# Systematic Review of Cost Effectiveness Analyses of IGRAs

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# Background

- Economic analyses can be useful to inform the global TB control community as to the best possible options for disease control.

- Different analyses of the same intervention may produce contradictory results. This may lead to confusion and even discredit the value of these analyses.

- Example- Several recent economic evaluations of Interferon Gamma Release Assays (IGRAs) for LTBI screening – have produced very different results

- Why?

# Primary Objectives:

- To conduct a systematic review of *methodologic aspects* (study quality, choice of model inputs and approach to modeling) of Cost Effectiveness Analyses (CEA) that evaluate IGRA's for the detection of LTBI

- To quantify the impact of the *observed differences in model inputs* that were used in the studies identified in the systematic review on *predicted outcomes* (ie. costs and effectiveness measures)

- **Overall Goal**: To generate information that can be used to improve **methods** of future economic analyses in TB diagnostics – **more transparent, standardized and comparable.**

# Methods

# 1) Systematic review:

**Included:**

- Cost Effectiveness Analyses (CEA) that evaluated test and treat strategies for Latent TB – using at least one IGRA test compared to at least one other strategy for latent TB infection

**Excluded:**

- Animal studies; studies on the detection of active disease; conference abstracts and proceedings; studies on non-tuberculous mycobacterial infection; and studies that used non-standard methods for testing.

**Model Predicted Outcomes (for each tests scenario):**

- cost per person screened
- effectiveness measures (QALYs or active cases)

## Search Strategy:

- No language or time constraints were imposed.

- Searched the following databases: Scopus, Web of Science, Medline, Embase, Cinhal, Cochrange Library, CRD, Econlit, CEA registry and Lilacs

## Study Selection:

- Two independent reviewers (OO and MP) reviewed all titles and abstracts

- Full text review to finalize study selection was done independently by the same two reviewers and any disagreements were resolved by a third reviewer (DM).

# 2) Assessment of variability in study inputs and predicted results:

- In addition to model predicted outcomes (ie. cost and effectiveness outcomes) the following **model inputs** were extracted:

  - test characteristics (eg. test sensitivity/specificity)
  - transitional probabilities (eg risk of disease if infected)
  - input costs

All costs were then adjusted and inflated to USD 2011

- Summary statistics for each model input were generated
- Model predicted outcomes were not pooled- qualitative comparison only

# 3) Assessment of the impact of variability in study inputs:

- We quantitatively assessed the variability in model inputs across studies on predicted findings using our own "common" decision analysis Markov model

- Simple model that incorporated the basic structure and consequences of all of the models used in the studies included in the review

- Included only 2 test and treat strategies: IGRA vs. TST

# 3) Assessment of the impact of variability in study inputs (cont…)

- Model inputs (costs, pathogenetic probabilities and test characteristics) were defined using distributions based on minimum, median and maximum values **obtained from studies included in the review**

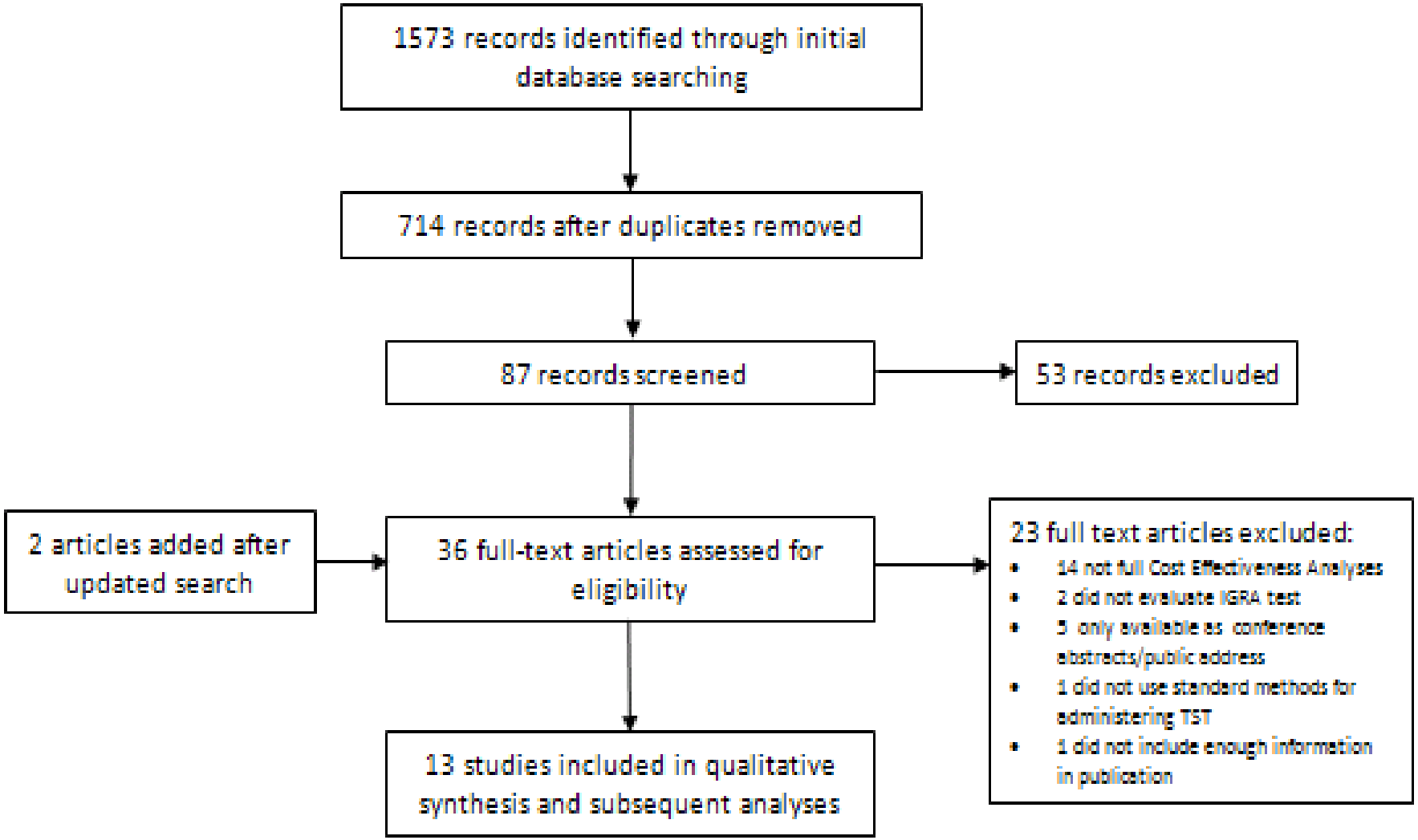
- Monte Carlo probabilistic sensitivity analysis (PSA) was used to predict a distribution of outcomes (costs and effectiveness) for each test scenario.

# 4) Qualitative assessment of interpretation of study results

- Studies were reviewed to see how predicted data presented in results table was interpreted and presented in corresponding published manuscript abstract (or title)

# Results- 1) Systematic Review

# Flow Chart of Study Selection:



# Characteristics of studies included in review

| Authors | Year Published | Population | Mean age at start of analysis (Basecase) |
|---|---|---|---|
| Burgos et al. | 2009 | Mexico- high TB/HIV risk sub population | Adult |
| de Perio et al. | 2009 | US Health Care workers | 35 |
| Deuffic-Burban et al. | 2010 | France, Contacts | 35 |
| Diel et al. | 2007 | Germany, Close contacts | 20 |
| Diel et al. | 2007 | Swiss, Contacts | 20 (or 40) |
| Kowada et al. | 2010 | Japan, Pre-transplant | 40 |
| Kowada et al. | 2010 | Japan, elderly | 65 |
| Kowada et al. | 2008 | Japan, contacts | 20 |
| Linas et al. | 2011 | US, 19 different high risk groups | Risk groups varied by age |
| Marra et al. | 2008 | Canada, Contacts (mix of populations) | Age Weighted (16-35, 36-55, >56) |
| Oxlade et al. | 2007 | Canada, Migrants or contacts | 35 |
| Pareek et al. | 2011 | UK, Migrants | 35 yrs and younger |
| Pooran et al. | 2010 | UK, Contacts | Not specified |

# Results- 2a) Variability in study inputs

# Summary of Variability in model inputs by studies included in SR: Test Characteristics

| Model Variable | Range of values used in studies included in the SR |
|---|---|
| Sensitivity of TST | 67% to 99% |
| Sensitivity of IGRA | 76% to 99% |
| Specificity of IGRA | 96% to 100% |
| Specificity of TST | 15% to 99% |

# Summary of Variability in model inputs by studies included in SR : Costs (2011 USD)

| Model Variable | Range of values used in studies included in the SR |
|---|---|
| Cost of an adverse event | $183 to $14,006 |
| Cost of IGRA | $21 to $219 |
| Cost of TST | $15 to $121 |
| Cost of treating active TB | $5,318 to $63,120 |
| Cost of treating LTBI | $224 to $1,577 |

# Summary of Variability in model inputs by studies included in SR : Other key variables

| Model Variable | Range of values used in studies included in the SR |
|---|---|
| Reactivation rate (annual) in the absence of effective LTBI therapy | 0.02% to 1.25% |
| Completion rate for LTBI therapy | 21% to 100% |
| Prevalence of LTBI | 5% to 58% |
| Probability of an adverse event from LTBI therapy. | 0 to 18% |

# Some key questions about the observed variability in inputs:

1) Is the observed variability in model inputs justified?

2) Are all of these model inputs equally influential in a determining results?

# Q1- Is observed variability justified?- Test Characteristics

| Model Variable | Assessment of observed variability | Explanation |
|---|---|---|
| Specificity of TST | partially justified | Differences could be justified based on BCG status of study population.<br><br>Within each sub populations should have similar estimates derived from meta analyses |
| Sensitivity of TST | predominantly unjustified | Should see similar estimates from meta analyses |
| Sensitivity of IGRA | predominantly unjustified | Should see similar estimates from meta analyses |
| Specificity of IGRA | predominantly unjustified | Should see similar estimates from meta analyses |

# Q1- Is observed variability justified?- Other important variables

| Model Variable | Assessment of observed variability | Explanation |
|---|---|---|
| Reactivation rate in the absence of effective LTBI therapy | predominantly unjustified | -Differences could be justified based on study population (ie. immunosuppressed, close contacts etc.),<br>- Inputs used in 11/13 studies were for the general population. |
| Prevalence of LTBI | predominantly justified | Different populations/ sub-groups considered |
| Probability of an adverse event from LTBI therapy. | predominantly unjustified | -Mostly young populations that should experience similar types and rates of adverse events.<br>-One study considered an elderly population with justified use of higher rates of adverse events. |
| Completion rate for LTBI therapy | partially justified | -Estimates should be similar for studies set in general population.<br>-Differences based on duration of regimen justified. |
| Efficacy of LTBI therapy. | partially justified | Differences justified for different regimens, but within each regimen estimate should be similar and derived from meta analyses |

# Q1- Is observed variability justified?- Costs

| Model Variable | Assessment of observed variability | Explanation |
|---|---|---|
| Cost of treating active TB | predominantly unjustified | Similar costing components should be included<br>Costs should be similar for high income settings.<br>Some variability could be due to economic perspective |
| Cost of treating LTBI | partially justified | Similar costing components should be included<br>Costs should be similar as most are high income settings.<br>Duration of prophylactic regimen will result in some justified variability in costing |
| Cost of an adverse event | predominantly unjustified | Similar costing components should be included |
| Cost of IGRA/TST | predominantly unjustified | Similar costing components should be included<br>Costs should be similar for high income settings. |

# Some key questions about the observed variability in inputs:

1) Is the observed variability in model inputs justified?

*RARELY*

2) Are all of these model inputs equally influential in a modeling study of screening using IGRA or TST ?

*STAY TUNED*

# Results- 2b) Variability in predicted results

# Predicted Total Cost per person in 2011 USD by Screening Strategy. Lifetime horizon

| Study Author, Year | Population | TST | IGRA | Cost difference (IGRA vs TST)* |
|---|---|---|---|---|
| de Perio, 2009 | BCG –ve | $280 | $262 | -$18 |
| | BCG +ve | $287 | $177 | -$110 |
| Deuffic-Brown, 2010 | BCG +ve | $805 | $703 | -$102 |
| Kowada, 2010 | BCG –ve | $1,920 | $1,099 | -$821 |
| | BCG +ve | $2,206 | $1,099 | -$1,107 |
| Kowada, 2010 | BCG +ve | NA | $550.88 | NA |
| Kowada, 2008 | BCG +ve | $625 | $513 | -$112 |
| Linas, 2011 | Close contacts | $125, 610 | $125, 620 | $10 |
| | Recent immigrant | $122,700 | $122,700 | $0 |

*A negative number represents a savings with IGRA relative to TST

# Predicted Total Cost per person in 2011 USD by Screening Strategy. 20 year horizon

| Study Author, Year | Population | TST | IGRA | Cost difference (IGRA vs TST)* |
|---|---|---|---|---|
| **Burgos, 2009** | BCG +ve | No data on total cost | No data on total cost | NA |
| **Diel, 2007** | BCG +ve | $342 | $271 | -$71 |
| **Diel, 2007** | Mostly BCG+ve | $1,376 | $748 | -$628 |
| **Marra, 2008** | Mostly BCG+ve | $495 | $525 | $30 |
| | Foreign born BCG -ve | $460 | $452 | -$8 |
| **Oxlade, 2007** | Foreign born BCG - ve | $307 | $348 | $41 |
| | Foreign born BCG +ve (infancy) | $321 | $348 | $27 |
| | Foreign born BCG +ve (older) | $382 | $348 | -$34 |
| **Pareek, 2011** | BCG not specified | NA | $142 | NA |

*A negative number represents a savings with IGRA relative to TST

# Predicted Effectiveness by Screening Strategy- Life time analytical horizon

| Study Author, Year | Effectiveness Measure | Population / BCG vaccination status | Effect. with TST | Effect. with IGRA | Gain in effectiveness using IGRA (vs TST) |
|---|---|---|---|---|---|
| De Perio, 2009 | QALYs | BCG –ve | 23.55657 | 23.55671 | 0.00014 QALYs **(0.05 days)** |
| | QALYs | BCG +ve | 23.55751 | 23.55826 | 0.00075 QALYs **(0.27 days)** |
| Deuffic-Brown, 2010 | LE | BCG +ve | 25.072 | 25.073 | 0.001 Yrs **(0.37 days)** |
| Kowada, 2010 | QALYs | BCG –ve | 22.98153 | 23.03499 | 0.053 QALYs **(19.51 days)** |
| | QALYs | BCG +ve | 22.98153 | 23.03499 | 0.053 QALYs **(19.51 days)** |
| Kowada, 2010 | QALYs | BCG +ve | NA | 14.6516 | NA |
| Kowada, 2008 | QALYs | BCG +ve | 28.1079 | 28.1099 | 0.002 QALYs **(0.73 days)** |
| Linas, 2011 | LE | Close contacts | 23.43917 | 23.44 | 0.00083 Yrs **(0.30 days)** |
| | LE | Recent immigrant | 25.6925 | 25.6925 | 0 Yrs **(0 days)** |

# Predicted Effectiveness by Screening Strategy- 20 year horizon

| Study Author, Year | Effectiveness Measure | Population / BCG vaccination status | Effect. with TST | Effect. with IGRA | Gain in effectiveness using IGRA (vs TST) |
|---|---|---|---|---|---|
| **Burgos, 2009** | QALYs | BCG +ve | NA | 11.99 | NA |
| | Active cases | BCG +ve | NA | 0.177 | NA |
| **Diel, 2007** | Active cases | Mostly BCG+ve | 0.0058 | 0.0058 | 0 Cases prevented |
| **Diel, 2007** | Active cases | Mostly BCG+ve | 0.0158 | 0.0196 | -0.018 Cases prevented* |
| **Marra, 2008** | QALYs | Foreign born BCG -ve | 15.1141 | 15.1145 | 0.0004 QALYs (0.15 days) |
| | QALYs | Foreign born BCG + ve | 15.1203 | 15.1206 | 0.0003 QALYs (0.11 days) |
| | Active cases | Foreign born BCG -ve | 0.0127 | 0.0126 | 0.0001 Cases prevented |
| | Active cases | Foreign born BCG + | 0.0064 | 0.0063 | 0.0001 Cases prevented |
| **Oxlade, 2007** | Active cases | BCG +ve or BCG-ve | 0.085 | 0.085 | 0 Cases prevented |
| **Pareek, 2011** | Active cases | BCG not specified | NA | 0.00834 | NA |

*Negative sign indicates more cases predicted with IGRA strategy relative to TST

# Key Observations:

**Predicted costs**:

- Vary widely across studies and between sub-populations considered within the same study

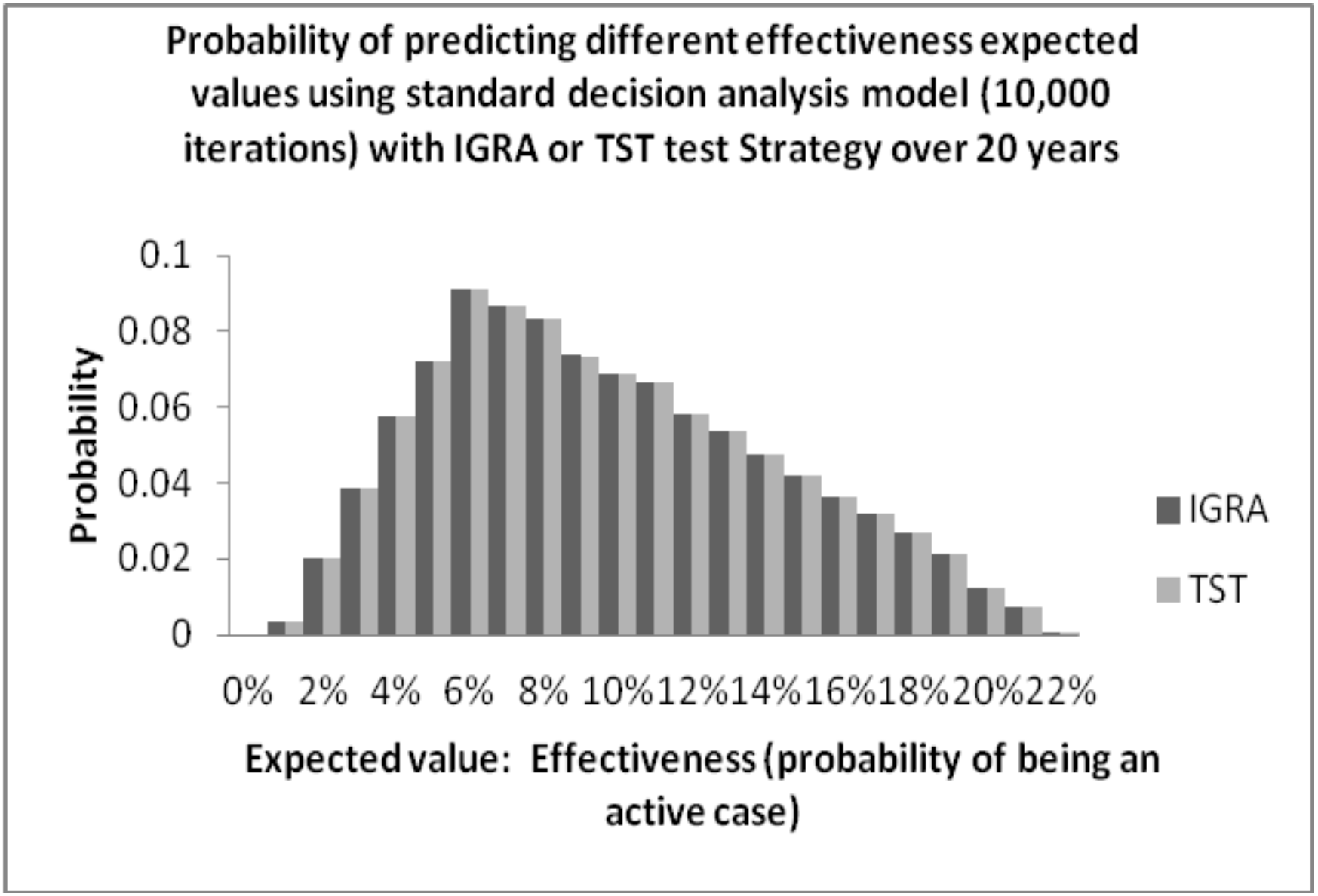
**Predicted effectiveness measures:**

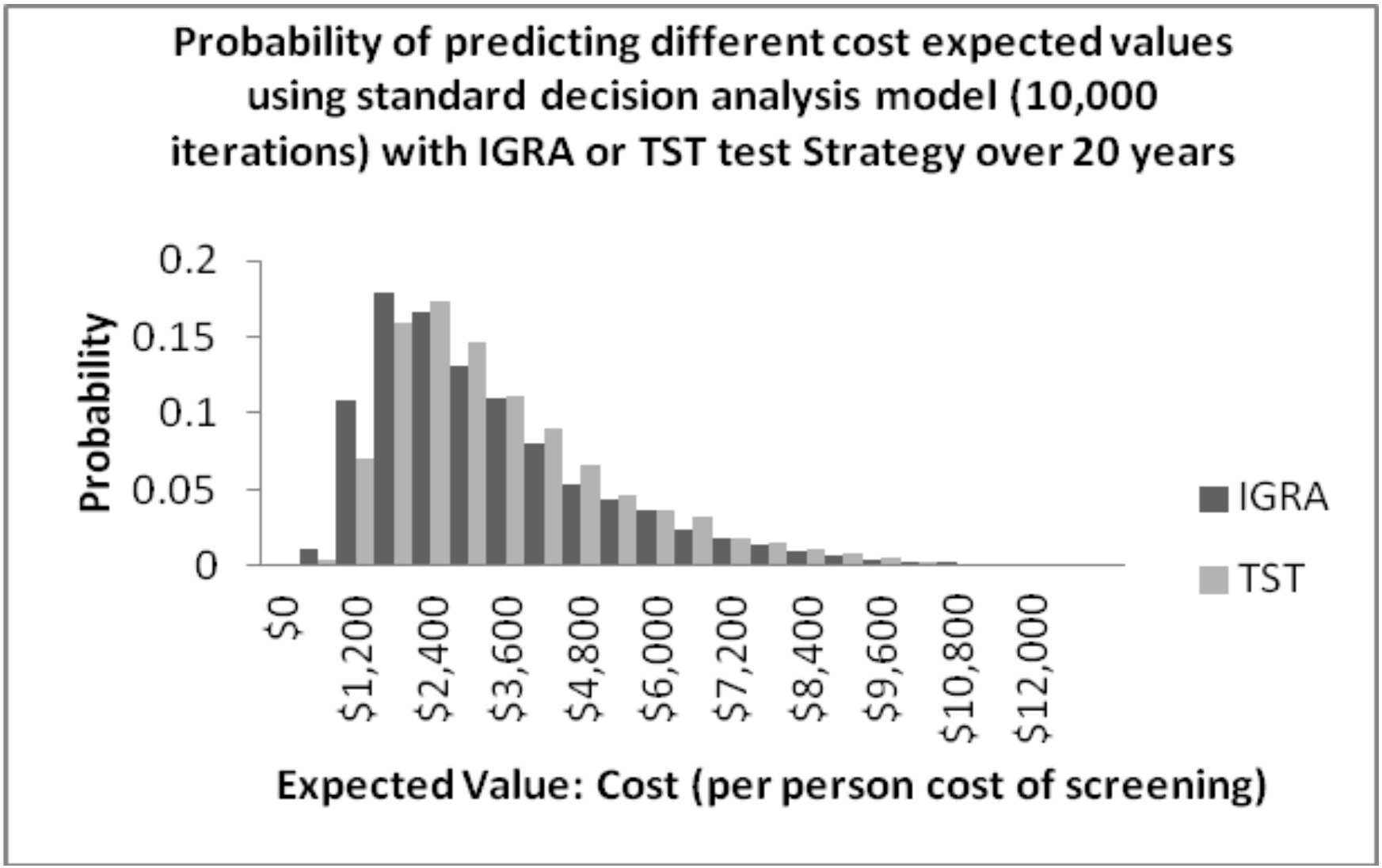
- Within each study were almost identical for each test scenarios
- Of all studies that compared effectiveness with use of IGRA versus TST, only one study predicted a gain of more than 1 day with use of the IGRA over an analytic horizon of 20 years of more

# Results- 3) Assessment of impact of variability in study inputs using a “common model”

# Assessment of impact of variability in study inputs using a "common model"

- Model developed and run using input ranges defined by data extracted from studies included in the SR
- Monte Carlo probabilistic sensitivity analysis (PSA) was used to predict a distribution of "expected values" for both costs and effectiveness measure (active case) for each test scenario (IGRA and TST).
- Differences in the distribution of expected values by test scenario compared


Probability of predicting different effectiveness expected values using standard decision analysis model (10,000 iterations) with IGRA or TST test Strategy over 20 years
Probability
0.1
0.08
0.06
0.04
0.02
0
0% 2% 4% 6% 8% 10% 12% 14% 16% 18% 20% 22%
IGRA
TST
Expected value: Effectiveness (probability of being an active case)


Probability of predicting different cost expected values using standard decision analysis model (10,000 iterations) with IGRA or TST test Strategy over 20 years
Probability
0.2
0.15
0.1
0.05
0
$0
$1,200
$2,400
$3,600
$4,800
$6,000
$7,200
$8,400
$9,600
$10,800
$12,000
IGRA
TST
Expected Value: Cost (per person cost of screening)

# Key Observations:

- The wide variation in model inputs leads to very similar distributions of expected values for the IGRA and TST scenarios

# Q2- Are all inputs equally influential in a modeling study of screening using IGRA or TST ?

- Using common model- Assessed the "influence" of each input variable on predicted results using a Tornado diagram
- Calculate the "spread" of expected values when model is run using the lowest/ highest value of each model input
- Calculate the "influence" = spread/mean expected value at baseline
- Rank model inputs by influence

# Ranking of Influence of model input on predicted results

| Input | Range of input | IGRA strategy | | TST strategy | |
|---|---|---|---|---|---|
| | | SPREAD | INFLUENCE | SPREAD | INFLUENCE |
| Reactivation rate with out effective LTBI therapy | 0.02% to 1.25% | $5959 | **194%** | $5959 | **181%** |
| Cost of treating active TB | $5318 to $63120 | $5461 | **178%** | $5462 | **166%** |
| Cost of treating LTBI | $224 to $1577 | $375 | **12%** | $704 | **21%** |
| Specificity of TST | 15% to 99% | - | **-** | $635 | **19%** |
| Prevalence of LTBI | 5% to 58% | $532 | **17%** | $316 | **10%** |

# Ranking of Influence of model input on predicted results (cont…)

| Input | Range of input | IGRA strategy | | TST strategy | |
|---|---|---|---|---|---|
| | | SPREAD | INFLUENCE | SPREAD | INFLUENCE |
| Probability of an adverse event from LTBI therapy. | 0 to 18% | $277 | 9% | $517 | 16% |
| Cost of an adverse event | $183 to $14006 | $236 | 7% | $442 | 13% |
| Cost of IGRA/TST | $21 to $219/ $15 to $121 | $198 | 6% | $106 | 3% |
| Sensitivity of TST | 67% to 99% | - | - | $101 | 3% |
| Sensitivity of IGRA | 76% to 99% | $73 | 2% | - | - |
| Specificity of IGRA | 96% to 100% | $31 | 1% | - | - |
| Completion rate for LTBI therapy | 21% to 100% | $13 | 0% | $13 | 0% |
| Efficacy of LTBI therapy. | 65% to 90% | $5 | 0% | $5 | 0% |

# Key Observations:

- Not all model inputs are equally important
- Most influential in our model:

1. Reactivation rate with out effective LTBI therapy
2. Cost of treating active TB
3. Cost of treating LTBI
4. Specificity of TST
5. Prevalence of LTBI

# Final question: Are CEA findings clearly/accurately reported in publications?

- In 8/13 studies issues were identified relating to how findings were reported

| **Conclusions reported in abstract/title vs. data in results tables** |
|---|
| Main study title does not accurately report the intervention evaluated, nor the population considered. |
| Abstract does not report the most cost effective scenario |
| Abstract does not report that combined scenario is best |
| Abstract does not report the most cost effective scenario |
| Abstract does not accurately report the most cost effective strategy by population evaluated |
| Abstract highlights the "most cost effective test", however no definition of "cost effectiveness" provided |
| Abstract does not state the most cost effective strategy by population evaluated |
| Abstract doesn't contradict conclusion, however no definition of "cost effectiveness" provided |

# Summary and Implications:

# Summary of findings:

- Largely unjustified wide range of user selected study inputs- pathogenic parameters, costs, test characteristics
- Predicted costs varied by study but predicted effectiveness (using QALY) was very similar across studies, therefore Cost-Effectiveness (and overall study results) will be driven mostly by cost
- When the IGRA versus TST test strategies were analysed using our common model predicted outcomes largely overlapped
- Major inconsistency in how CEA results are presented/ interpreted in the literature

# Implications/Recommendations

- In order to improve quality of CEAs more specific and relevant guidelines are needed in order to help authors standardized inputs and assumptions used in analyses
- In the meantime, findings from CEA may not be useful or accurate
- More meaningful effectiveness measures are needed for modeling studies considering diagnostics
- More effort needs to be put into presentation of results in published studies- peer reviewers and editors need to pay particular attention to how study results are presented and interpreted.