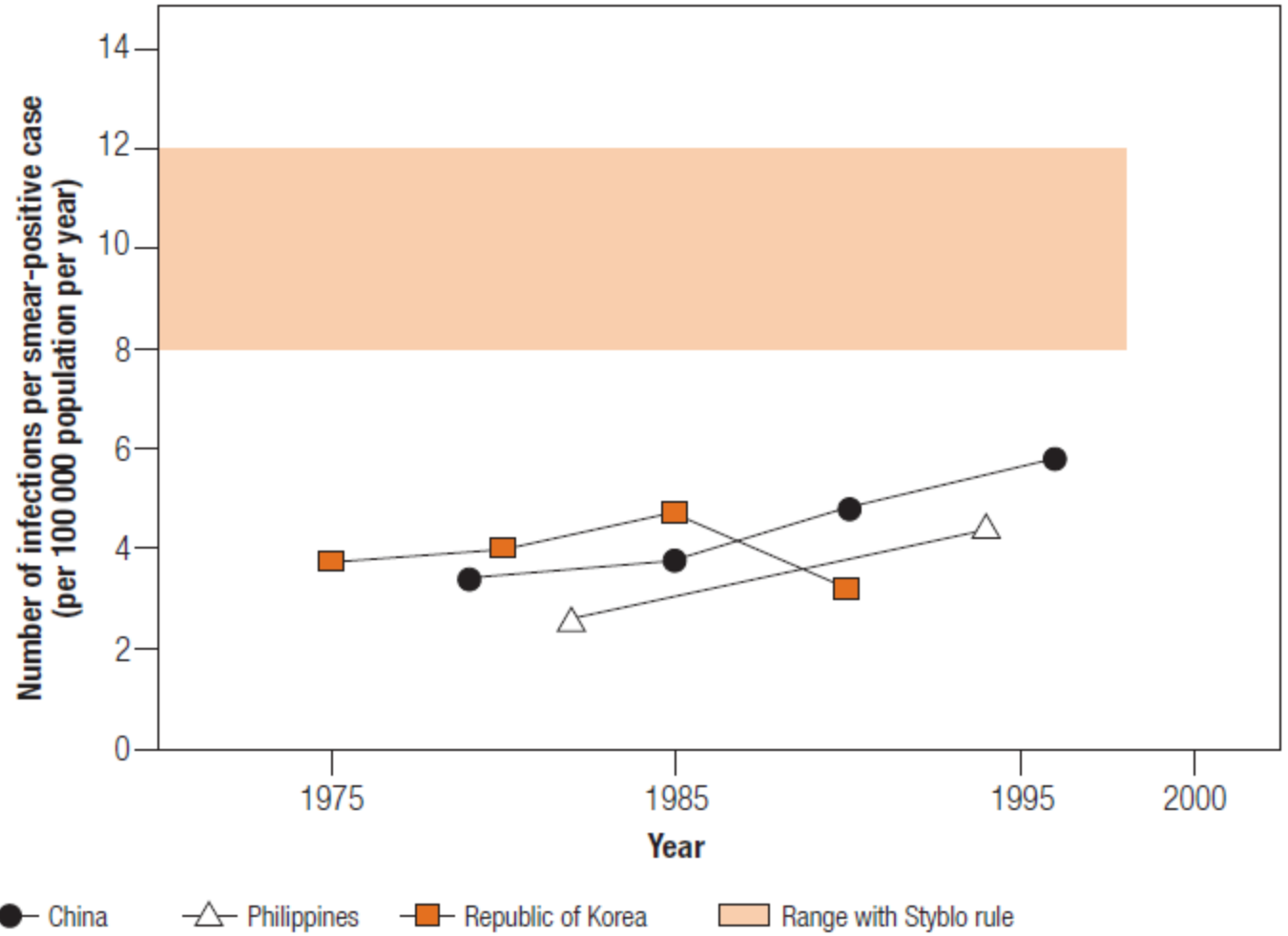
Source	Period	Disease parameter	ARTI (%)	Ratio between ARTI (%) and		
				mortality[a]	incidence[a]	prevalence[a]
Netherlands	1921–1928	Mortality	2.7–6.0	**19**	38	–
Netherlands	1951–1976	Incidence	0.038–0.4	–	**37**	–
Developing countries	1956–1961	Prevalence	2.0–8.0	–	40–60	**80–120**
Alaska	1948–1951	Mortality	25	**26**	52	–
India	1961–1968	Prevalence	1.5	–	53	**106**
India	1969–1971	Prevalence	4.1	–	51	**102**

(1 case per 100,000) *(10 infections) = ARTI of 1 in 10,000 (0.01%) = 1/100 ratio

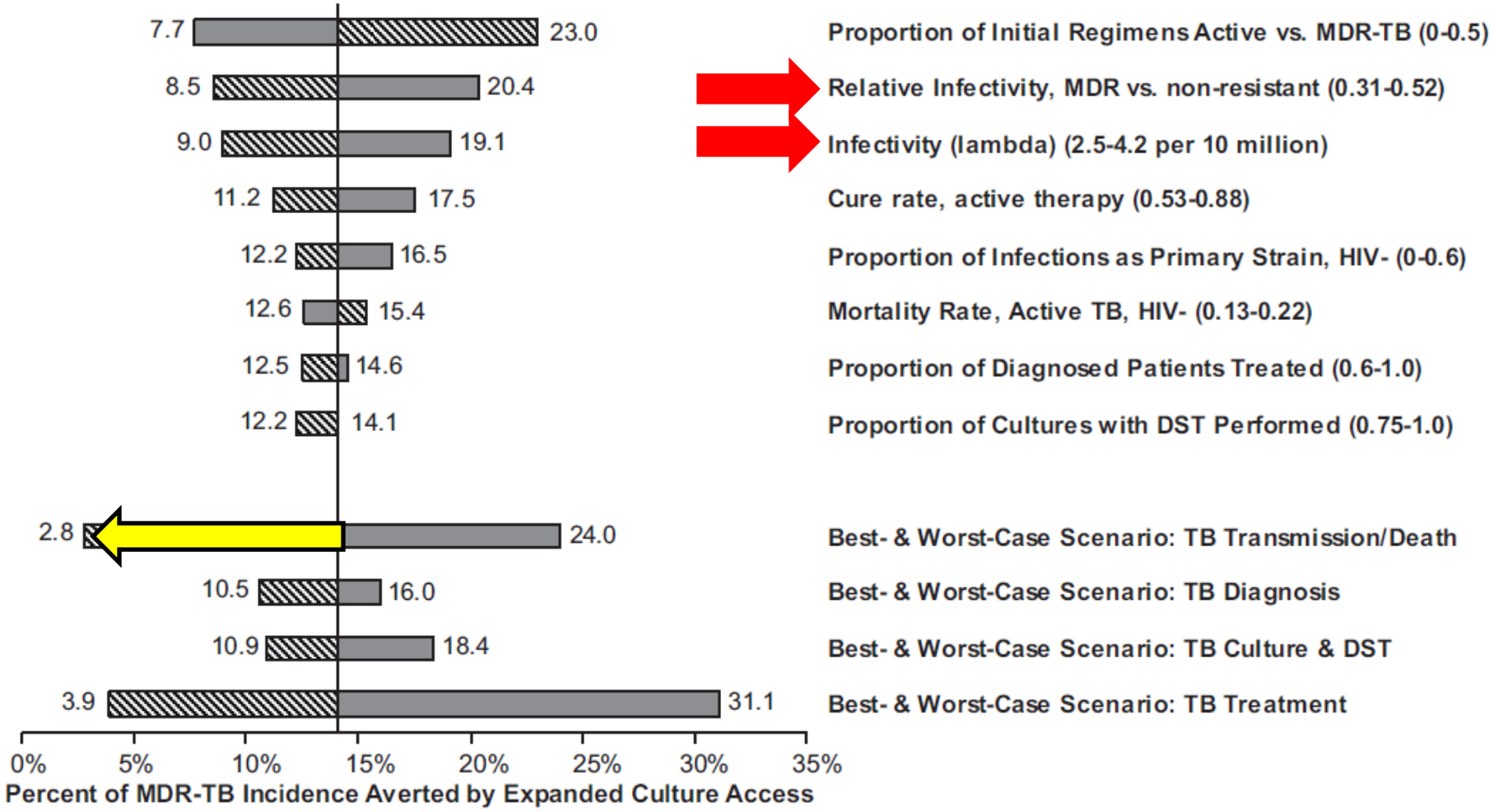
- This rule used by virtually every TB model to define transmissibility or CDR
  - An essential parameter

But when looking at more data:

Fig. 5. **Number of tuberculosis infections per prevalent smear-positive TB cases**



Potential effect on model output



Limitation 1: Model Parameters

- Mis-estimated parameters can cause gross errors in model output.
- Certain essential parameters have little (or no) data, and may vary by place & time.
  - Transmissibility of TB
    - Smear-negative vs. smear-positive
  - Baseline case-detection rate/sensitivity
  - Reinfection vs. reactivation
  - Duration of infectiousness before presentation

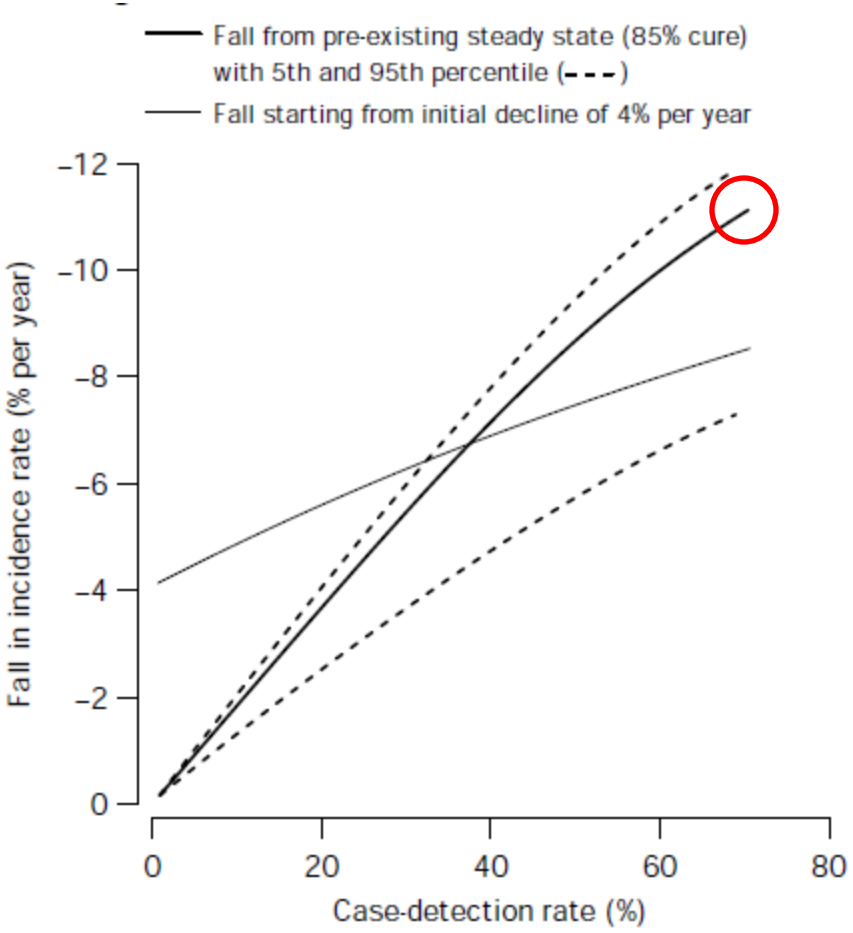
Models don't always achieve their goals.

The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection

David W Dowdy[a] & Richard E Chaisson[a]

Bull World Health Organ 2009;87:296–304

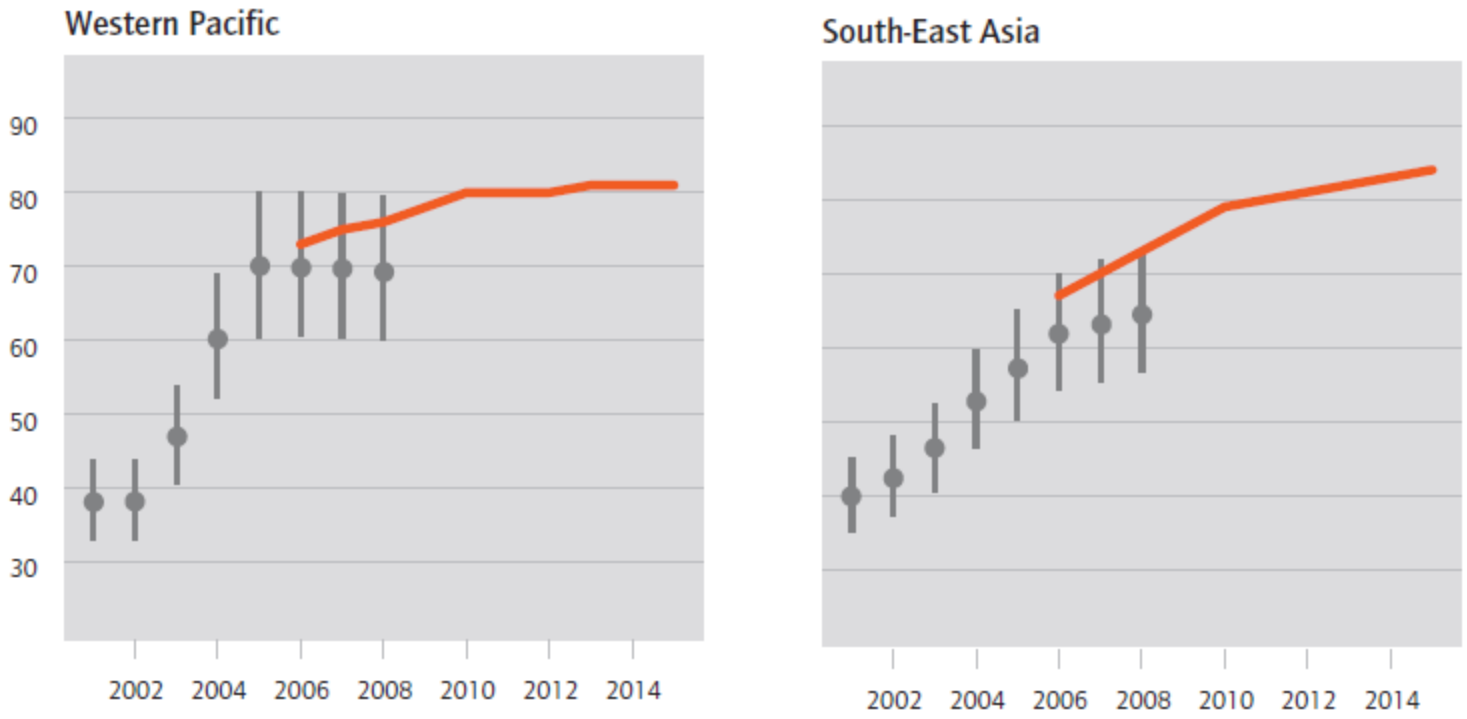
Dye et al (1998): Initial projections of DOTS impact



70% CDR =
10% drop in incidence per year

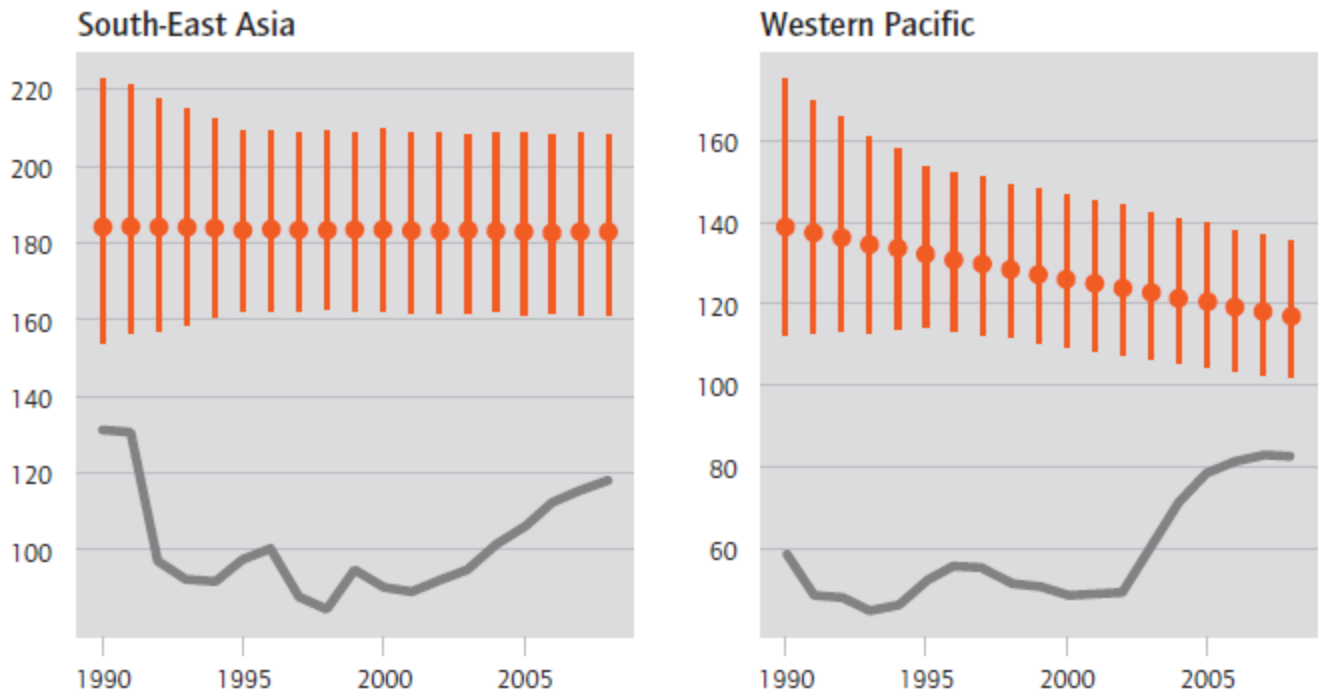
2008: CDR nearing 70%...

FIGURE 3
Case detection rates 1995–2008 (grey) compared with Global Plan targets/milestones (red), globally and in seven sub-regions



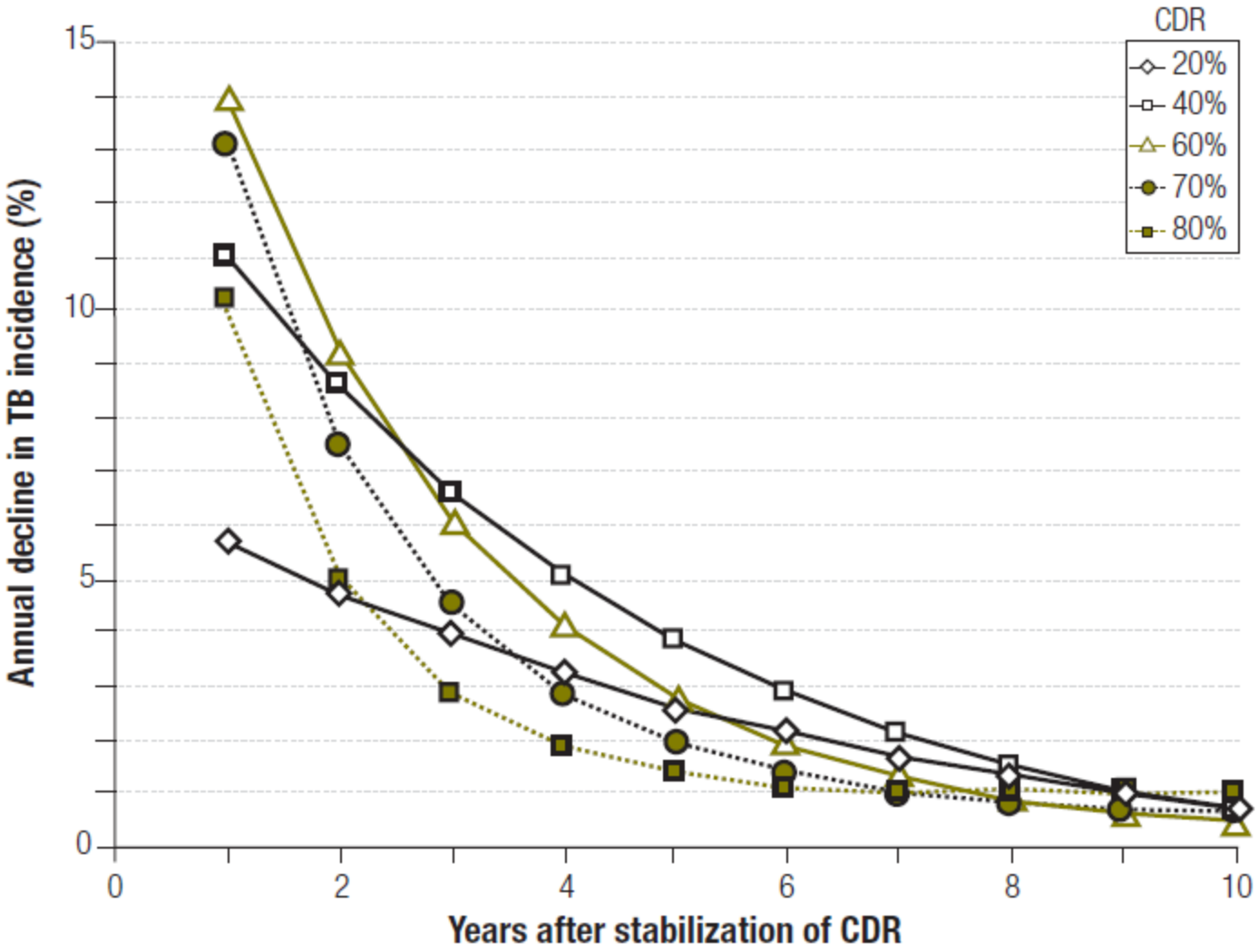
…but incidence not falling 10%/yr

FIGURE 21
Trends in estimated incidence rates (red) and notification rates (grey) in nine subregions, 1990–2008



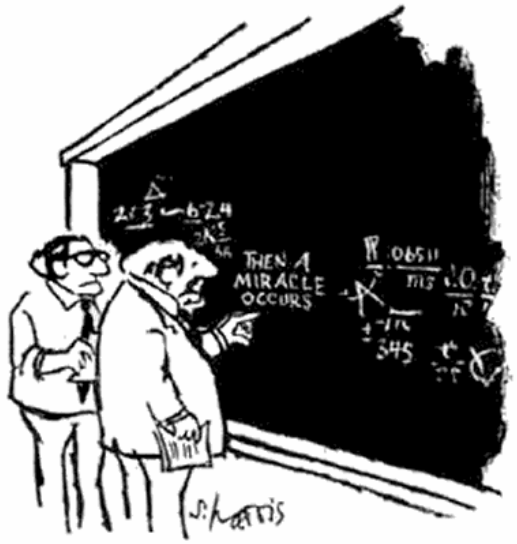
The reason:

Fig. 2. **Annual decline in TB incidence under stable case detection**[a]



Limitation 2: Model Assumptions

- Model assumptions are "tuned" to provide a specific message.
  - Immediate vs. long-term impact of DOTS scale-up
- Misinterpretation of assumptions can lead to misuse of model output.



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

Summary: Model Limitations

- Parameters
  - Must include them, whether data exist or not
  - Are often incorrect, sometimes grossly so
- Assumptions
  - Crafted to answer a specific question
  - Easily misinterpreted

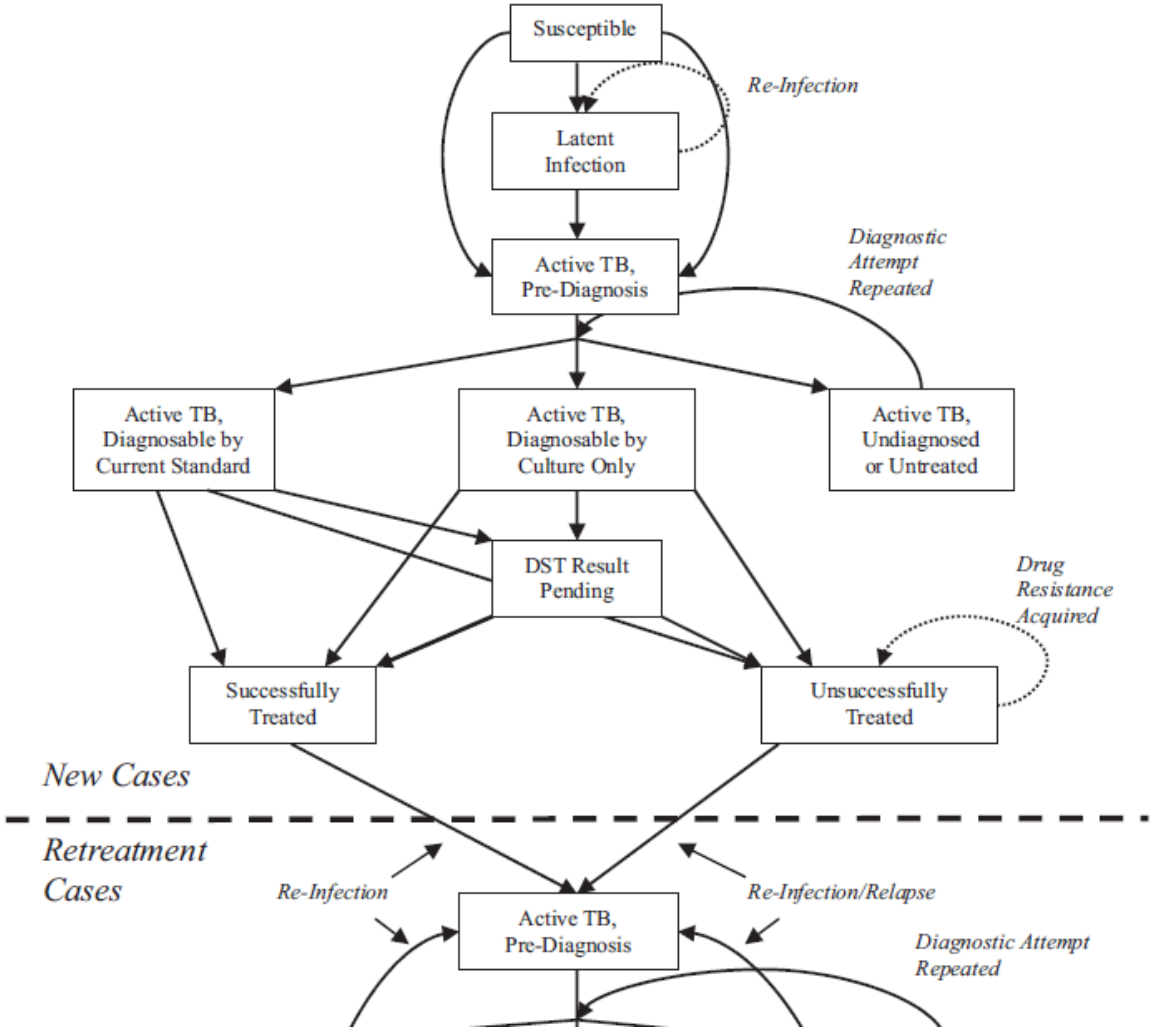
"All models are wrong, some are useful"

George Box

TB Diagnostic Models: Advances and Future Directions

- Example of a model created for evaluating TB culture (MGIT) in South Africa
- Illustrate 2 key areas for improvement as the field progresses from awareness-raising to policy-guiding:
  - User-defined parameters
    - If parameters are wrong, at least they reflect beliefs of end-users.
  - Diagnostic-specific assumptions
    - Focus models on diagnosis as a specific process with specific interventions.

Model of TB Culture in RSA



Advance 1: User-defined parameters

- End-users know TB incidence, prevalence, mortality.
  - Not transmissibility, duration of disease, TB annual death vs. self-cure rate
- End-users also know local utility of diagnostic tests.
  - After accounting for operational realities
- Therefore, create models that allow end-users to define model parameters.

User-defined parameters in RSA

Table S2. Parameter estimates for model of TB epidemic in South Africa

Variable	Initial value	Data used for model fit*	Final value	Range for sensitivity analysis
		Recruitment and mortality		
Population size (15–49 years old)	25.5×10^6		25.5×10^6	None
Annual mortality rate				
HIV+, no TB	0.11		0.11	0.08–0.13
HIV+, infectious TB	2.0	TB mortality, HIV+	0.82	0.61–1.02
HIV−, no TB	0.006		0.006	0.004–0.007
HIV−, infectious TB	0.5	TB mortality, HIV−	0.17	0.13–0.22
Mortality ratio, highly vs. less infectious TB				
HIV+	1		1	0.75–1.25
HIV−	0.29		0.29	0.21–0.36
		TB transmission and infection		
Number of secondary TB infections per highly infectious person-year	6.2	TB incidence	7.8	5.9–9.8
Relative infectivity				
Less infectious TB	0.22		0.22	0.16–0.28
MDR/XDR-TB (vs. non-resistant)	0.3	Percent of new TB cases MDR	0.39	0.29–0.48

User-defined parameters in RSA

Table S1. Culture utilization rates in Free State, South Africa

Year	Smear status	No. of patients (% of annual total)	No. (%) with culture performed
		New cases	
2004	Positive	9,210 (61.3%)	672 (7.3%)
	Negative	3,140 (20.9%)	231 (7.4%)
	Not available	2,668 (17.8%)	39 (1.5%)
2005	Positive	9,065 (61.9%)	294 (3.2%)
	Negative	2,966 (20.3%)	152 (5.1%)
	Not available	2,602 (17.8%)	35 (1.3%)
Total		29,651	1,423 (4.8%)

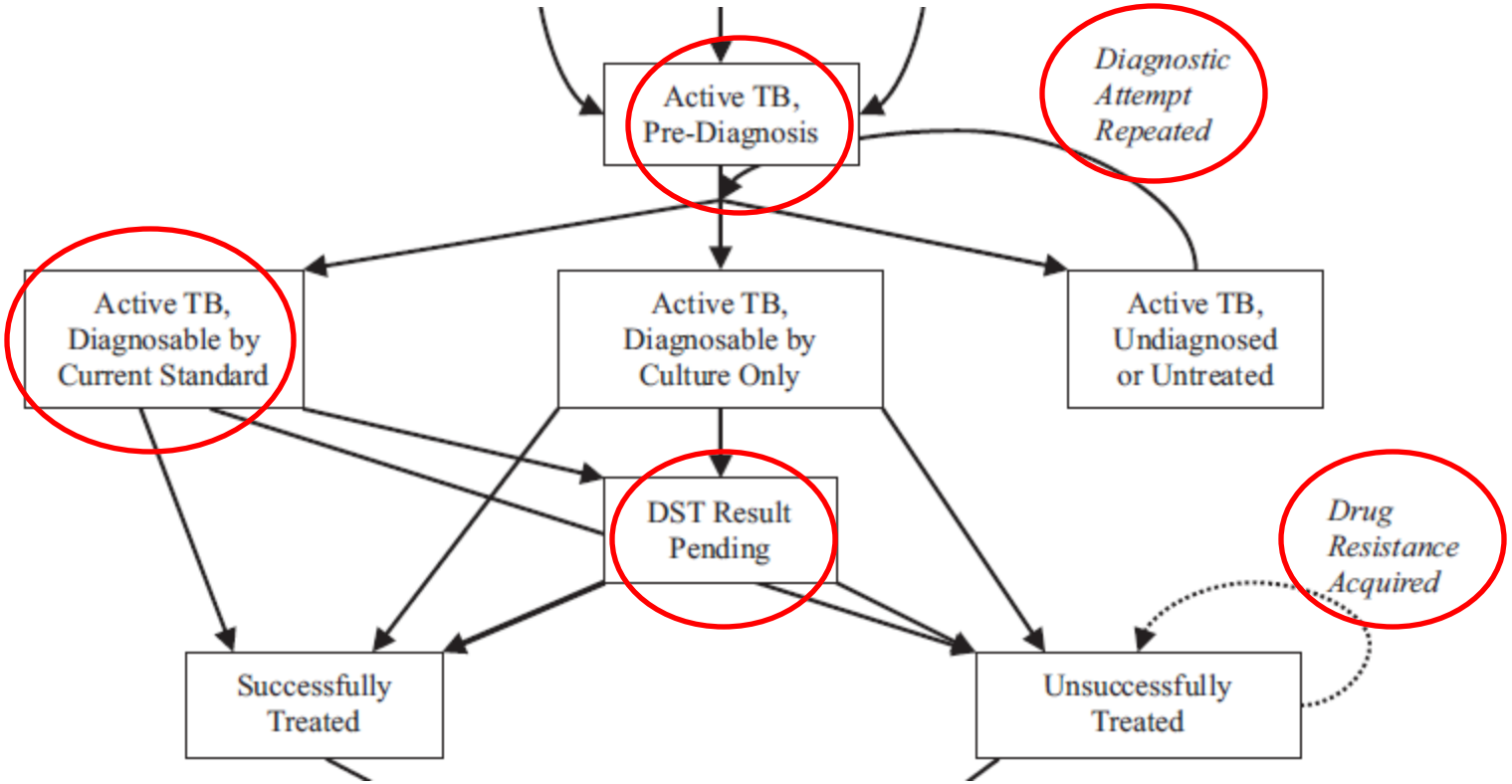
User-defined parameters: Potential future directions

- Local ability to scale-up novel diagnostic tests (e.g. GeneXpert)
- Evaluation of optimal diagnostic strategies in various locations
- "Holy grail":
  - End-user inputs local parameters
    - TB/HIV epidemiology
    - Assumptions about utility of diagnostic tests
  - Standardized model structure uses those parameters to define model inputs
  - Accessible (e.g., web-based) outputs created

Advance 2: Diagnostic-Specific Assumptions

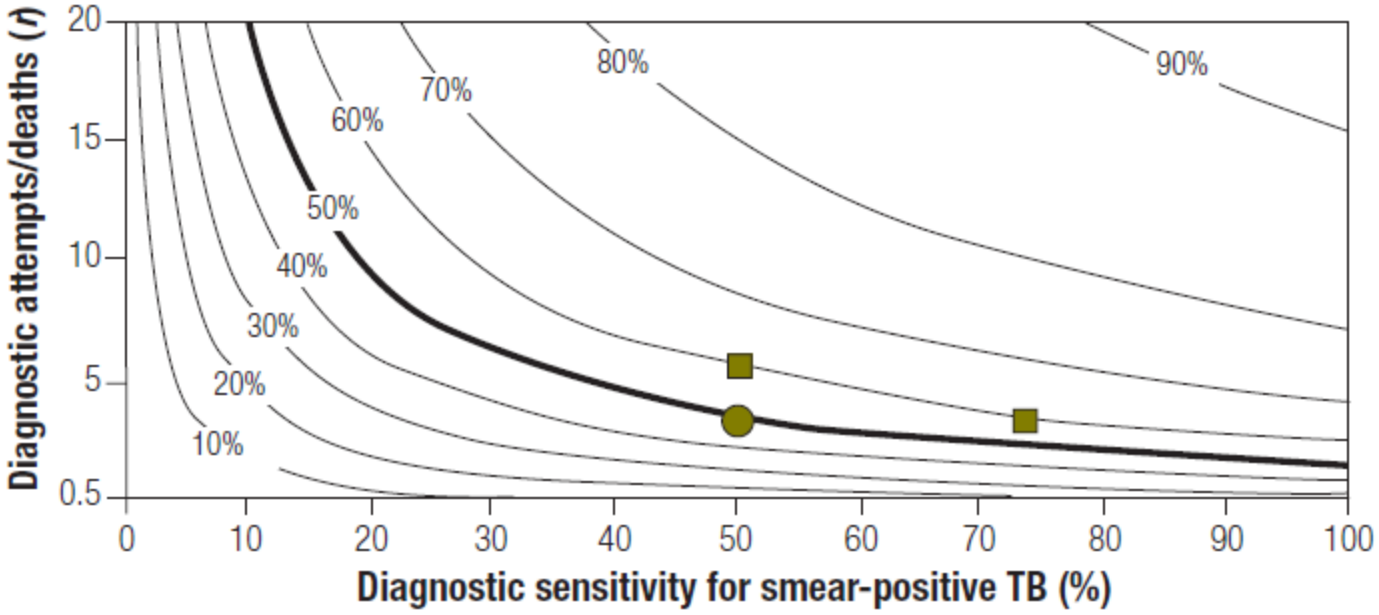
- Most models consider diagnostics as one of many interventions.
- Thus, the model isn't crafted to evaluate the specific steps in diagnosis.
  - Time before presentation
  - Diagnostic delay
  - Empiric treatment
  - Repeat diagnostic attempts
  - "Broken links" between diagnosis and treatment

Diagnostic-Specific Assumptions



Diagnostic-Specific Assumptions

Fig. 5. **TB CDR, according to diagnostic sensitivity and ratio of diagnostic attempts to deaths, under the assumption of no active case-finding efforts for TB[a]**



Diagnostic-specific assumptions: Potential future directions

- Empiric treatment as a strategy for TB control
- Centralized vs. decentralized diagnostic infrastructure
- Defining a target product profile:
  - Accuracy vs. ease of use/accessibility
  - Accuracy vs. diagnostic delay
  - Importance of detecting drug resistance

Conclusions

- Models often fail to achieve their goals.
  - Parameters may lack data.
    - Styblo rule
  - Assumptions reflect the modeling question.
    - Immediate impact of DOTS
- Advances in TB diagnostic models attempt to address these limitations.
  - User-defined parameters
  - Diagnostic-specific assumptions
- These advances will enable TB diagnostic models to:
  - Craft policy
  - Conceptualize
  - Project
  - Operationalize

Questions?

- Thanks to:
  - Dr. Madhukar Pai
  - Dr. Richard Chaisson
  - Dr. Susan Dorman
  - Dr. Karen Steingart
  - Dr. Liz Corbett
  - Each of you for sticking through