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

The “Styblo Rule”

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

(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

[Graph showing the number of infections per smear-positive case (per 100,000 population per year) over years 1975 to 2000 for China, Philippines, Republic of Korea, and a range with Styblo rule.]
Potential effect on model output

- Proportion of Initial Regimens Active vs. MDR-TB (0-0.5)
- Relative Infectivity, MDR vs. non-resistant (0.31-0.52)
- Infectivity (lambda) (2.5-4.2 per 10 million)
- Cure rate, active therapy (0.53-0.88)
- Proportion of Infections as Primary Strain, HIV- (0-0.6)
- Mortality Rate, Active TB, HIV- (0.13-0.22)
- Proportion of Diagnosed Patients Treated (0.6-1.0)
- Proportion of Cultures with DST Performed (0.75-1.0)

Best- & Worst-Case Scenario: TB Transmission/Death
Best- & Worst-Case Scenario: TB Diagnosis
Best- & Worst-Case Scenario: TB Culture & DST
Best- & Worst-Case Scenario: TB Treatment

Percent of MDR-TB Incidence Averted by Expanded Culture Access
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 & Richard E Chaisson

Bull World Health Organ 2009;87:296–304

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
The reason:

Fig. 2. Annual decline in TB incidence under stable case detection

![Graph showing annual decline in TB incidence under stable case detection.](image)
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.
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

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

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Smear status</th>
<th>No. of patients (% of annual total)</th>
<th>No. (%) with culture performed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>New cases</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Positive</td>
<td>9,210 (61.3%)</td>
<td>672 (7.3%)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>3,140 (20.9%)</td>
<td>231 (7.4%)</td>
</tr>
<tr>
<td></td>
<td>Not available</td>
<td>2,668 (17.8%)</td>
<td>39 (1.5%)</td>
</tr>
<tr>
<td>2005</td>
<td>Positive</td>
<td>9,065 (61.9%)</td>
<td>294 (3.2%)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>2,966 (20.3%)</td>
<td>152 (5.1%)</td>
</tr>
<tr>
<td></td>
<td>Not available</td>
<td>2,602 (17.8%)</td>
<td>35 (1.3%)</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>29,651</strong></td>
<td><strong>1,423 (4.8%)</strong></td>
</tr>
</tbody>
</table>
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.©
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
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  - Dr. Karen Steingart
  - Dr. Liz Corbett
  - Each of you for sticking through