# The potential for new diagnostics to improve TB case detection

## *A transmission dynamic model of nine high-burden countries*

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October 13, 2017
48th Union World Conference on Lung Health, Guadalajara

TB Modelling and Analysis Consortium

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

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# Motivation I

- Improving case detection for active disease a central challenge for efforts to accelerate TB control in high burden settings

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Modelling to assess feasibility and cost-effectiveness of achieving End TB 2025 targets:

- *Improving case detection one of the most impactful strategies considered*
- *Better case detection critical for chances of reaching 2025 incidence and mortality targets*


*Houben et al Lancet GH 2016; Menzies et al Lancet GH 2016*

# Motivation II

- Recent tech development provides more sensitive diagnostics

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GeneXpert MTB/RIF:

- *Identifies more than two-thirds of the TB cases that would be missed by sputum-smear microscopy*
- *Detects rifampicin resistance with high sensitivity and specificity*


*Boehme et al NEJM 2010; Boehme et al Lancet 2011; Steingart et al Cochrane Rev 2013*

# Motivation II

- Recent tech development provides more sensitive diagnostics

GeneXpert MTB/RIF:

- *Early projections suggested large impact of Xpert as replacement for smear in key high-burden settings*
- *Xpert adoption projected to be both effective and cost-effective*

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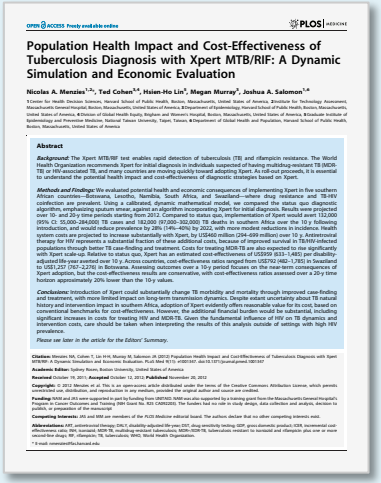
**Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis**

Anna Vassall[1,2], Sanne van Kampen[3], Hojoon Sohn[4], Joy S. Michael[4], K. R. John[5], Saskia den Boon[6], J. Lucian Davis[7], Andrew Whitelaw[8,9], Mark P. Nicol[8,9], Maria Tarcela Gler[10], Anar Khaliqov[11], Carlos Zamudio[12], Mark D. Perkins[13], Catharina C. Boehme[13], Frank Cobelens[14]*



OPEN ACCESS Freely available online PLOS | MEDICINE

**Population Health Impact and Cost-Effectiveness of Tuberculosis Diagnosis with Xpert MTB/RIF: A Dynamic Simulation and Economic Evaluation**

Nicolas A. Menzies[1,2]*, Ted Cohen[3,4], Hsien-Ho Lin[5], Megan Murray[3], Joshua A. Salomon[1,6]

*Vassall et al PLoS Med 2011; Menzies et al PLoS Med 2012*

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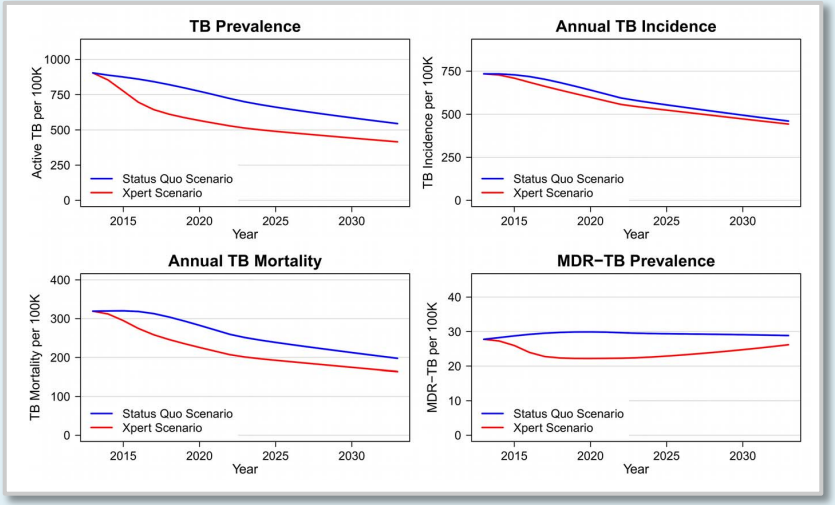


*Menzies et al PLoS Med 2012*

# Motivation III

- Despite promise, pragmatic trials of Xpert adoption show modest effects

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- Despite promise, pragmatic trials of Xpert adoption show modest effects

Empirical studies of Xpert introduction

- Smaller impact on case notifications that originally anticipated, little impact on mortality
- High rates of empirical treatment for individuals testing negative to the first diagnostic test
- Negative Xpert results generating fewer requests for culture, fewer patients diagnosed empirically


*McCarthy et al JAIDS 2016; Churchyard Lancet GH 2015; Theron et al Lancet ID 2014; Theron et al Lancet 2014*

# Research questions

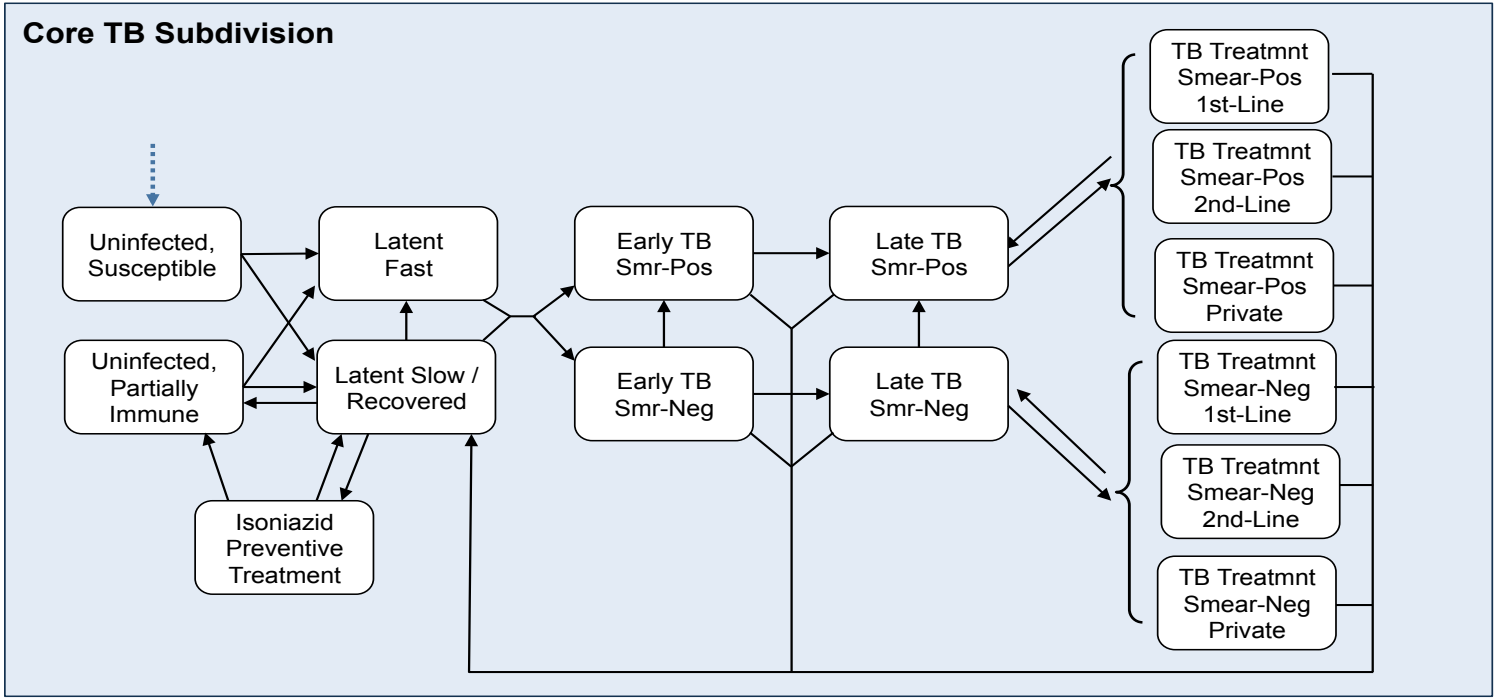
- How does the effect of Xpert adoption on diagnostic outcomes and TB epidemiology depend on other dimensions of algorithm performance?

- How might the impact of Xpert adoption differ across a range of high-burden countries?

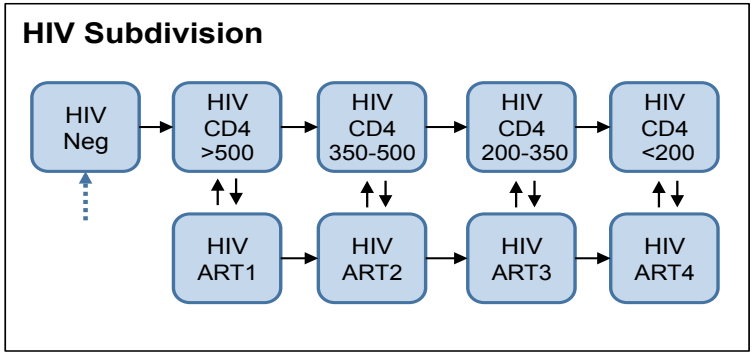
# Analytic approach I

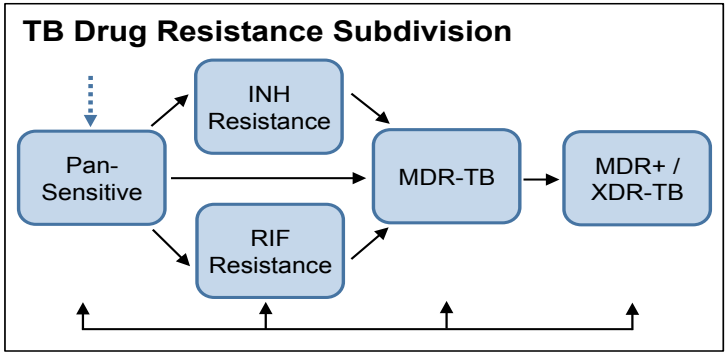
- Developed a transmission dynamic TB model to estimate implications of algorithm performance for TB outcomes and epidemiology
- Model parameterized for 9 high burden countries: Brazil, Cambodia, DRC, Kenya, Myanmar, the Philippines, Russia, Thailand, Zimbabwe
- Each country: calibration to range of data describing population demography, TB and HIV epi, and service utilization / quality

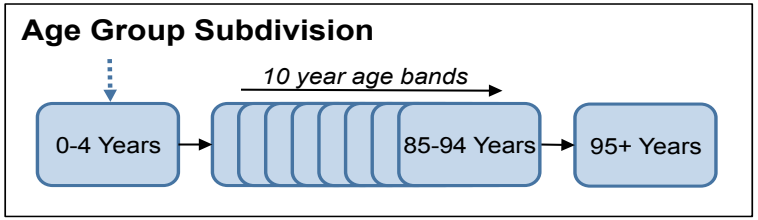
# Study model: core TB subdivision

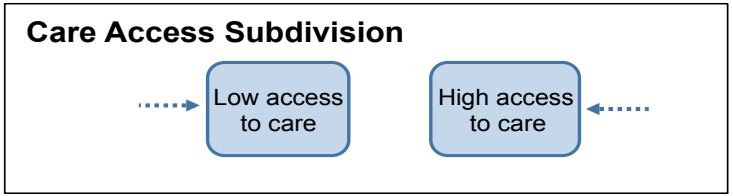


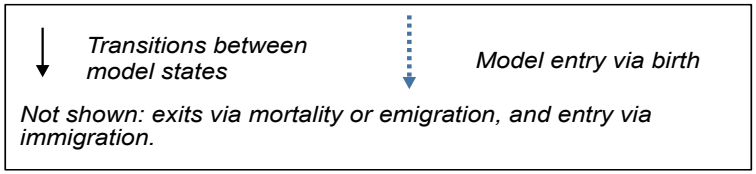
# Study model: other model subdivisions

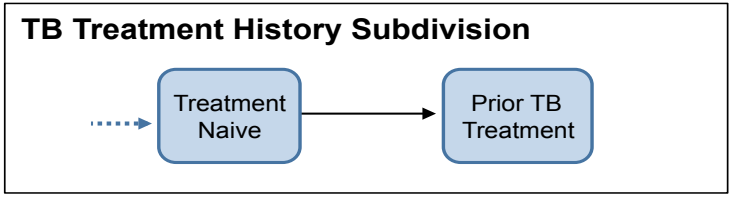


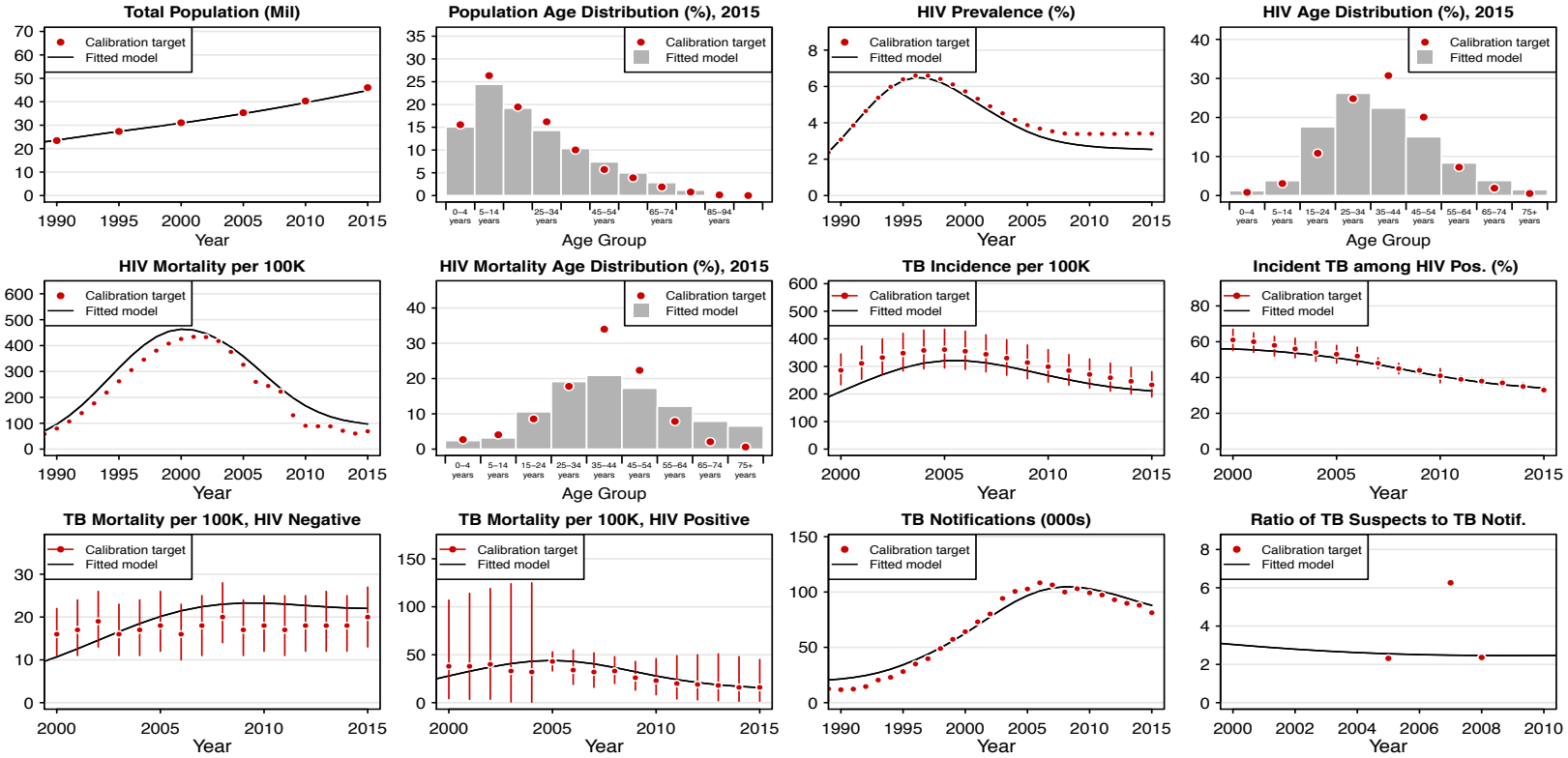



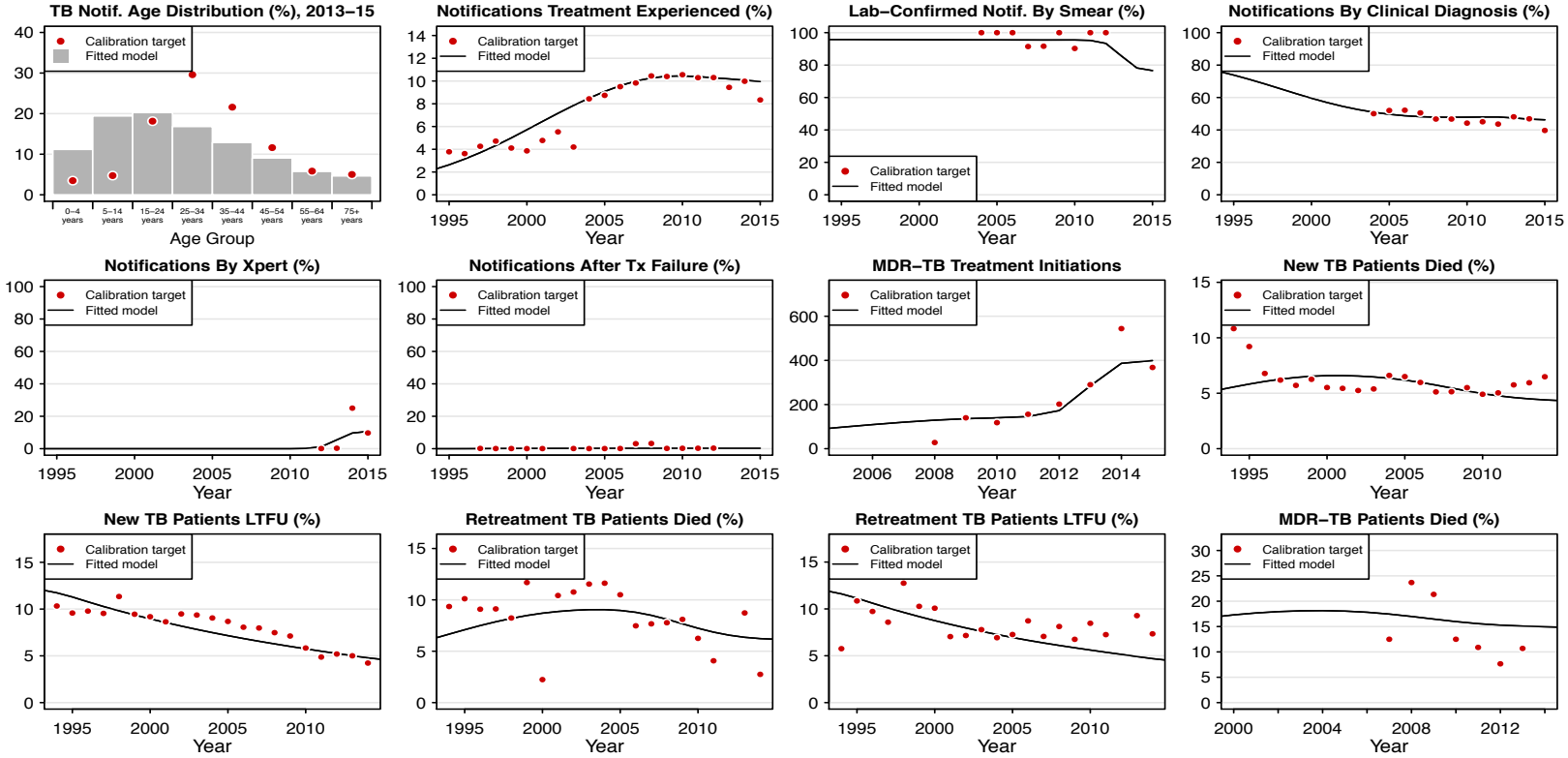



# Model calibration I (Kenya)



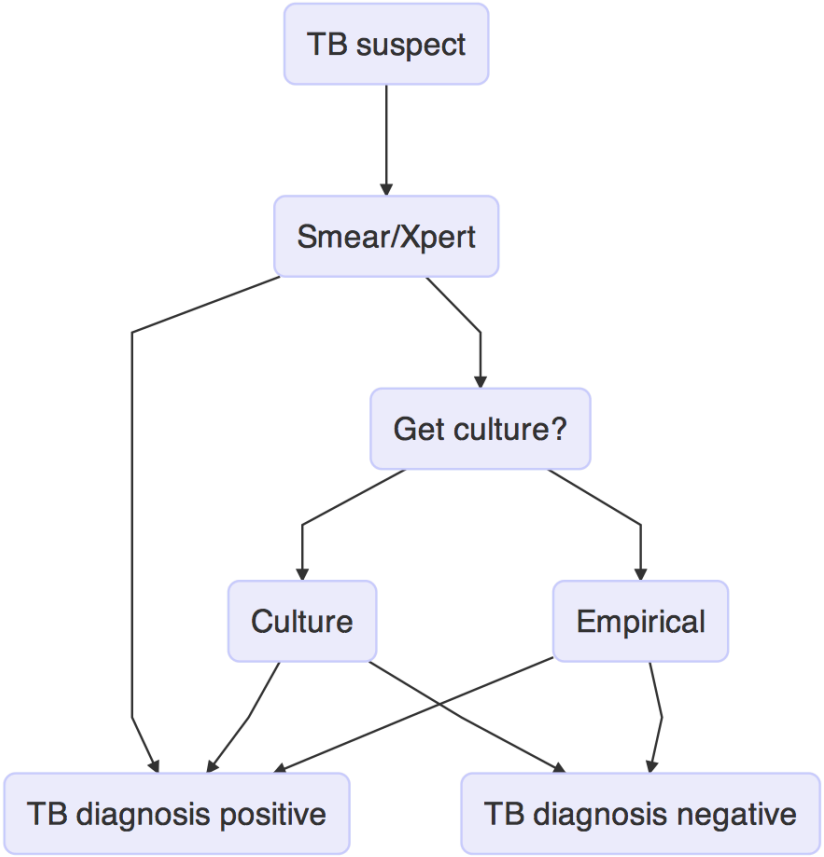
# Model calibration II (Kenya)



# Analytic approach II

- Calibrated model used to project TB diagnostic performance and epi outcomes over 10 years (2017-2027)
- Two scenarios:
  (1) Status-quo (predominantly smear)
  (2) Xpert adoption to fully replace smear for diagnosis
- Sensitivity analyses to describe how responses to Xpert adoption (changes in rates of culture, clinical diagnosis, and referral for 2nd-line regimens) influence policy effects

# Basic algorithm structure



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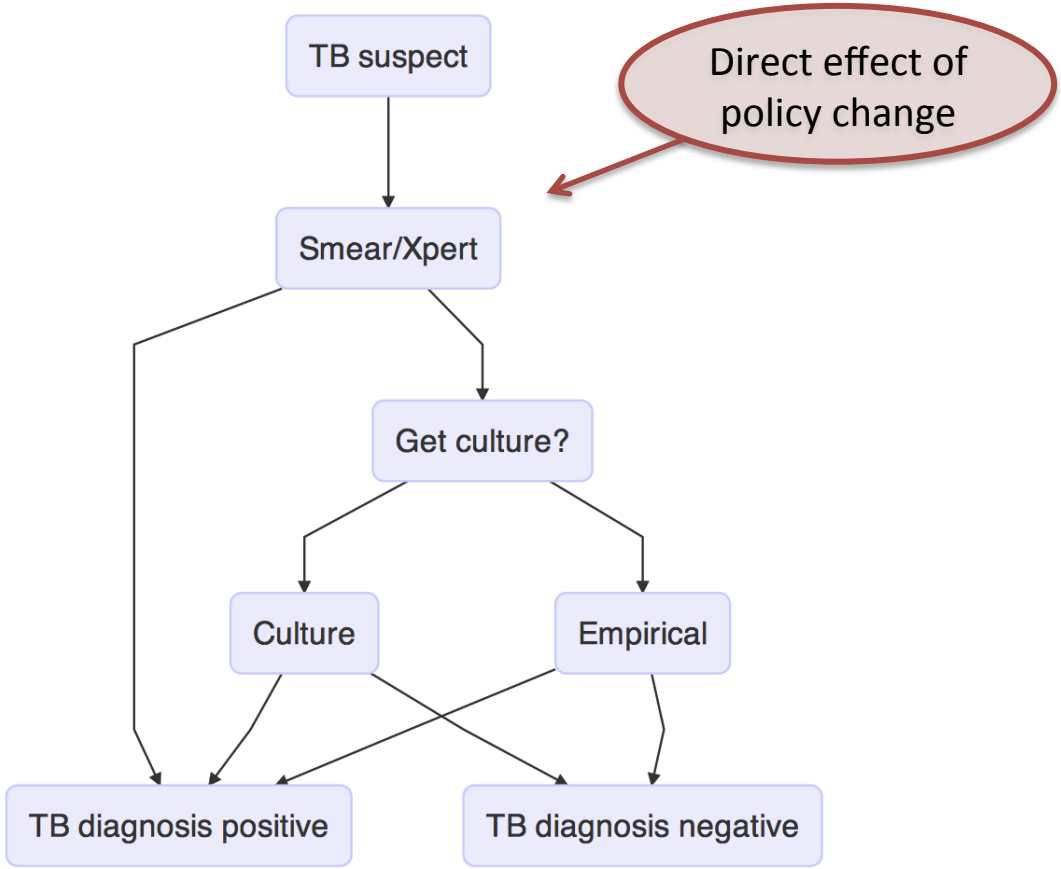

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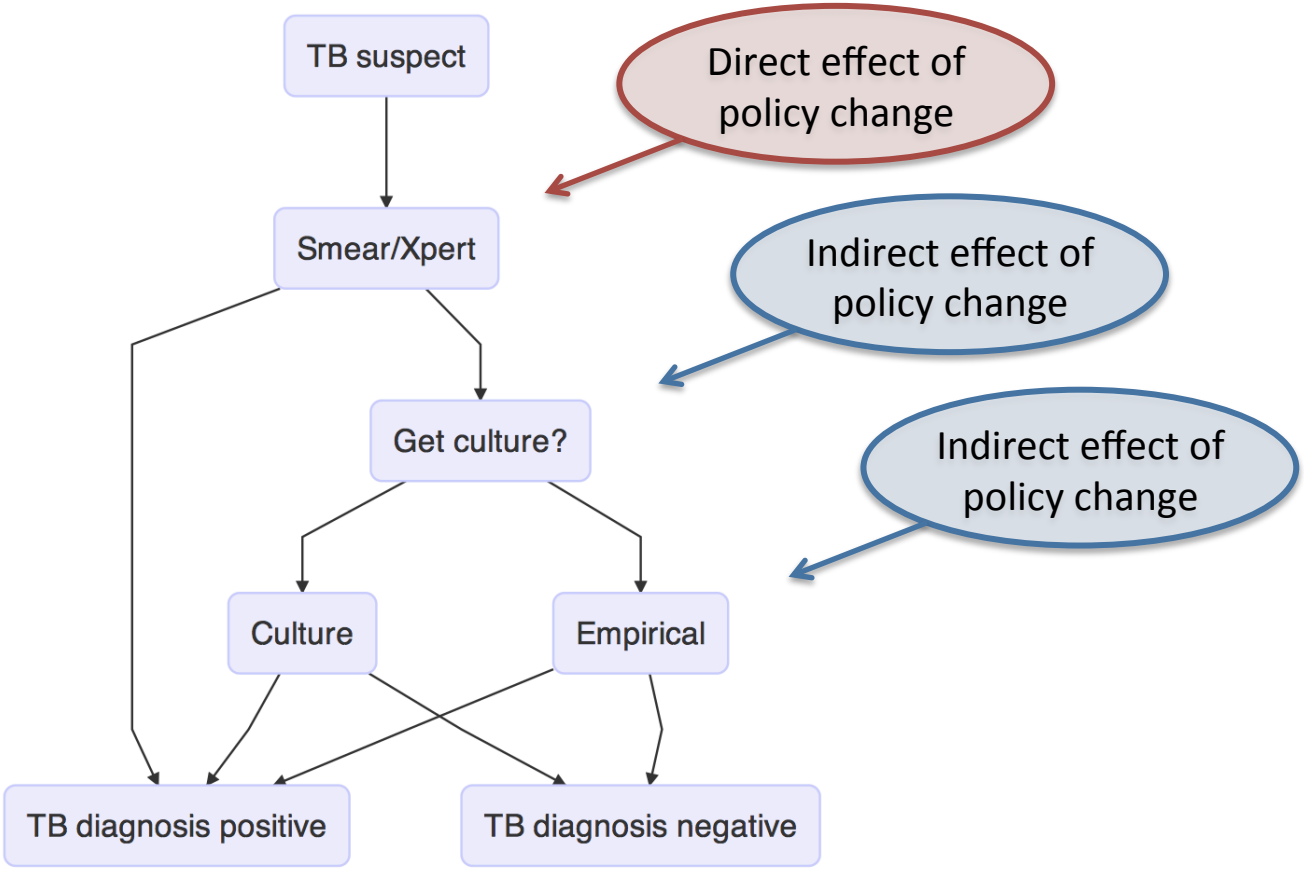
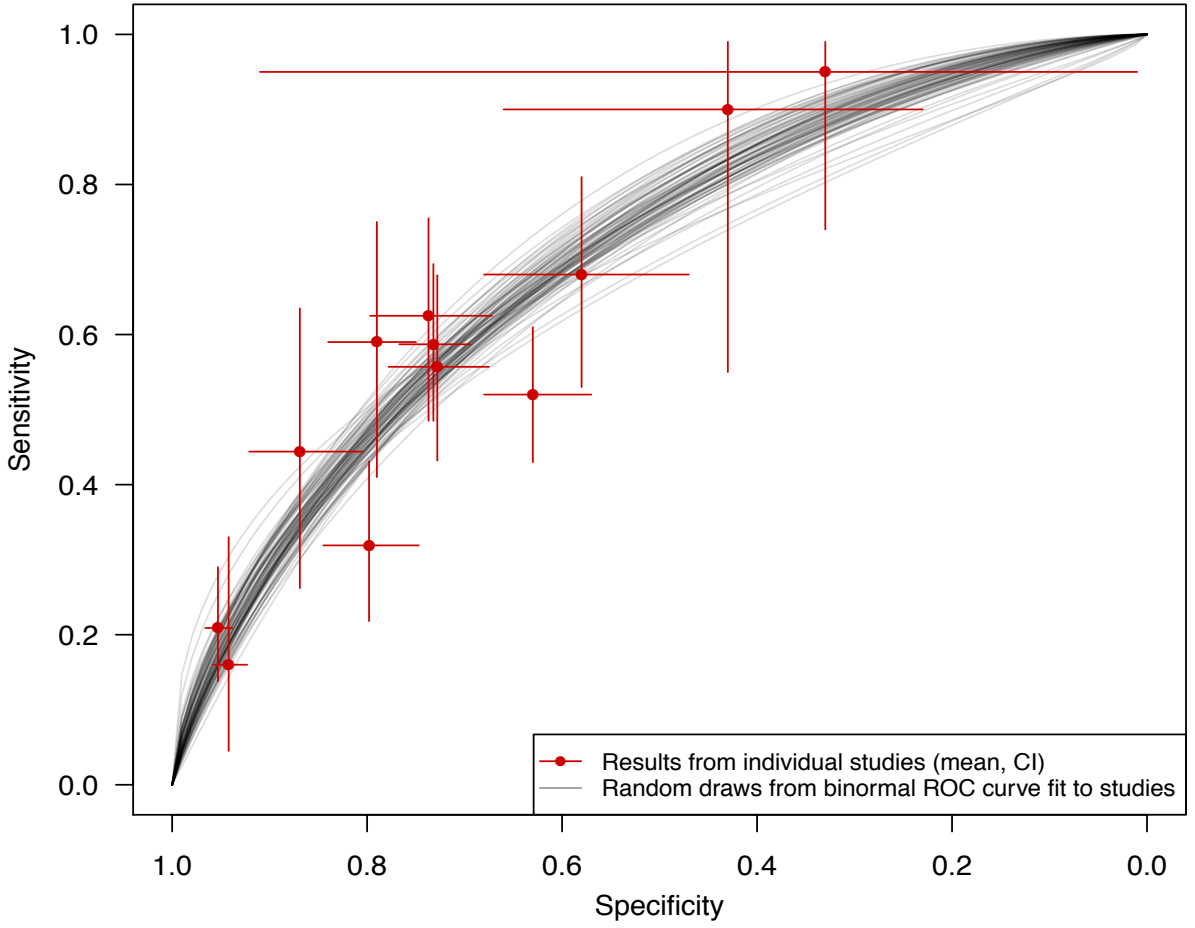


# Sensitivity and specificity of clinical diagnosis



# RESULTS

# Base case results: Outcomes for diagnostic performance in 2019 under **status-quo scenario**

| Country | Notifications per 100K | True Pos Notif per 100K | Positive Predictive Value | Negative Predictive Value |
|---|---|---|---|---|
| COD | 159 | 99 | 61.9 | 97.5 |
| KEN | 179 | 109 | 60.7 | 94.0 |
| ZMB | 248 | 151 | 60.9 | 94.4 |
| BRA | 37 | 29 | 78.8 | 97.9 |
| KHM | 271 | 120 | 44.2 | 98.0 |
| THA | 92 | 36 | 39.7 | 98.8 |
| RUS | 73 | 61 | 82.5 | 88.3 |
| MMR | 306 | 118 | 38.5 | 97.3 |
| PHL | 319 | 133 | 41.6 | 94.9 |

# Base case results: Outcomes for diagnostic performance in 2019 under Xpert adoption scenario

| Country | Notifications per 100K | True Pos Notif per 100K | Positive Predictive Value | Negative Predictive Value |
|---|---|---|---|---|
| COD | 162 (102%) | **116 (118%)** | 71.5 (116%) | 99.4 (102%) |
| KEN | 182 (102%) | 114 (105%) | 62.5 (103%) | 97.8 (104%) |
| ZMB | 252 (102%) | 157 (104%) | 62.1 (102%) | 98.0 (104%) |
| BRA | 41 (109%) | 30 (104%) | **75.0 (95%)** | 99.5 (102%) |
| KHM | 274 (101%) | 125 (104%) | 45.6 (103%) | 99.5 (102%) |
| THA | **80 (87%)** | 39 (106%) | **48.6 (122%)** | **99.7 (101%)** |
| RUS | **81 (110%)** | 67 (110%) | 82.3 (100%) | **97.2 (110%)** |
| MMR | 305 (100%) | **120 (102%)** | 39.4 (102%) | 98.9 (102%) |
| PHL | 313 (98%) | 142 (107%) | 45.2 (109%) | 98.8 (104%) |

# Base case results: Outcomes for epidemiological outcomes in 2019 under **status-quo scenario**

| Country | TB Incidence per 100K | TB Mortality per 100K | MDR-TB Prevalence per 100K |
|---|---|---|---|
| COD | 159 | 99 | 61.9 |
| KEN | 179 | 109 | 60.7 |
| ZMB | 248 | 151 | 60.9 |
| BRA | 37 | 29 | 78.8 |
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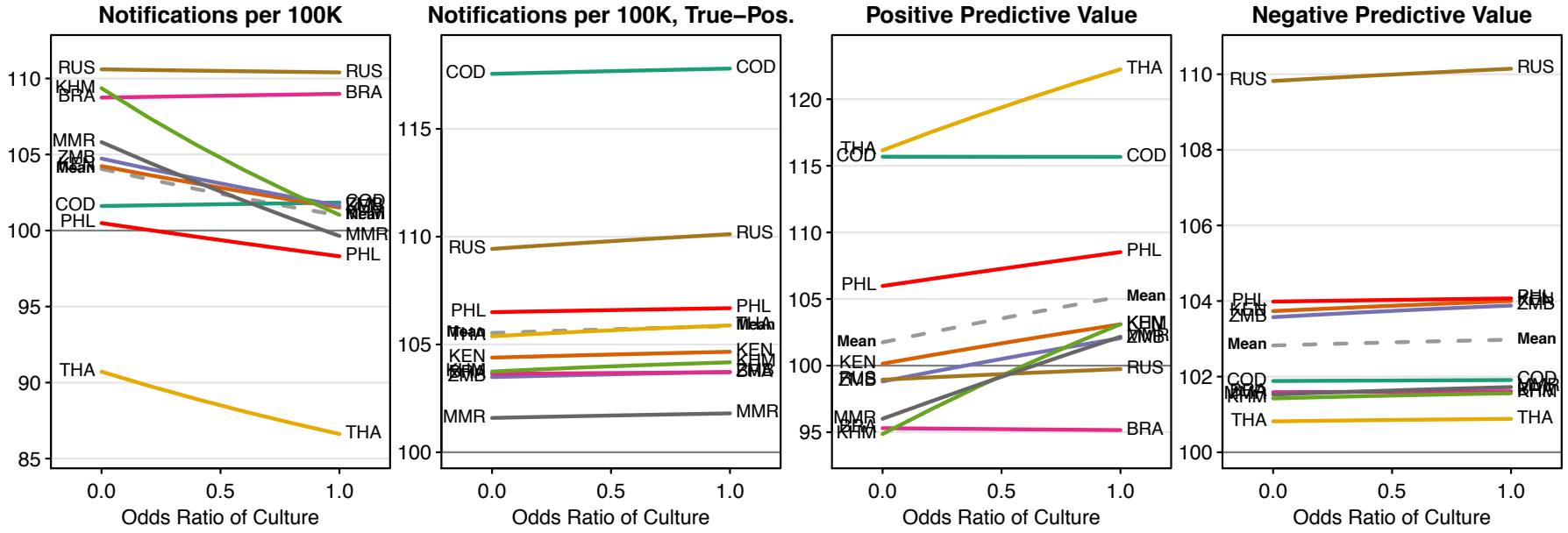
# Base case results: Outcomes for epidemiological outcomes in 2019 under Xpert adoption scenario

| Country | TB Incidence per 100K | TB Mortality per 100K | MDR-TB Prevalence per 100K |
|---|---|---|---|
| COD | 130 (94%) | **34 (88%)** | 5.4 (86%) |
| KEN | 229 (99%) | 42 (97%) | 5.9 (94%) |
| ZMB | **459 (100%)** | **116 (99%)** | **34.1 (98%)** |
| BRA | 30 (97%) | 4 (95%) | 0.3 (80%) |
| KHM | 86 (97%) | 14 (91%) | 1.4 (81%) |
| THA | 57 (96%) | 15 (94%) | 2.4 (86%) |
| RUS | **60 (92%)** | 13 (93%) | **9.1 (80%)** |
| MMR | 181 (100%) | 50 (99%) | 18.6 (97%) |
| PHL | 207 (98%) | 15 (93%) | 15.5 (92%) |

# Sensitivity analysis 1: Reduced use of culture following negative Xpert result (as compared to smear)



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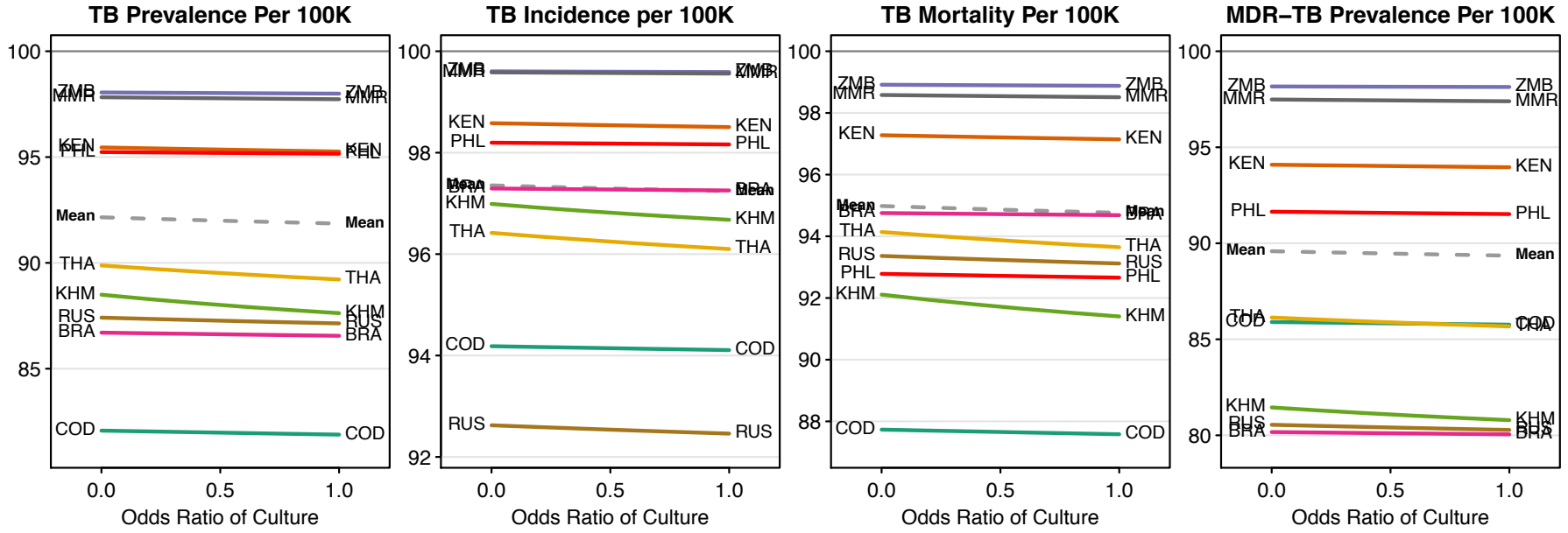
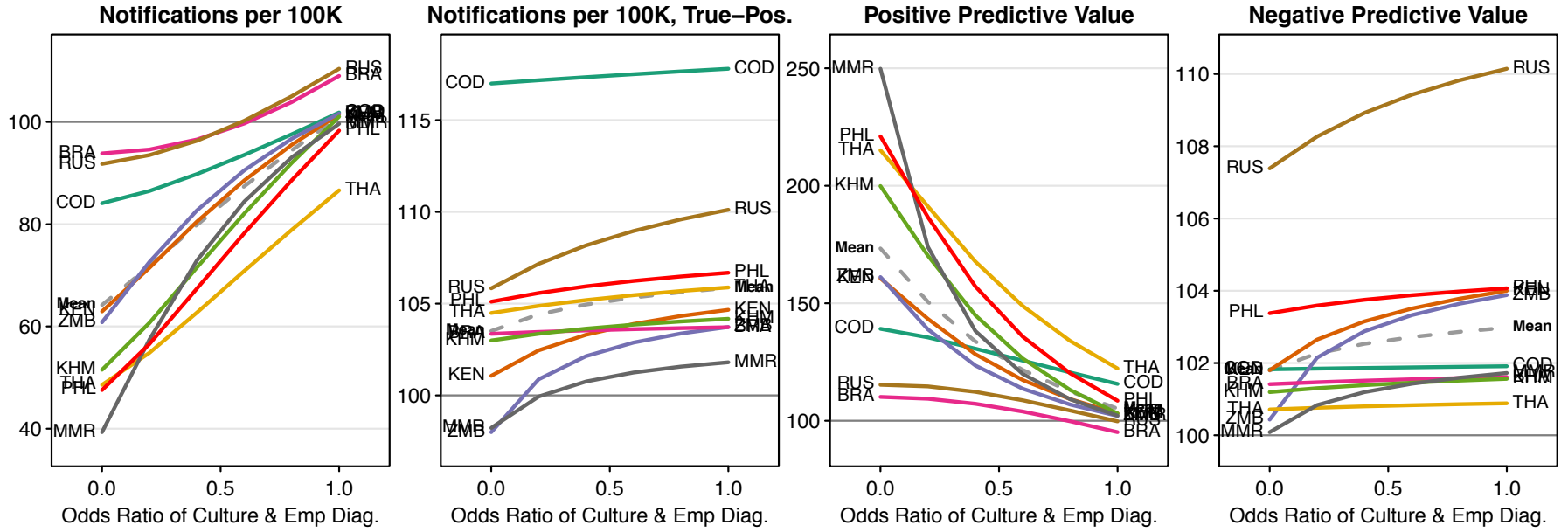


# Sensitivity analysis 2: Reduced use of culture and clinical diagnosis following negative Xpert result (vs. smear)



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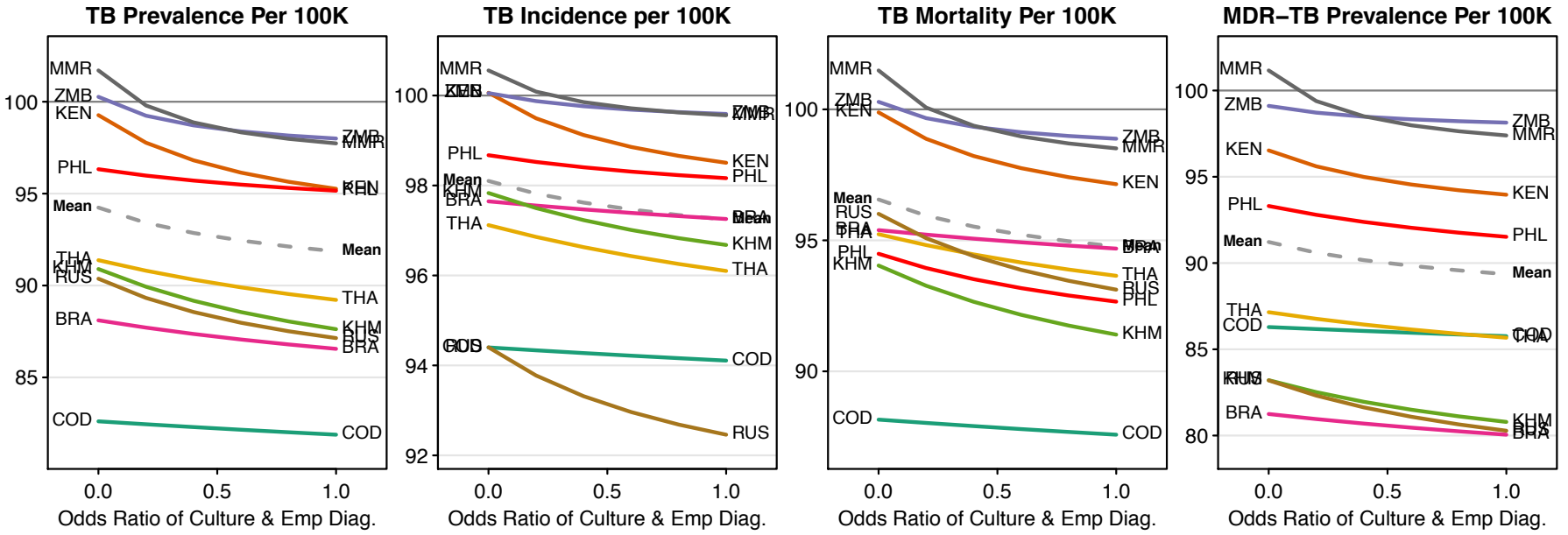
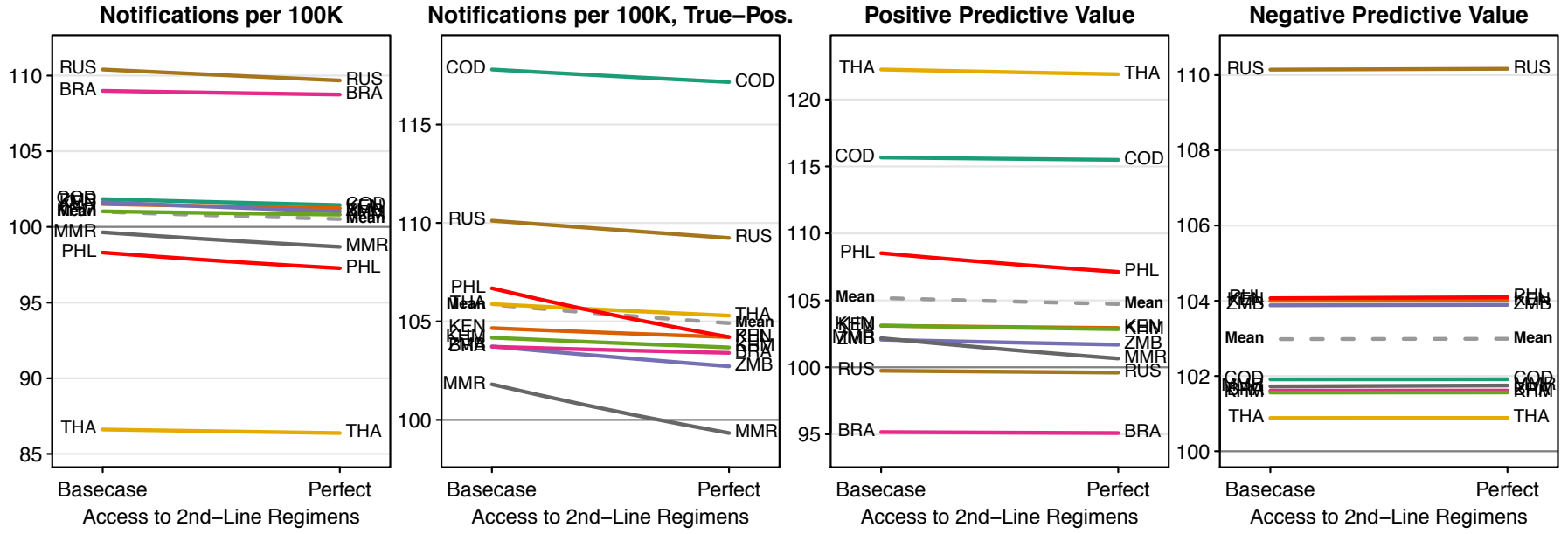


# Sensitivity analysis 3: Better access to 2nd line regimens for Xpert-RIF positive results



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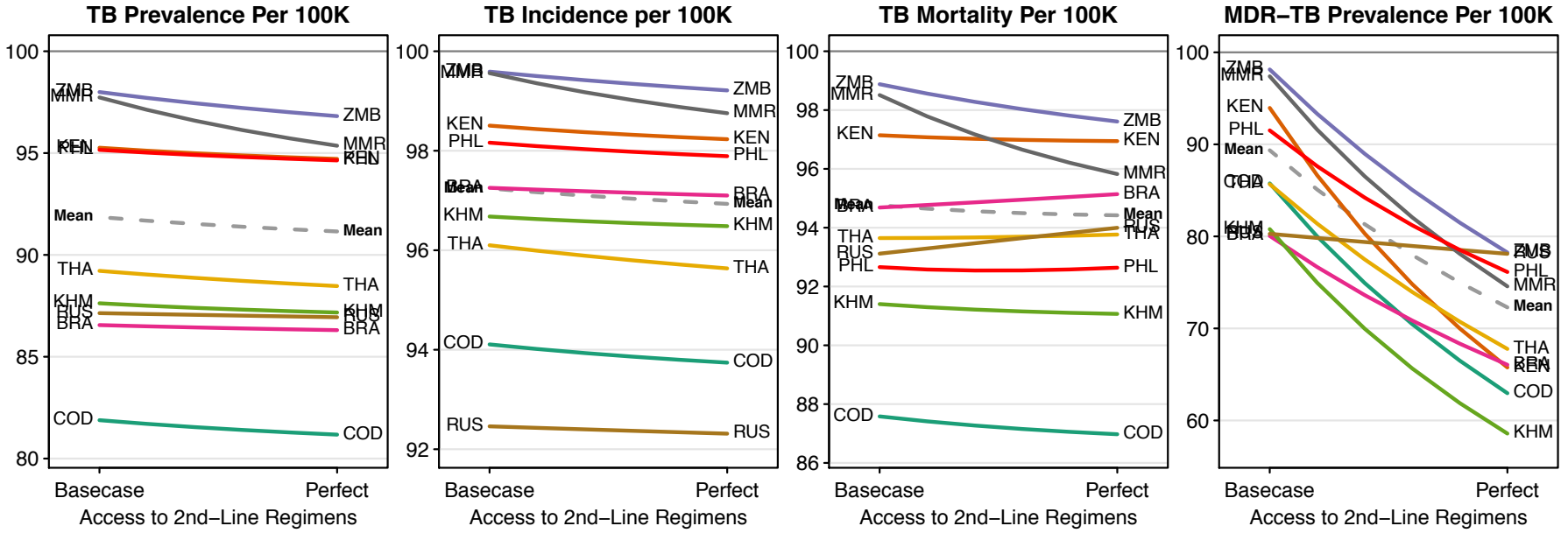

# Discussion I

- Knowing the relative test characteristics of Xpert and smear insufficient for understanding impact of Xpert adoption
- Even without effects on subsequent cascade, results suggest smaller impact for Xpert adoption than earlier studies: many TB cases missed by smear caught by culture or clinical diagnosis
- Epi impact of Xpert adoption smaller still if clinicians less likely to request culture or make clinical diagnoses following neg Xpert. At the extreme, incremental impact of Xpert adoption negligible

# Discussion II

- Reliance on clinical diagnosis is not harmless, given poor performance characteristics
- Given low specificity, substantial use of clinical diagnosis will increase false-positive diagnoses if pushing for greater sensitivity, or testing groups with lower TB prevalence
- With risks of false-positive diagnosis, important to take account of the consequences for these individuals
- Assessing optimality of diagnostic algorithms solely through TB epi impact is too narrow a set of criteria

# Limitations

- Study only deals with some of the programmatic issues encountered with Xpert adoption, not comprehensive
- Study relied heavily on reporting data to identify how TB diagnosis achieved in routine programs → results sensitive to reporting biases
- Culture is criterion standard for test evaluation, but ignores culture-negative TB

# Acknowledgements


## *Coauthors/collaborators*

Alyssa Bilinski, Reza Yaesoubi, Ted Cohen, Joshua Salomon

## *Funding*

TB MAC / Bill & Melinda Gates Foundation