Model Simulation to Reflect Programmatic Settings for TB Care

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Key question

- How can models project programmatic outcomes and inform responses in a manner that complements trial data?

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Background: a very brief history of Xpert, going from an ideal testing scenario to a programmatic setting

Xpert has great performance characteristics

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

- Xpert sensitivity was 98% in those with smear-positive TB and 73% in those with smear-negative TB

- Xpert specificity was 99%

Boehme et al., *N Engl J Med* 2010

Xpert may not reduce TB-related morbidity and mortality

TB-NEAT and XTEND studies

- Xpert did not reduce TB-related morbidity or mortality
  - High levels of *empiric treatment*
  - High levels of *loss to follow-up*

Theron et al., *Lancet* 2014; Churchyard et al., *Lancet Glob Health* 2015

Xpert may not improve the cost-effectiveness of TB diagnostics

Cost analysis and economic evaluation of XTEND study

- No evidence that Xpert improves the cost-effectiveness of TB diagnosis in South Africa

Vassall et al., *Lancet Glob Health* 2017

Outline: insights to be gained

- How can models project programmatic outcomes and inform responses in a manner that complements trial data?
  - New diagnostics: sputum provision and diagnostic yield
  - Empiric treatment
  - Cascade of care: linkage to treatment and loss to follow-up

Outline

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New diagnostics

- Clinical impact and cost-effectiveness depends on:

    1) Proportion of people able to provide a specimen (sputum, urine, etc.)

    2) The incremental diagnostic yield of the new test over the existing test, for an algorithm that includes tests done in parallel
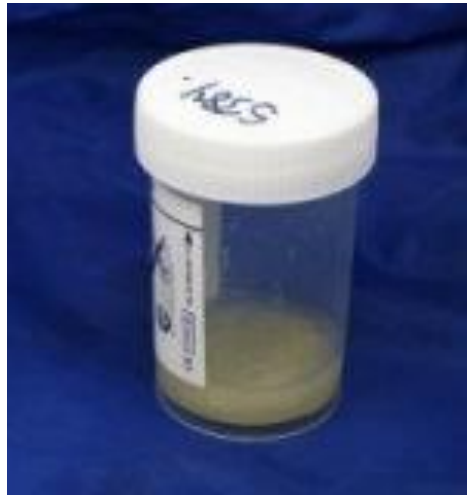
Sputum provision: example from STAMP trial and model-based analysis

- STAMP trial in Malawi and South Africa

  - Tested all hospitalized adults with HIV for TB

    - Control: sputum Xpert

    - Intervention: sputum Xpert + urine Xpert + urine AlereLAM

  - Primary outcome: all-cause mortality at 2 months

- Model-based cost-effectiveness analysis

  - Projected clinical and economic outcomes over a longer time horizon

  - Evaluated scenarios beyond that of the trial, including different probabilities of sputum provision

Gupta-Wright et al., *Lancet* 2018; Reddy et al., *Lancet Glob Health* 2019

Higher sputum provision leads to lower clinical impact of adding urine tests to sputum test

Model-projected gain in life expectancy from adding urine tests to sputum test, South Africa

*75% in STAMP trial
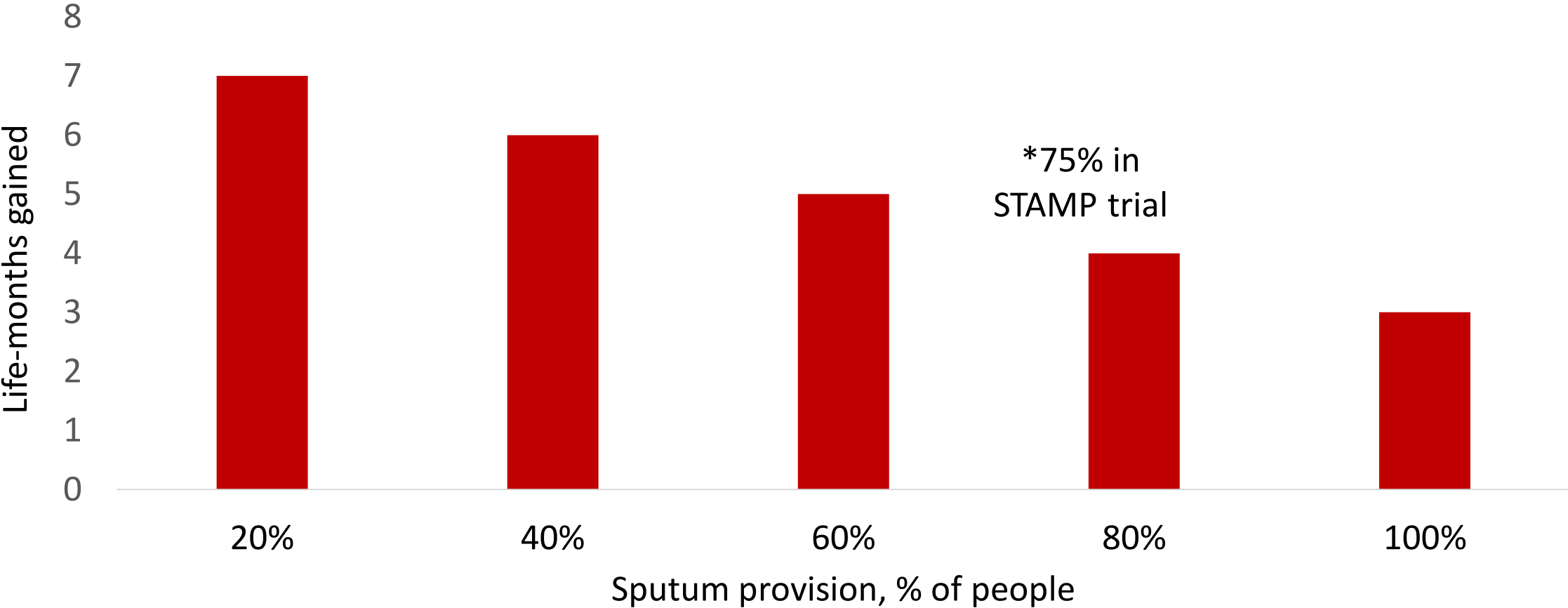
Adapted from Reddy et al., *Lancet Glob Health* 2019

Incremental diagnostic yield: example from FujiLAM study

- FujiLAM
  - Retrospective study comparing sensitivity and diagnostic yield of urine FujiLAM to other tests among hospitalized people with HIV in South Africa

  - Diagnostic yield: proportion of all TB cases that are detected by a particular test (Xpert sensitivity 80% x Sputum provision 50% = Sputum Xpert yield 40%)
  - Incremental yield: additional TB cases detected by a second test that are missed by a first test (e.g., incremental yield of FujiLAM over sputum Xpert)

Broger et al., *Lancet Infect Dis* 2019

Accounting for incremental yield of urine FujiLAM over sputum Xpert when both tests are done in parallel

Base case scenario
141 confirmed cases of TB
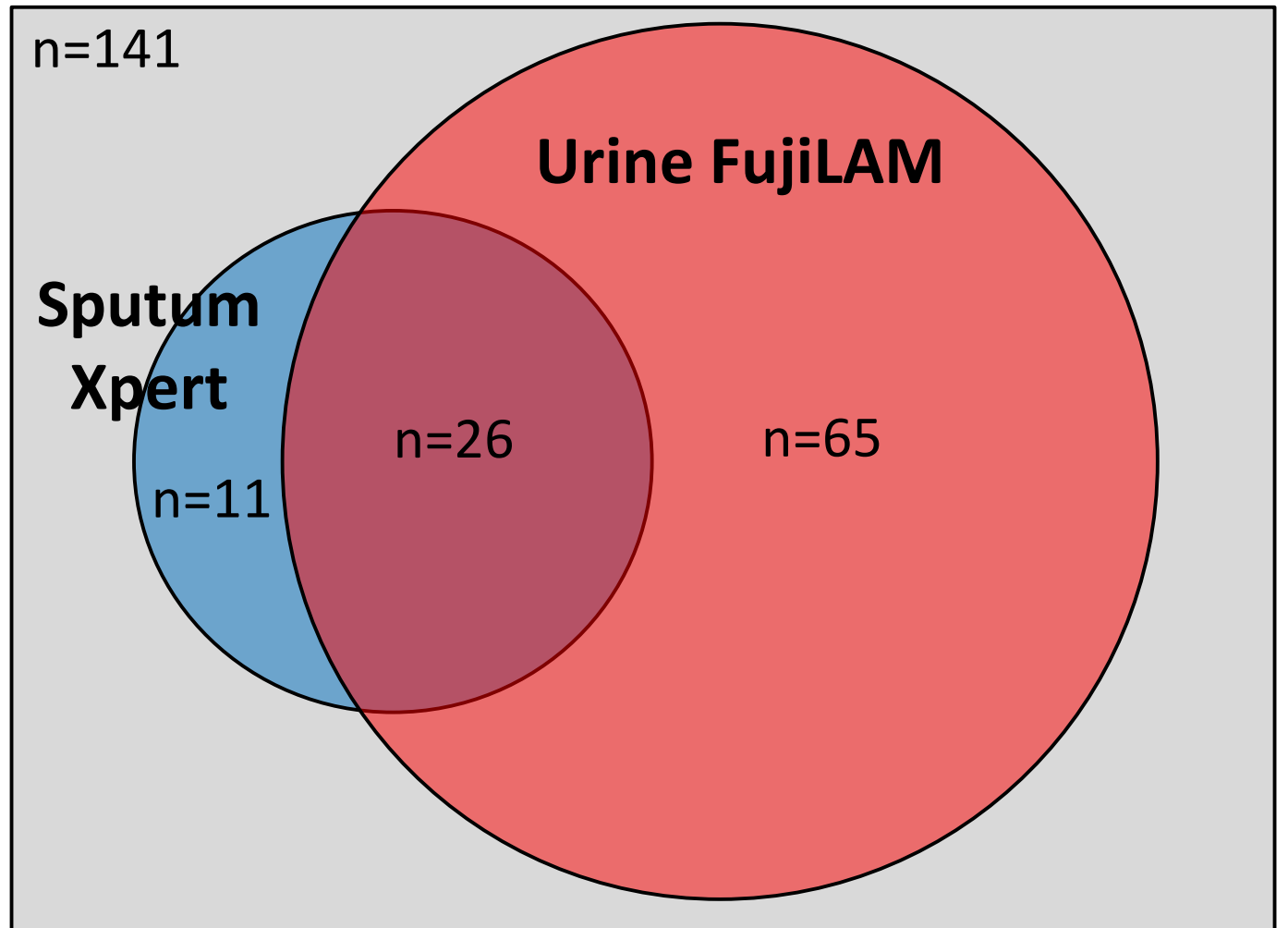
Sputum provision: 35%

Incremental yield of urine FujiLAM over sputum Xpert is 65 cases

n=141

Urine FujiLAM

Sputum Xpert

n=11

n=26

n=65

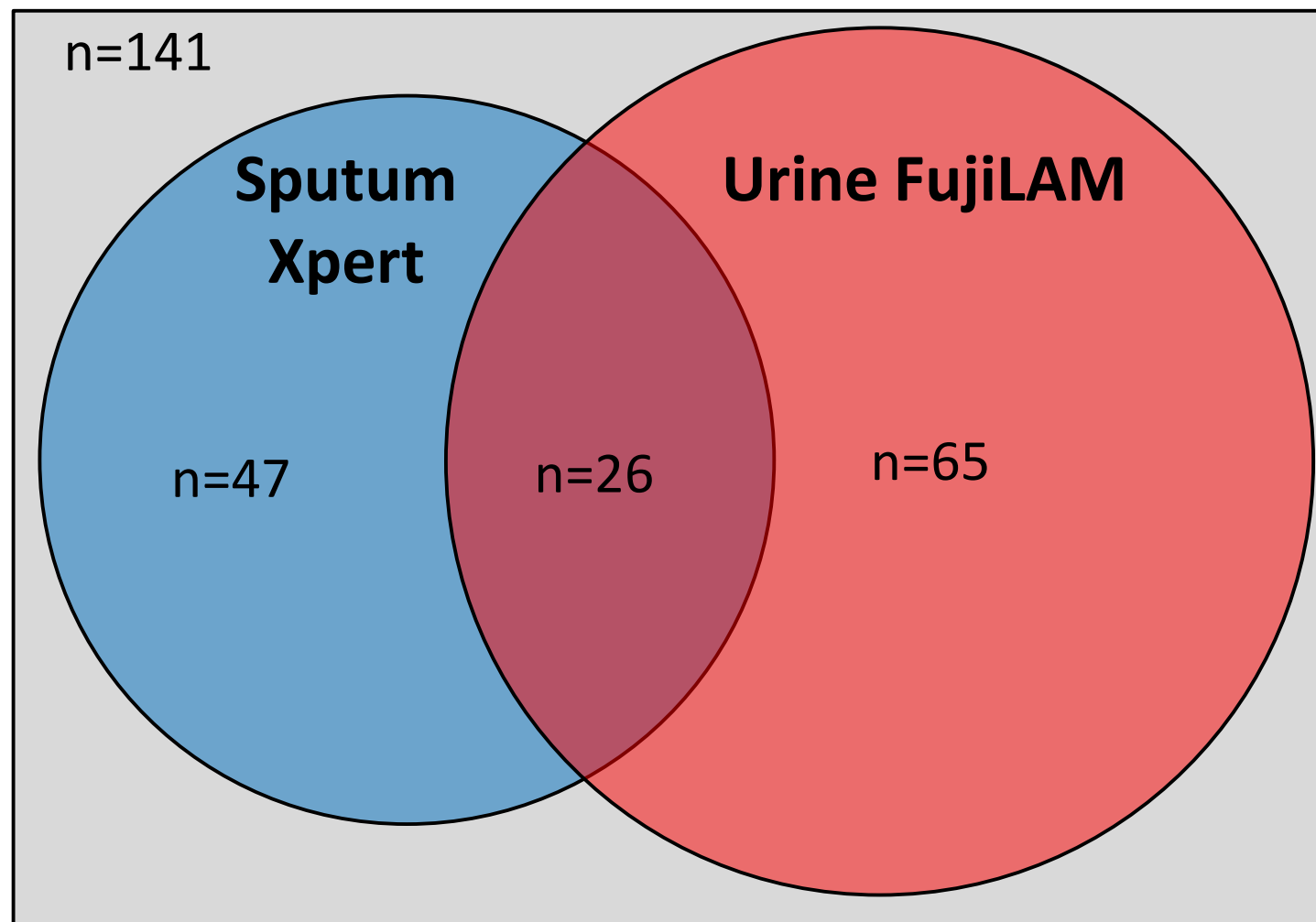Adapted from Broger et al., *Lancet Infect Dis* 2019
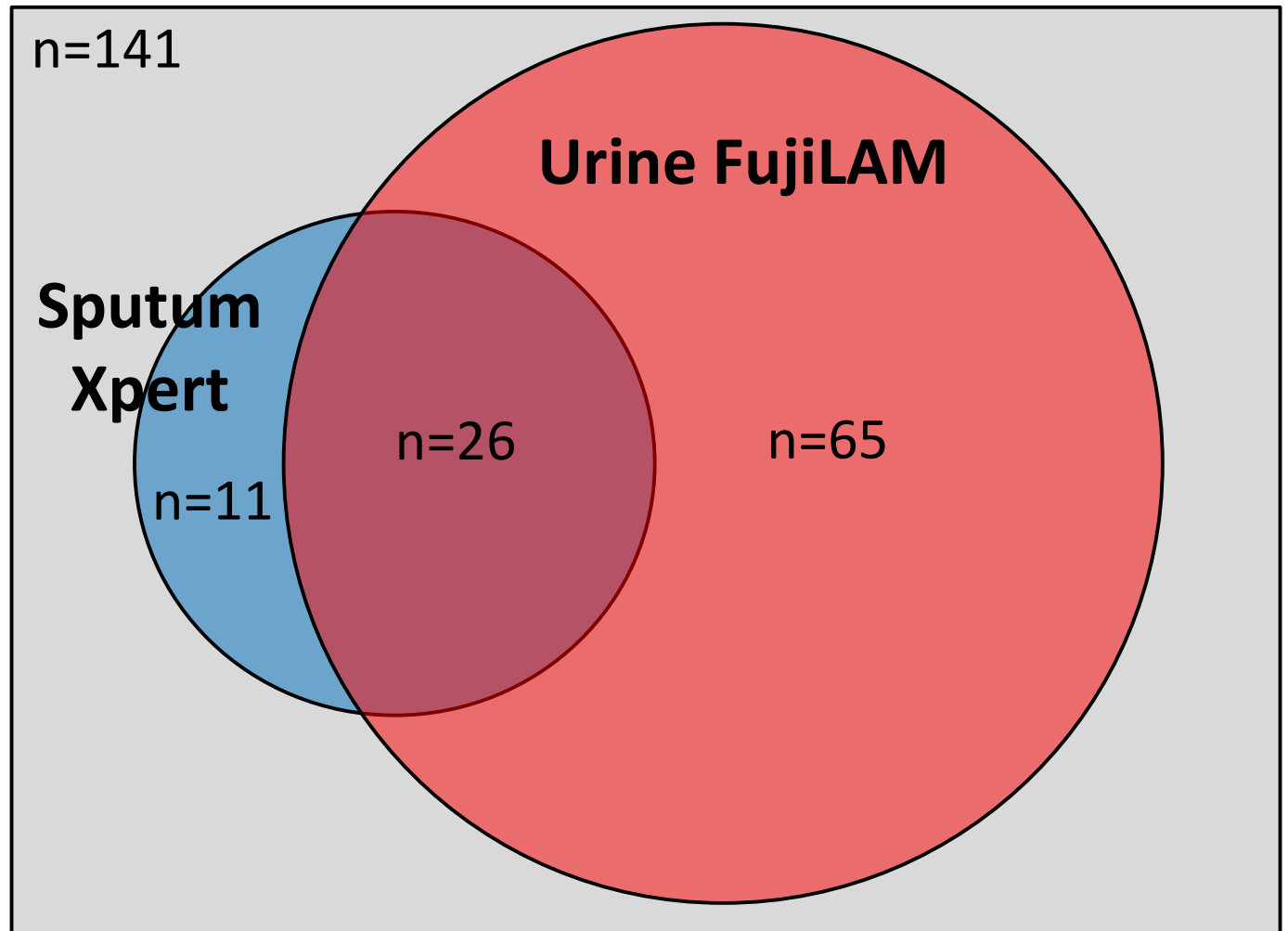
What if we want to model a scenario in which sputum provision doubles to 70%?

Alternative Scenario A: the increased yield of sputum Xpert are all cases undetected by FujiLAM

Incremental yield of urine FujiLAM over sputum Xpert is 65 cases

(same as Base Case Scenario)

n=141

Sputum Xpert

Urine FujiLAM

n=47

n=26

n=65

Alternative Scenario B: the increased yield of sputum Xpert are all cases already detected by FujiLAM

Incremental yield of urine FujiLAM over sputum Xpert is 29 cases

(decreased from 65 cases in Base Case Scenario and Alternative Scenario A)
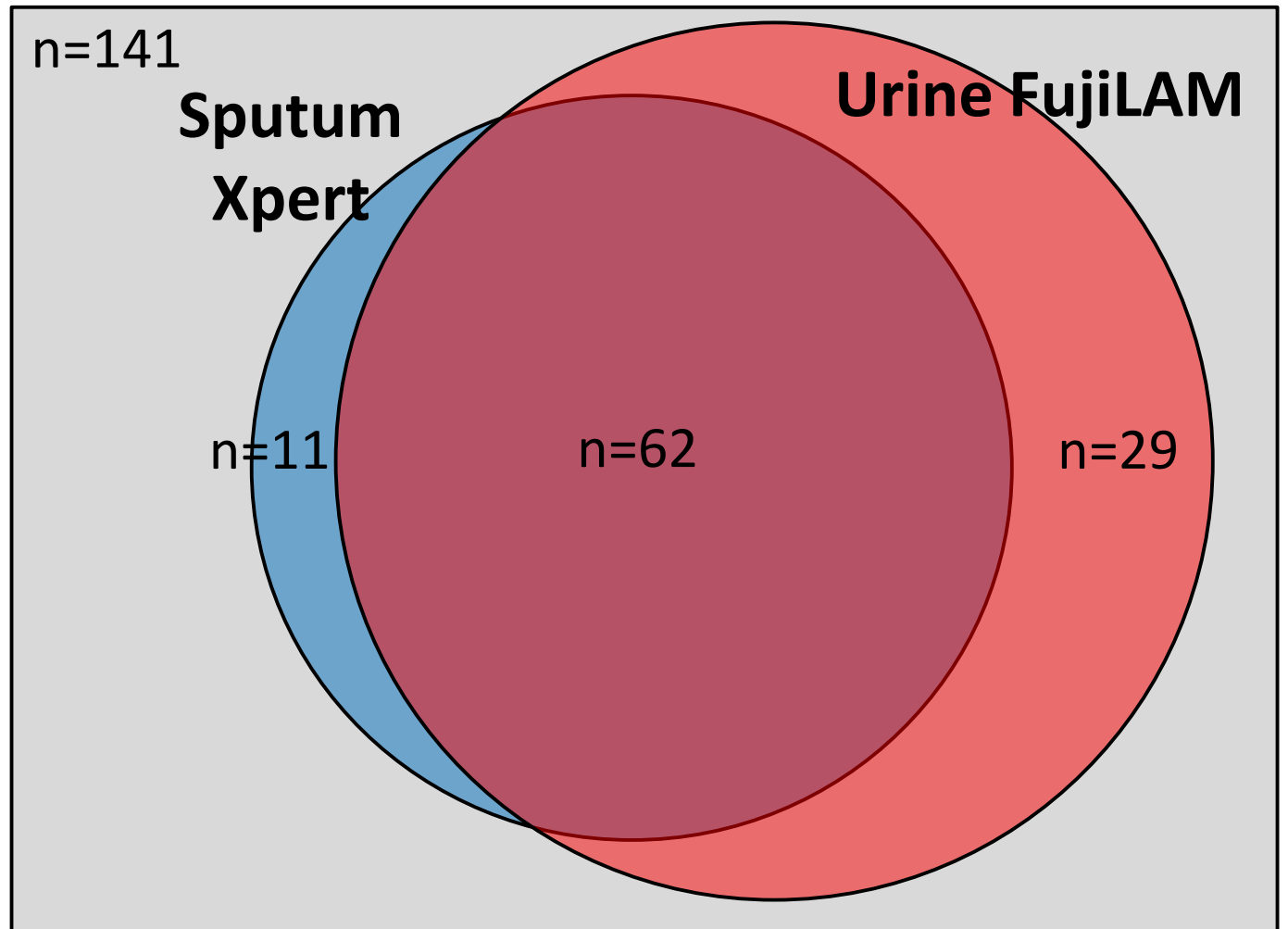
n=141

Sputum Xpert

Urine FujiLAM

n=11

n=62

n=29

Outline

- How can models project programmatic outcomes and inform responses in a manner that complements trial data?
  - New diagnostics: sputum provision and diagnostic yield
  - **Empiric treatment**
  - Cascade of care: linkage to treatment and loss to follow-up

Empiric treatment

- Empiric treatment is like a diagnostic test with high sensitivity and low specificity

- High prevalence of empiric treatment can reduce the clinical impact of a new diagnostic test
  - Those who truly have TB are more likely to receive empiric treatment than those who do not have TB (higher pre-test probability)
    - Can account for this in a model analysis

Empiric treatment

- Some negative consequences of empiric treatment
  - Treating some TB-negative patients unnecessarily
    - Toxicity of treatment
      - Especially for people with HIV on antiretroviral therapy – some stop taking medications
    - Not treating the true cause of illness (maybe)
    - Costs of treatment

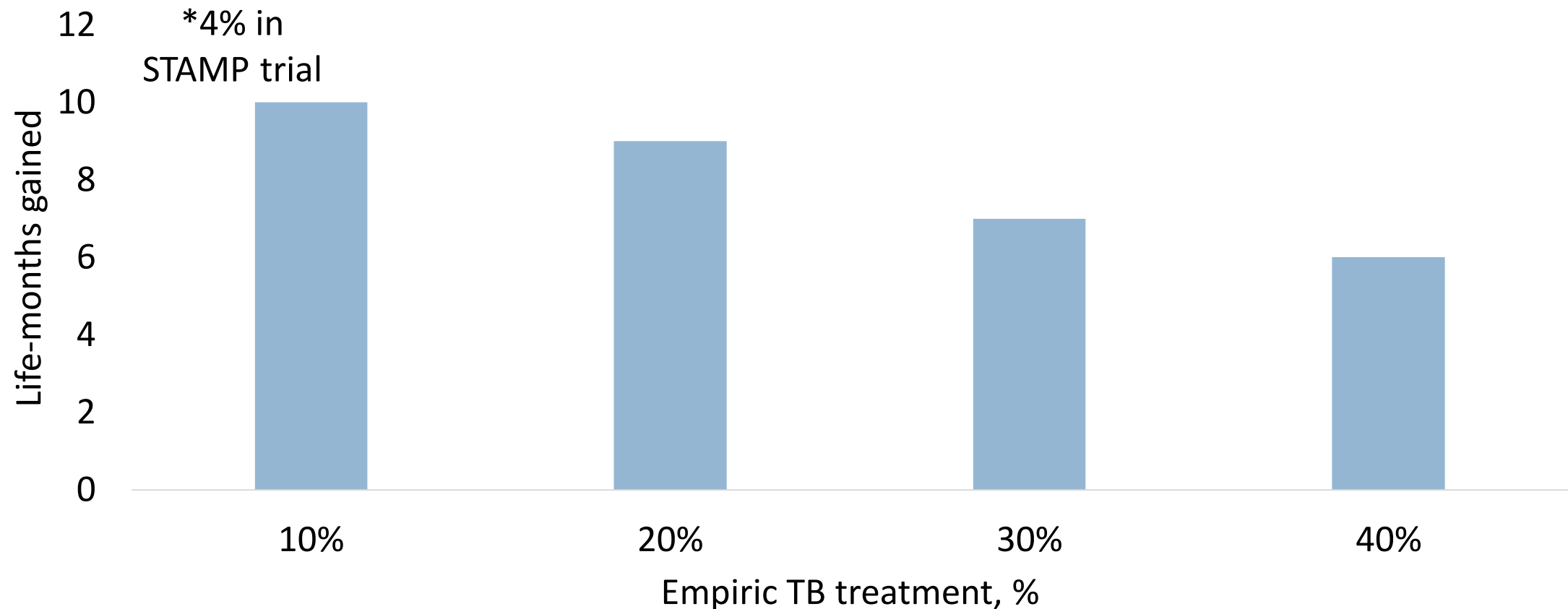 - Inadequate first-line treatment for MDR-TB

Empiric treatment

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  - Inadequate first-line treatment for MDR-TB

How much of an impact do these have in modeling analyses?

Higher empiric treatment leads to lower clinical impact of adding urine tests to sputum test

Model-projected gain in life expectancy from adding urine tests to sputum test, Malawi

*4% in STAMP trial

Y-axis: Life-months gained (0, 2, 4, 6, 8, 10, 12)

X-axis: Empiric TB treatment, %
- 10%: 10
- 20%: 9
- 30%: 7
- 40%: 6

Adapted from Reddy et al., *Lancet Glob Health* 2019

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Cascade of care

- *Efficacy* of new TB diagnostic and treatment strategies in trials is influenced by supervision and retention in care

- *Effectiveness* in programmatic settings may be dampened by failure to initiate treatment, imperfect adherence, and loss to follow-up (LTFU) during treatment

TB care cascade in India


Subbaraman et al., *PLoS Med* 2016
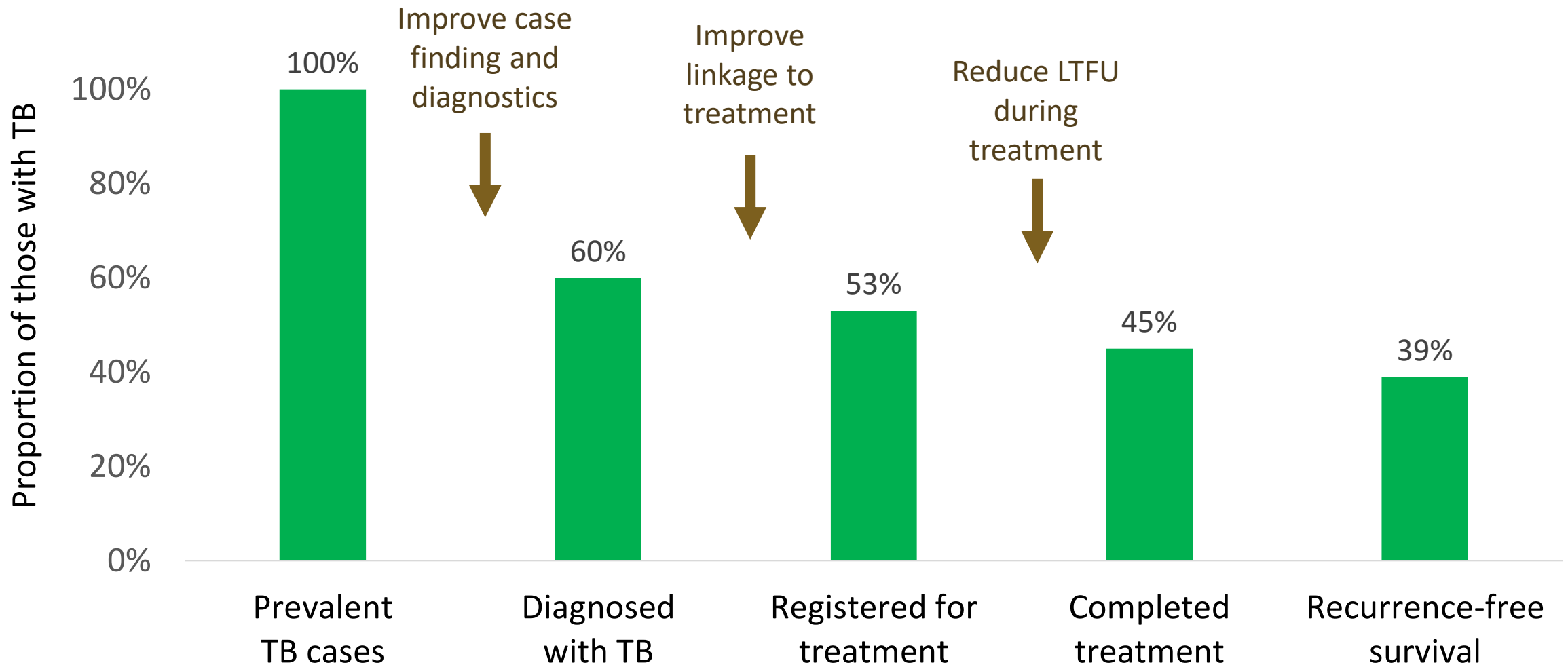
Improving linkage to treatment with a point-of-care molecular TB diagnostic: Truenat in India

- Truenat: novel, portable, battery-powered molecular diagnostic for detection of TB and rifampin resistance, developed in India

  - Can be used at point-of-care

  - Estimated cost per test is similar to Xpert

- Xpert: requires temperature control and continuous power supply

  - Centralized lab

  - Diagnostic delays and failure to link some patients to treatment

Truenat could be cost-effective compared to Xpert, because of greater linkage to treatment

Cost-effectiveness of Truenat compared to Xpert
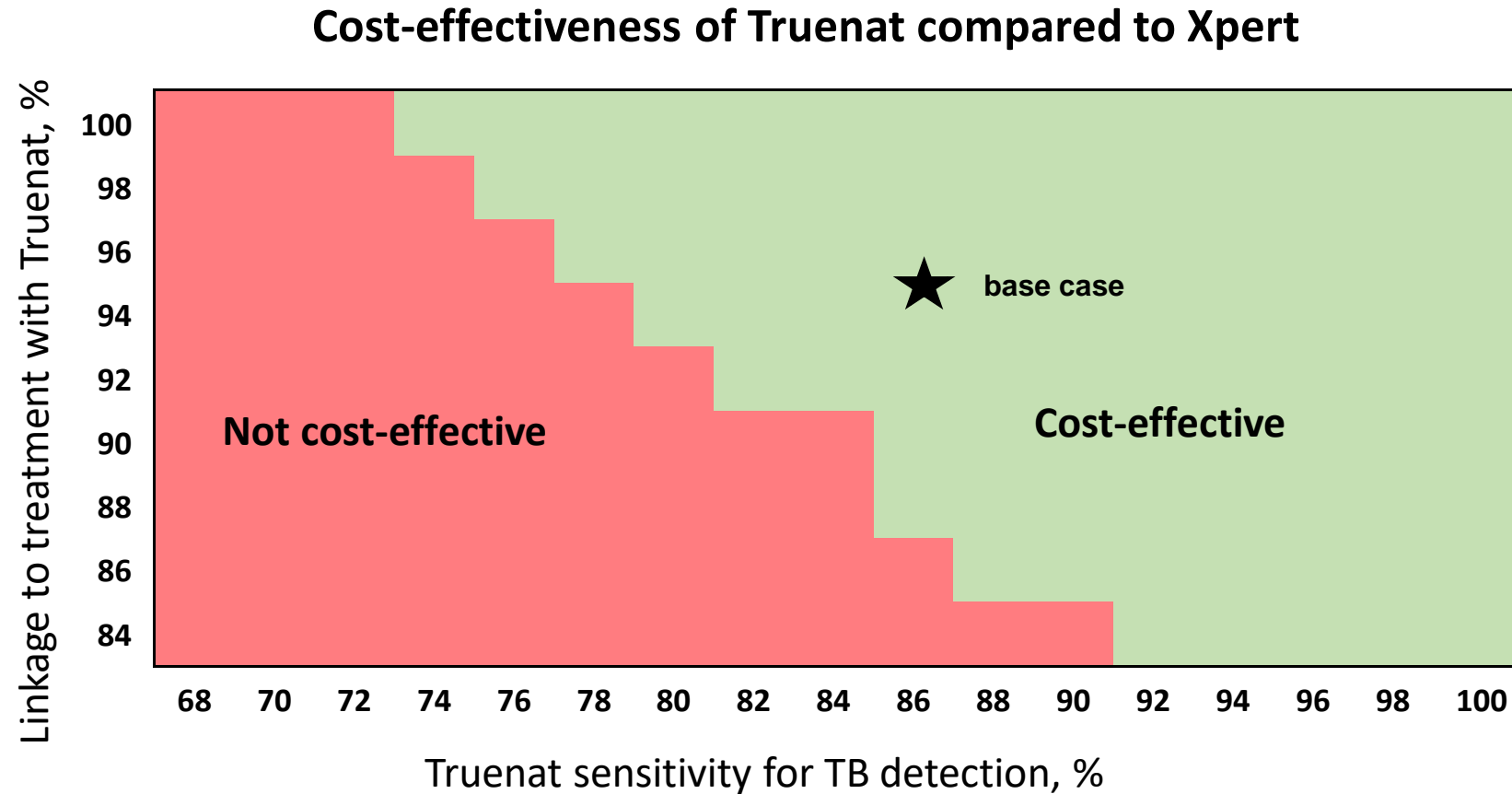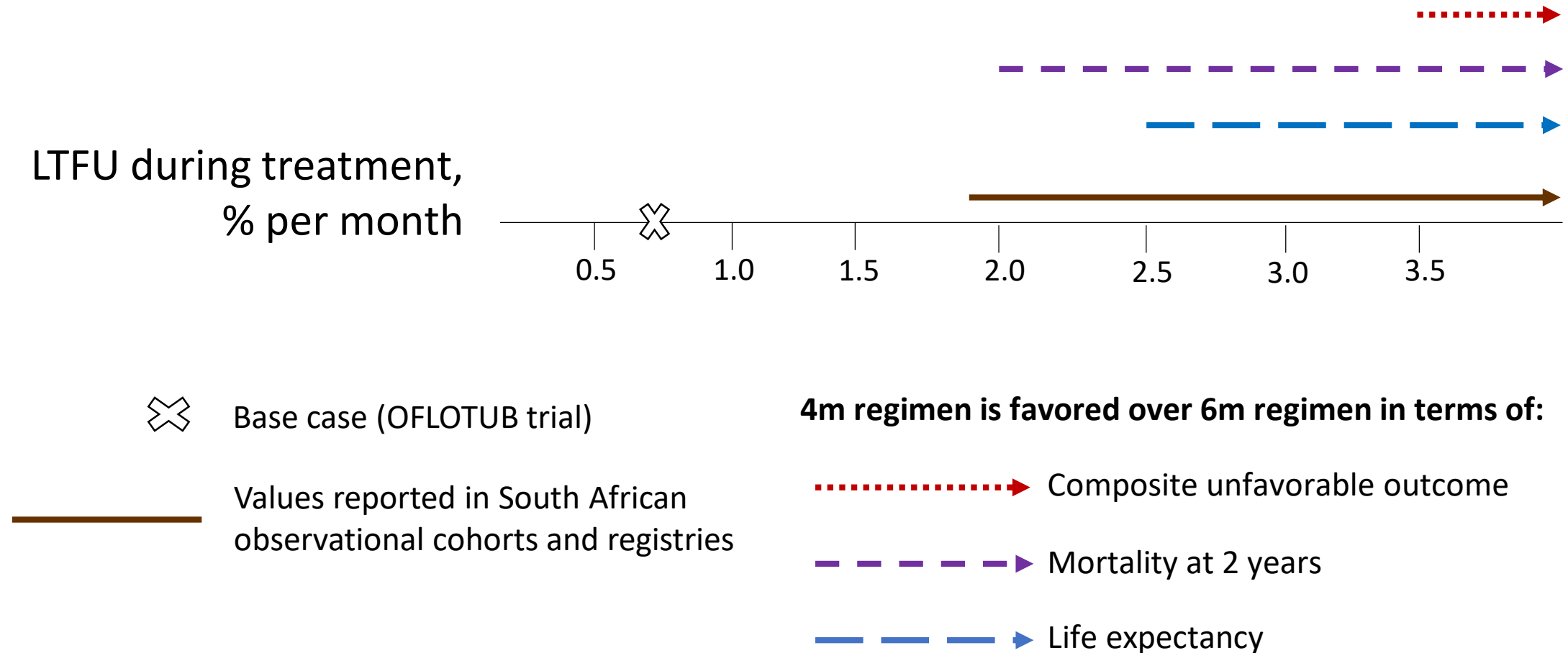
Green: Truenat is cost-effective compared to Xpert in India (incremental cost-effectiveness ratio <USD990 per year of life saved)

Red: Truenat is not cost-effective compared to Xpert in India

Lee et al., *PLoS One* 2019

Low LTFU in trials of shortened TB treatment regimens

- 4-month versus 6-month regimens for drug-susceptible TB
- Failed to show noninferiority in terms of a composite clinical outcome (LTFU, treatment failure, death, recurrence)
- LTFU was <1% per month in the trials

Merle et al., *N Engl J Med* 2014; Jindani et al., *N Engl J Med* 2014; Gillespie et al., *N Engl J Med* 2014

When LTFU reflects programmatic settings, TB treatment trial results might be interpreted differently

LTFU during treatment, % per month

0.5   1.0   1.5   2.0   2.5   3.0   3.5

⋈ Base case (OFLOTUB trial)

⎯⎯⎯ Values reported in South African observational cohorts and registries

4m regimen is favored over 6m regimen in terms of:

········▶ Composite unfavorable outcome

▬ ▬ ▬▶ Mortality at 2 years

▬ ▬ ▬▶ Life expectancy

Reddy et al., under review; Merle et al., *N Engl J Med* 2014

Conclusions

- How can models project programmatic outcomes and inform responses in a manner that complements trial data?
    - New diagnostics: sputum provision and diagnostic yield
        - Sputum provision probability affects impact of a new diagnostic
        - Incremental yield is more important than sensitivity in a parallel diagnostic algorithm
    - Empiric treatment
        - More empiric treatment leads to lower impact of a new diagnostic
    - Cascade of care: linkage to care and loss to follow-up
        - Linkage to care and LTFU during treatment differ between programmatic settings and trials

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