# THINKING ABOUT:
# Health systems as a determinant of the impact and cost-effectiveness of TB case detection

**TB MAC Meeting (Session 4, Health Systems)**

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**On behalf of MANY**

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## Operational Modelling of TB diagnostics - Objectives

1. **Develop** a dynamic and visual model of health system operations and patient pathways for diagnosis of TB and MDR-TB (e.g. Tanzania, Ethiopia, South Africa, Brazil and Philippines)

2. **Use** the models to analyse alternative strategies for roll-out of new TB diagnostics.

3. **Build national capacity** to use the modelling approach in future national policy decisions for new TB diagnostics

# Sputum Collection Morning-Spot
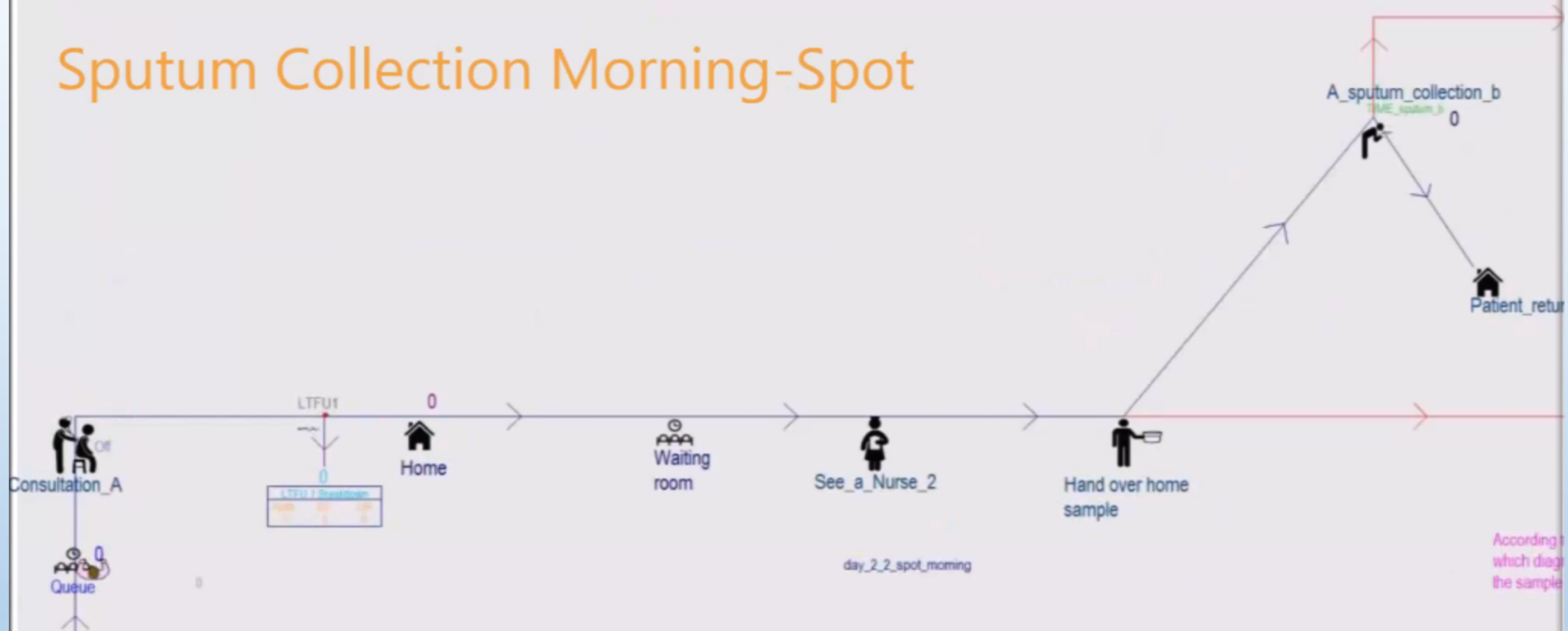
# Opportunities in TB diagnostic technology

*- What are the opportunities in TB and MDR-TB diagnosis?*

❑ The scale-up of new rapid tools for the diagnosis of Tuberculosis has the potential to make a huge difference e.g.
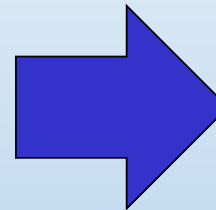


LED Fluorescence Microscopy



GeneXpert MTB/RIF



ULTRA & OMNI

| | |
|---|---|
| Sensitivity | 51-60% |
| Specificity | 98-100% |
| Turnaround | 1-3 days |
| Cost per test | ~ $1-3 |
| Extra Investment | ~$1,000 |

| | |
|---|---|
| Sensitivity | 67-88% |
| Specificity | 97-98% |
| Turnaround | <12hrs |
| Cost per test | ~$10 |
| Extra Investment | $17k |
| RIF Resistance tested | |

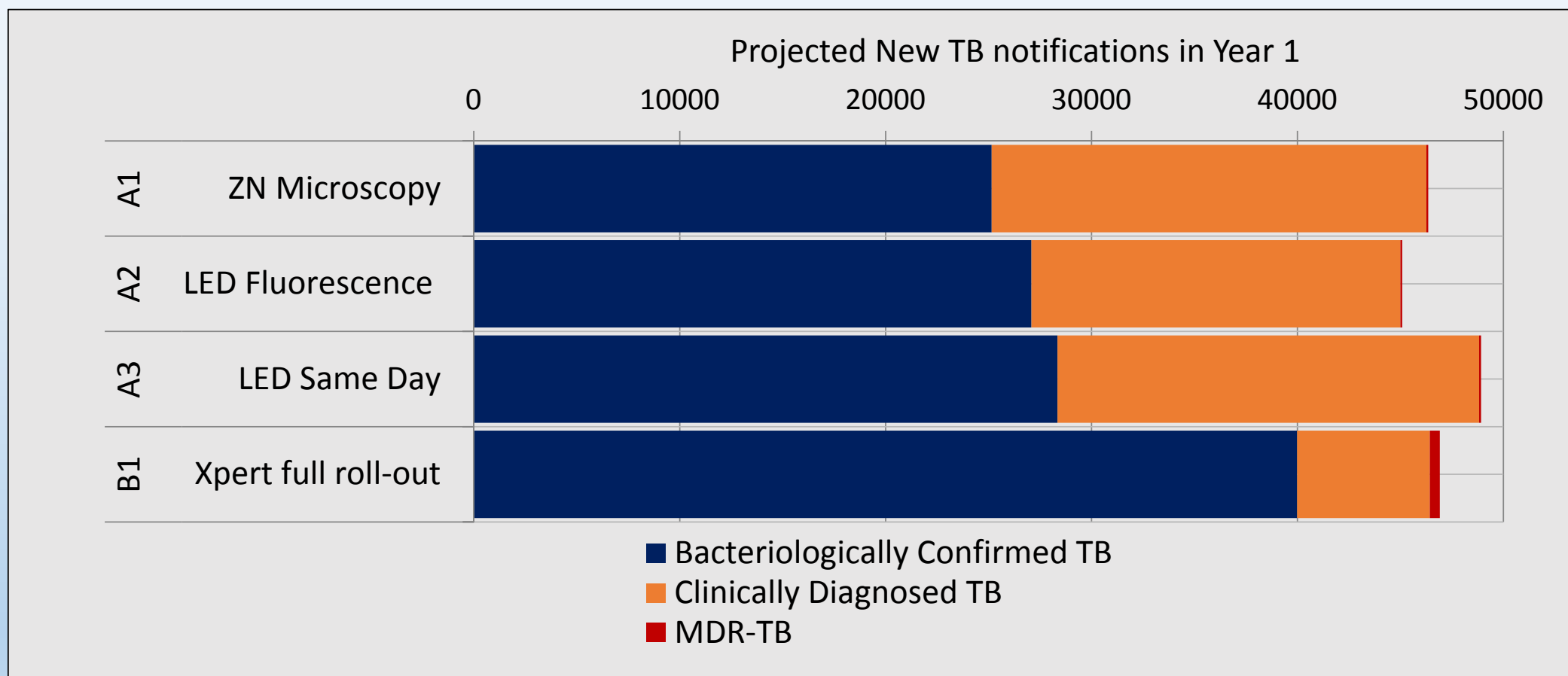| | |
|---|---|
| Sensitivity | 84-93%? |
| Specificity | 94-95%? |
| Turnaround | 2hrs? |
| Cost per test | ~$10 |
| Extra Investment | $3k? |
| RIF resistance tested | |

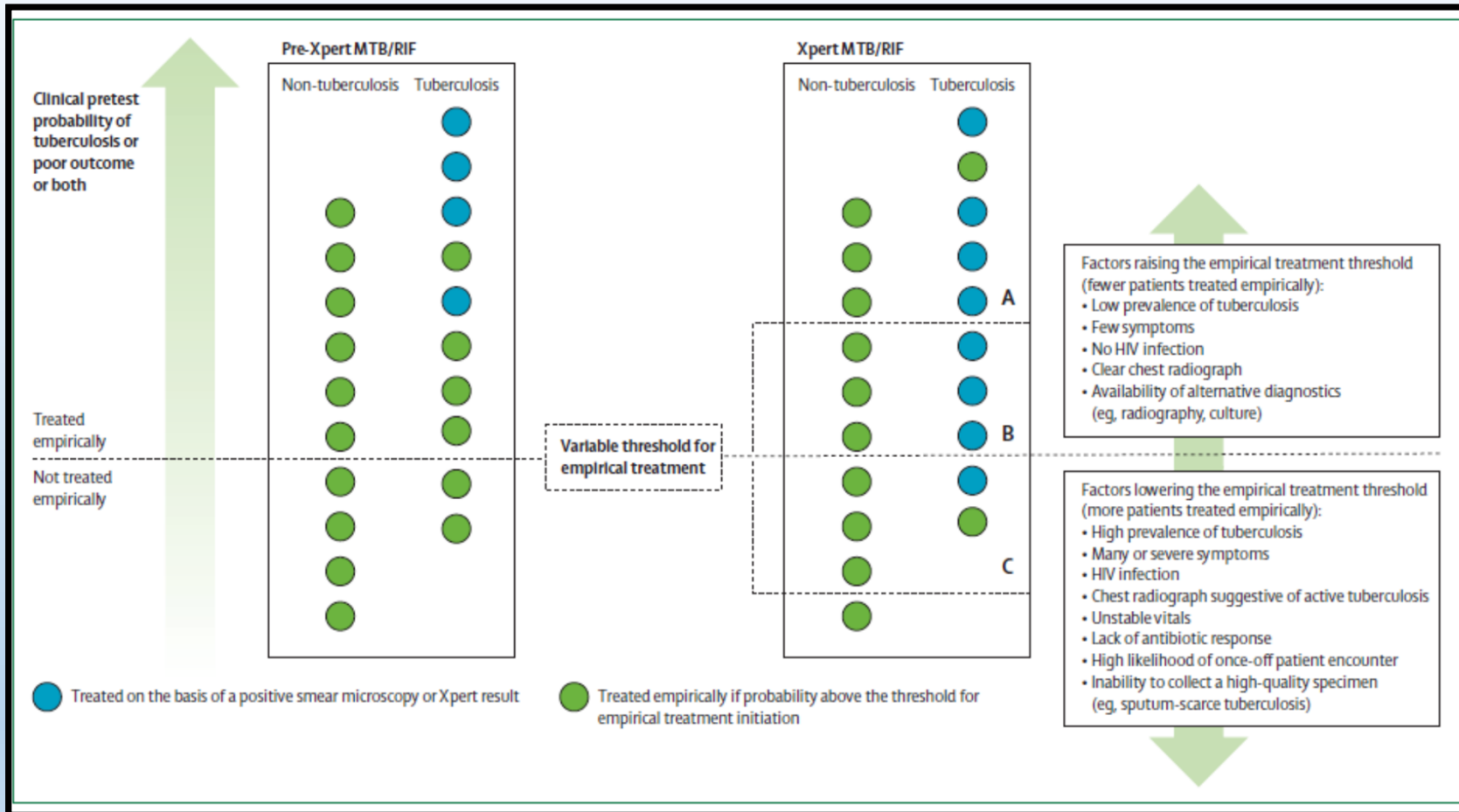**BUT, it's not only about the diagnostic tools, but also their place within health systems and other aspects of clinical decision-making**

# Assessment of effects of Xpert and alternative diagnostics in Tanzania (Langley, Lin *et al*, 2014)

# High rates of empirical treatment will influence the effect of new diagnostic tests (Theron *et al*, 2014)



Xpert implementation could change the threshold for empirical treatment

Threshold raised (A)
- Xpert will reduce false-positive treatment of people without TB, and increase true-positive treatment

Threshold constant (B)
- Xpert will not change the rates of false-positive treatments, but will increase true-positive treatments

Threshold lowered (C)
- Xpert will increase false-positive treatment of people without TB and increase true-positive treatments

Theron G, Peter J, Dowdy D, Langley I, Squire SB, Dheda K. Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings? Lancet Infect Dis 2014; 14: 527–32.

# Diagnostic options modelled - Philippines

0. Base case – the current routine diagnostic algorithm

1. Roll-out of LED Fluorescence Microscopy.

2. Xpert MTB/RIF as a replacement for microscopy.
   a. With standard Xpert cartridge,  b. With Xpert Ultra cartridge

3. Xpert MTB/RIF targeted to smear negative presumptive cases and high risk MDR-TB presumptive cases
   a. With standard Xpert cartridge, b. With Xpert Ultra cartridge

4. Xpert MTB/RIF for smear negative presumptive cases based on X-ray and high risk MDR presumptive cases.
   a. With standard Xpert cartridge. b. With Xpert Ultra cartridge

5. X-ray as a triage test prior to Xpert as replacement for microscopy
   a. With standard Xpert cartridge. b. With Xpert Ultra cartridge

6. Point of Care Test based on proposed Omni test using the Ultra cartridge

# Impact on **diagnosis** of tuberculosis (Notifications)
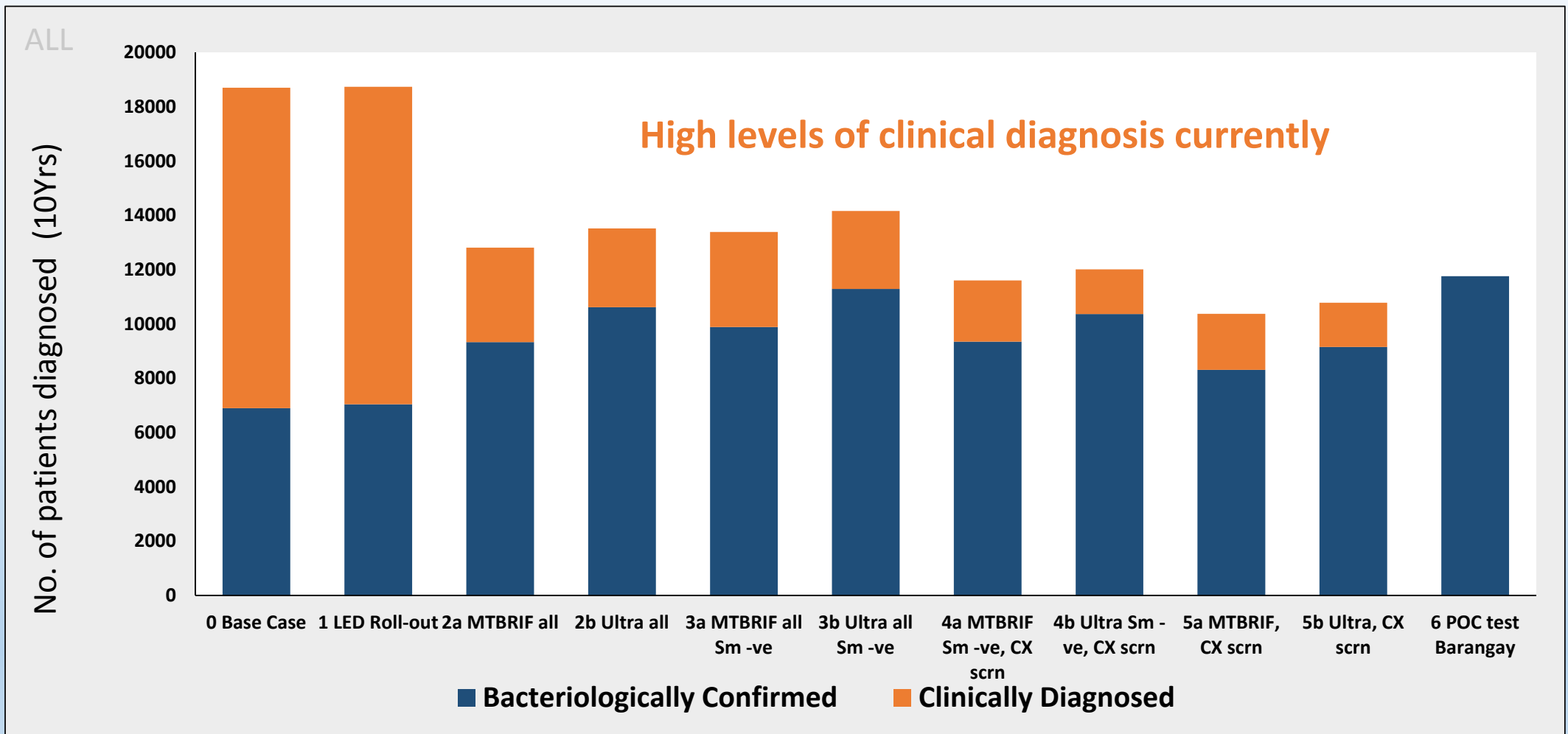


NOTE: Based on the 6 sites modelled in Cavite province over 10 years

# A key observation from the data – base case

Currently a high % of TB cases are clinically diagnosed – 63%

High % of sm negative presumptive TB cases are diagnosed with active TB
- Average 43%, and varies by site between 25% and 76%

Smear microscopy has poor sensitivity (<40%)

and/or

High over diagnosis amongst those clinically diagnosed with TB

and/or

High levels of microbiologically undetectable TB

# The process of Clinical Diagnosis in the Philippines
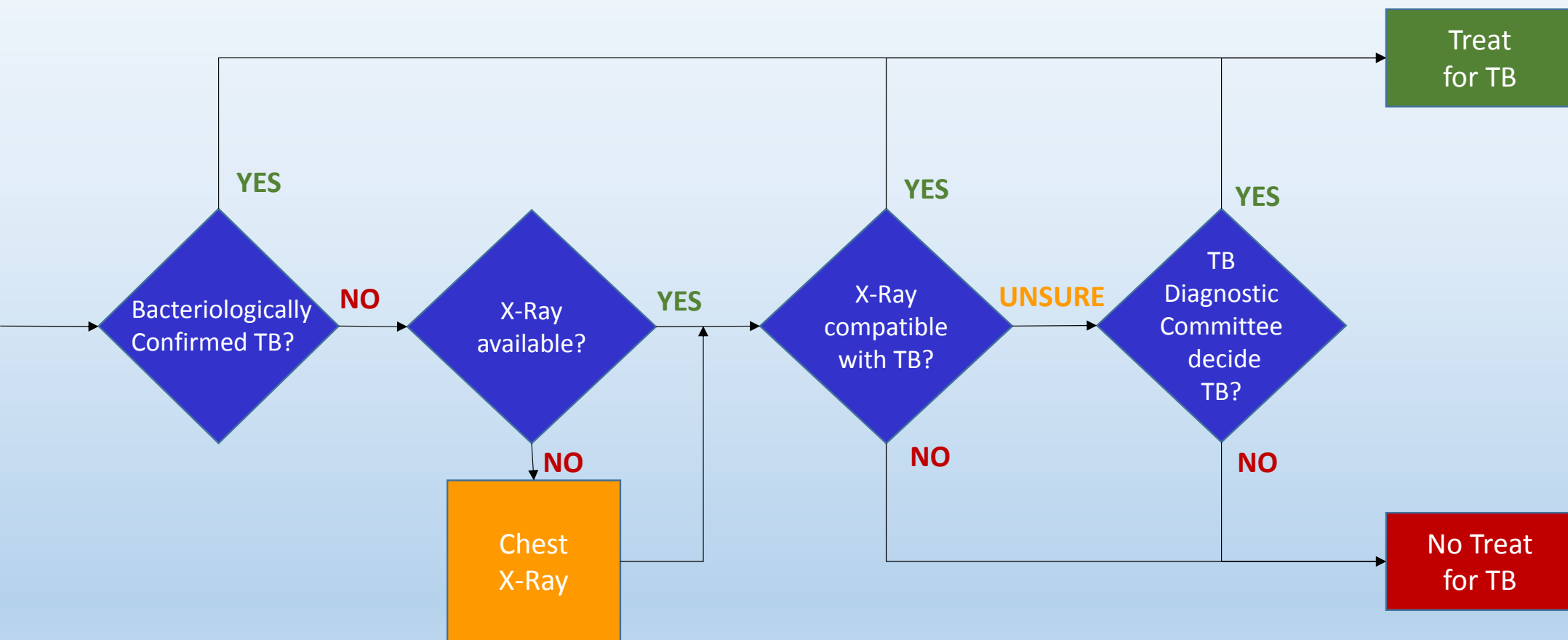


**The accuracy of these decisions is critical to impact**

# Some key assumptions

| TEST | Sensitivity | Specificity | Notes |
|---|---|---|---|
| Microscopy | 50 – 60% | 98 – 99% | Depending on sputum collection strategy, ZN or LED, and HIV status |
| Xpert | 67 – 88% | 97 – 98% | Depending on HIV and smear status |
| Xpert or OMNI with ULTRA | 84 – 93% | 94 – 95% | Depending on HIV and smear status |
| Chest X-ray compatible with TB | 90 – 98% | 1-70% | Depending on site (used to calibrate model) |
| Xpert for RIF resistance | 94% | 98% | |
| Xpert or OMNI with ULTRA for RIF resistance | 95% | 98% | |

**These assumptions very difficult to validate – Human judgement**

# Diagnosis of active **TB** disease, starting effective treatment

ALL

No. of patients starting effective TB treatment (10Yrs)

Legend:
- **Bacteriologically Confirmed DS** (blue)
- **Clinically Diagnosed DS** (orange)
- **'Bacteriologically Confirmed DR'** (red)

X-axis categories:
- 0 Base Case
- 1 LED Roll-out
- 2a MTBRIF all
- 2b Ultra all
- 3a MTBRIF all Sm -ve
- 3b Ultra all Sm -ve
- 4a MTBRIF Sm -ve, CX scrn
- 4b Ultra Sm -ve, CX scrn
- 5a MTBRIF, CX scrn
- 5b Ultra, CX scrn
- 6 POC test Barangay
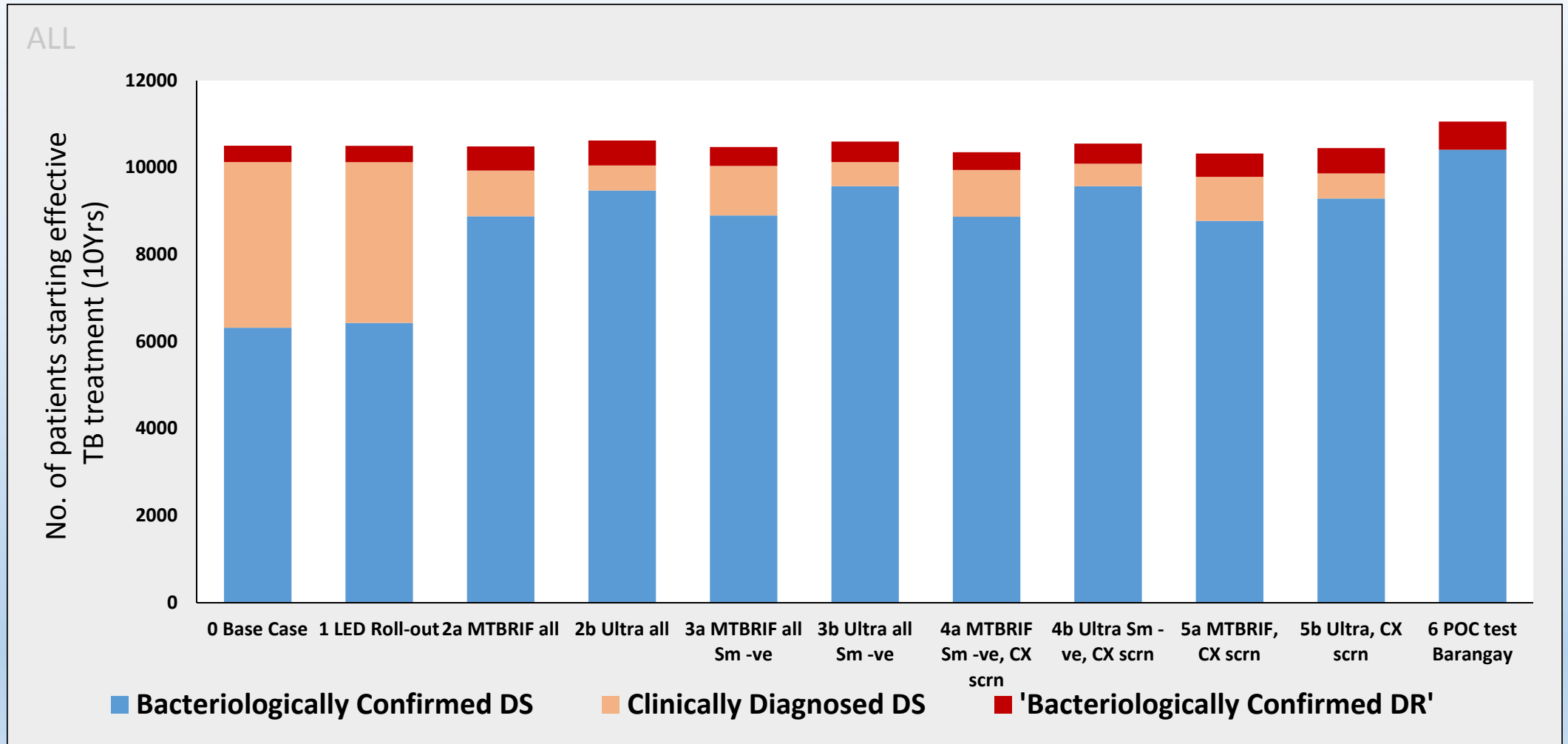
NOTE: Based on the 6 sites modelled in Cavite province over 10 years

# Patients with active TB disease who did not receive appropriate TB treatment



**ALL**

Patients with active TB disease not given appropriate treatment (10 Yrs)

Y-axis: Patients with active TB disease not given appropriate treatment (10yrs)

X-axis categories: 0 Base Case | 1 LED Roll-out | 2a MTBRIF all | 2b Ultra all | 3a MTBRIF all Sm -ve | 3b Ultra all Sm -ve | 4a MTBRIF Sm -ve, CX scrn | 4b Ultra Sm -ve, CX scrn | 5a MTBRIF, CX scrn | 5b Ultra, CX scrn | 6 POC test Barangay

Legend: DS LTFU | DR LTFU | DS diagnosed as no tb | DR given No Treatment | DR given DS Treatment

# Impact on **Health system** and **Patient** costs



ALL

Additional cost over the base case
Million Pesos

Categories:
- 0 Base Case
- 1 LED Roll-out
- 2a MTBRIF all
- 2b Ultra all
- 3a MTBRIF all Sm -ve
- 3b Ultra all Sm -ve
- 4a MTBRIF Sm -ve, CX scrn
- 4b Ultra Sm -ve, CX scrn
- 5a MTBRIF, CX scrn
- 5b Ultra, CX scrn
- 6 POC test Barangay

Legend:
- ■ Additional Diagnostic Costs
- ■ Additional Patient Costs
- ■ Additional Treatment Costs
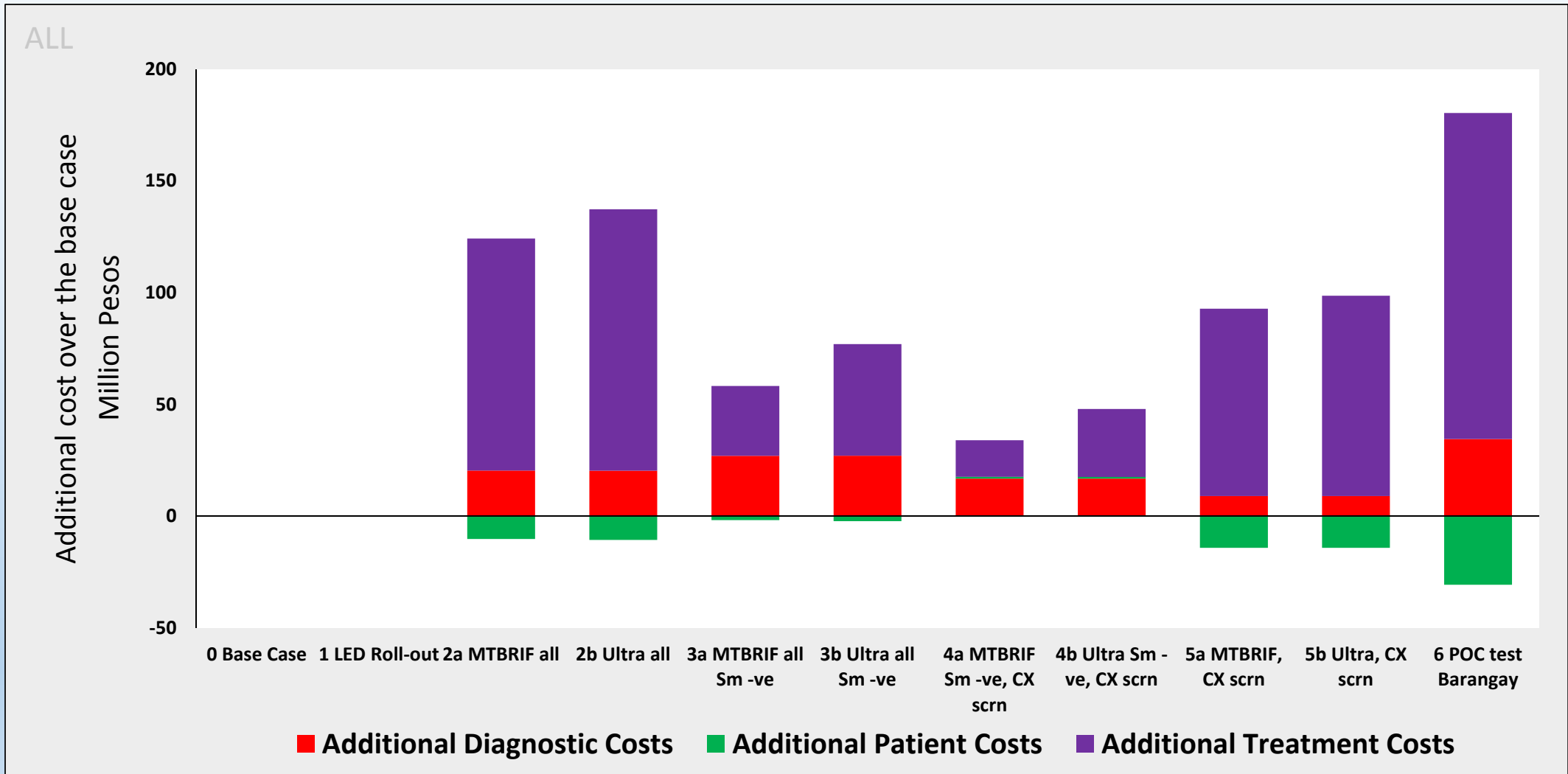
NOTE: Based on the 6 sites modelled in Cavite province over 10 years

**Summary thoughts**

1. The clinical diagnostic process/algorithm is a key determinant of the (cost) effectiveness of introducing new bacteriological/ molecular diagnostics.

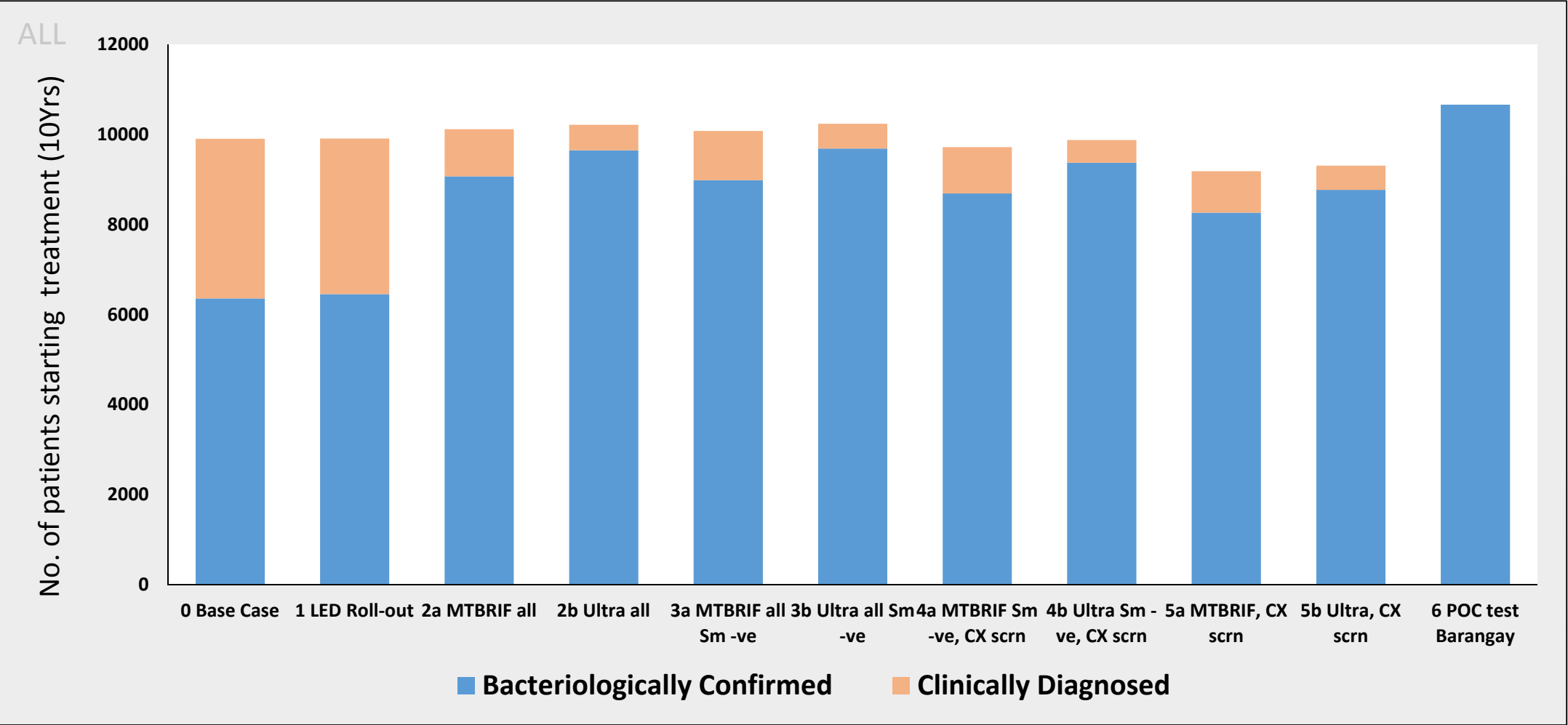2. The clinical diagnostic process is, in turn, dependent on the state of development of the six WHO building blocks of the relevant health system:

   a. Service delivery [private or public models of service with requirement for fee-paying or not]

   b. Health workforce [different cadres involved in different stages of TB case detection]

   c. Information (systems) [flow of information – test results]

   d. Medical products, vaccines and technologies [interaction of results between lab/molecular test outputs, radiology imaging services and clinical judgement]

   e. Financing [overall resources available]

   f. Leadership / Governance [effect of advocacy and political imperatives]

3. Operational Modelling offers an approach to capturing the health system elements behind empirical/clinical diagnosis

THANK YOU!

# Diagnosis of active **drug sensitive TB** disease, starting effective treatment

ALL

No. of patients starting treatment (10Yrs)

Legend: ■ Bacteriologically Confirmed ■ Clinically Diagnosed

Categories (x-axis):
0 Base Case | 1 LED Roll-out | 2a MTBRIF all | 2b Ultra all | 3a MTBRIF all Sm -ve | 3b Ultra all Sm -ve | 4a MTBRIF Sm -ve, CX scrn | 4b Ultra Sm -ve, CX scrn | 5a MTBRIF, CX scrn | 5b Ultra, CX scrn | 6 POC test Barangay

NOTE: Based on the 6 sites modelled in Cavite province over 10 years
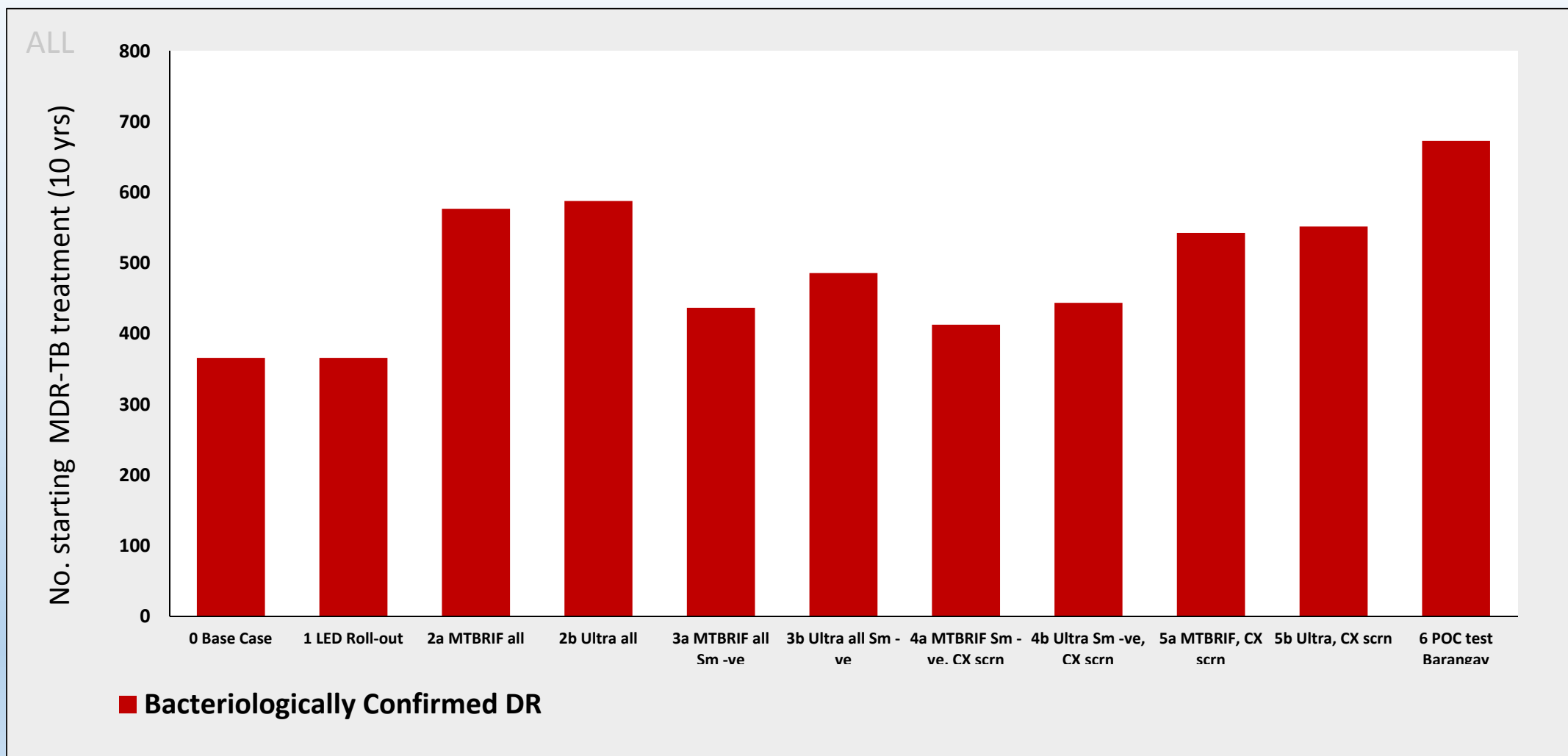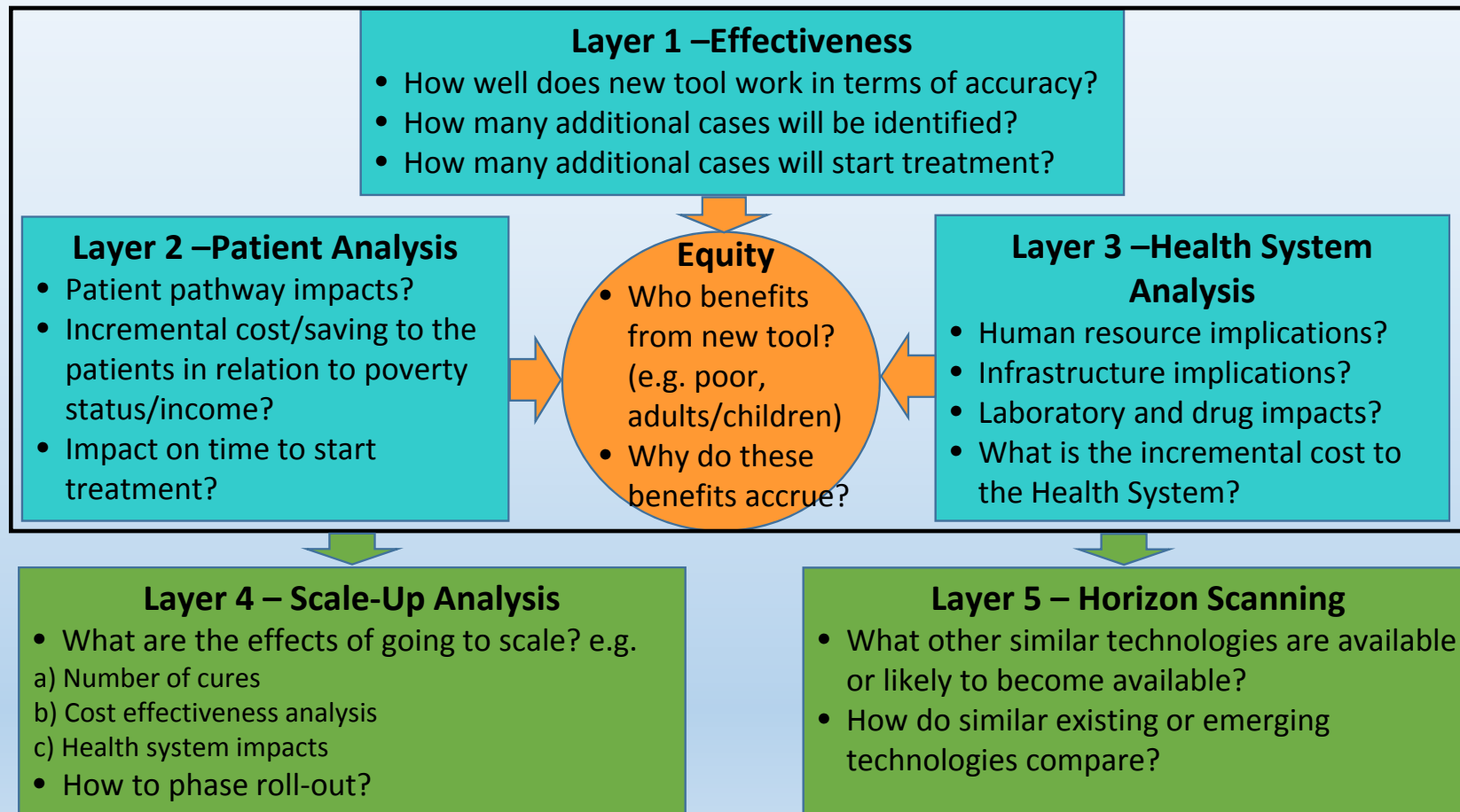
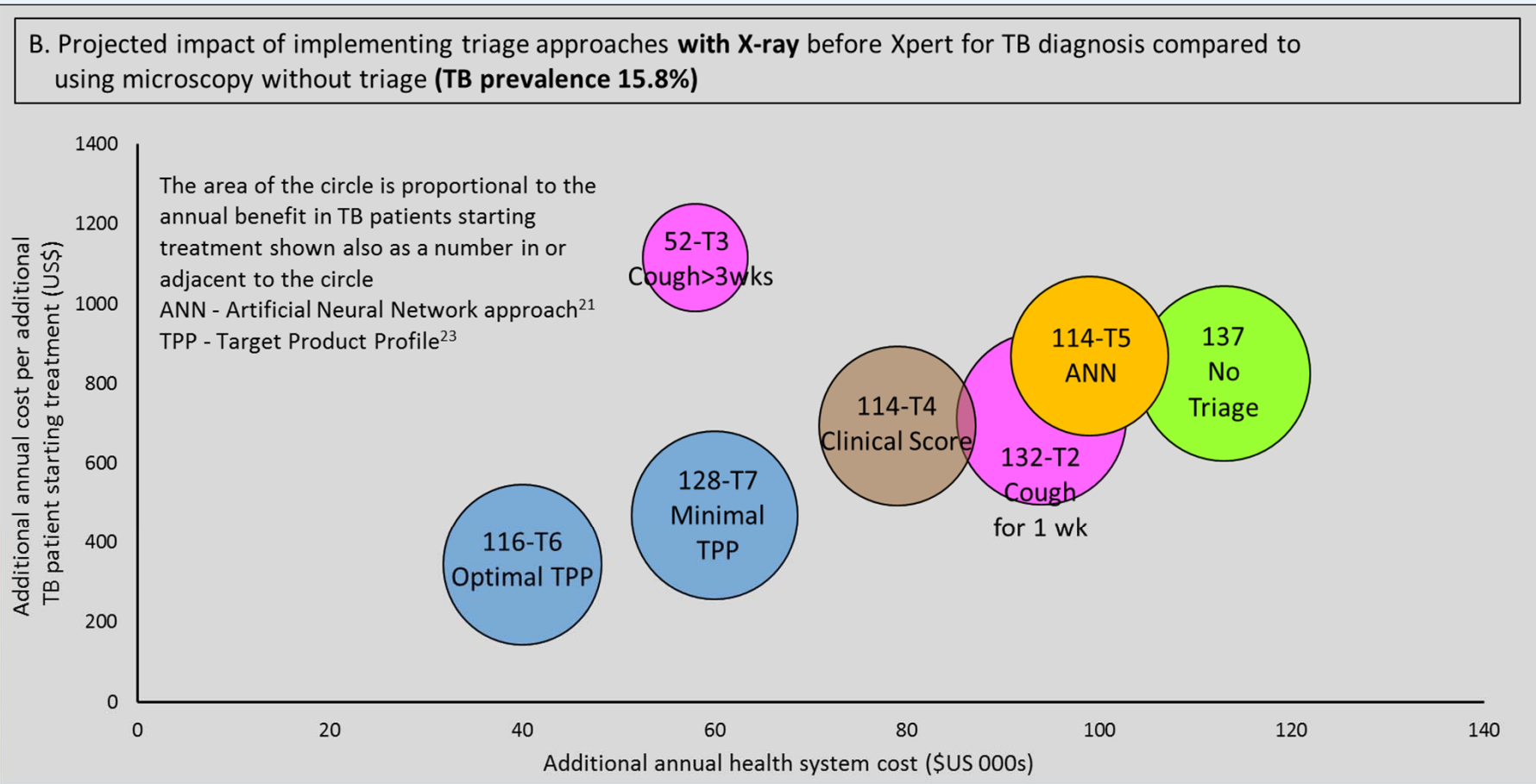# Diagnosis of active **drug resistant TB** leading to effective **MDR-TB** treatment



NOTE: Based on the 6 sites modelled in Cavite province over 10 years

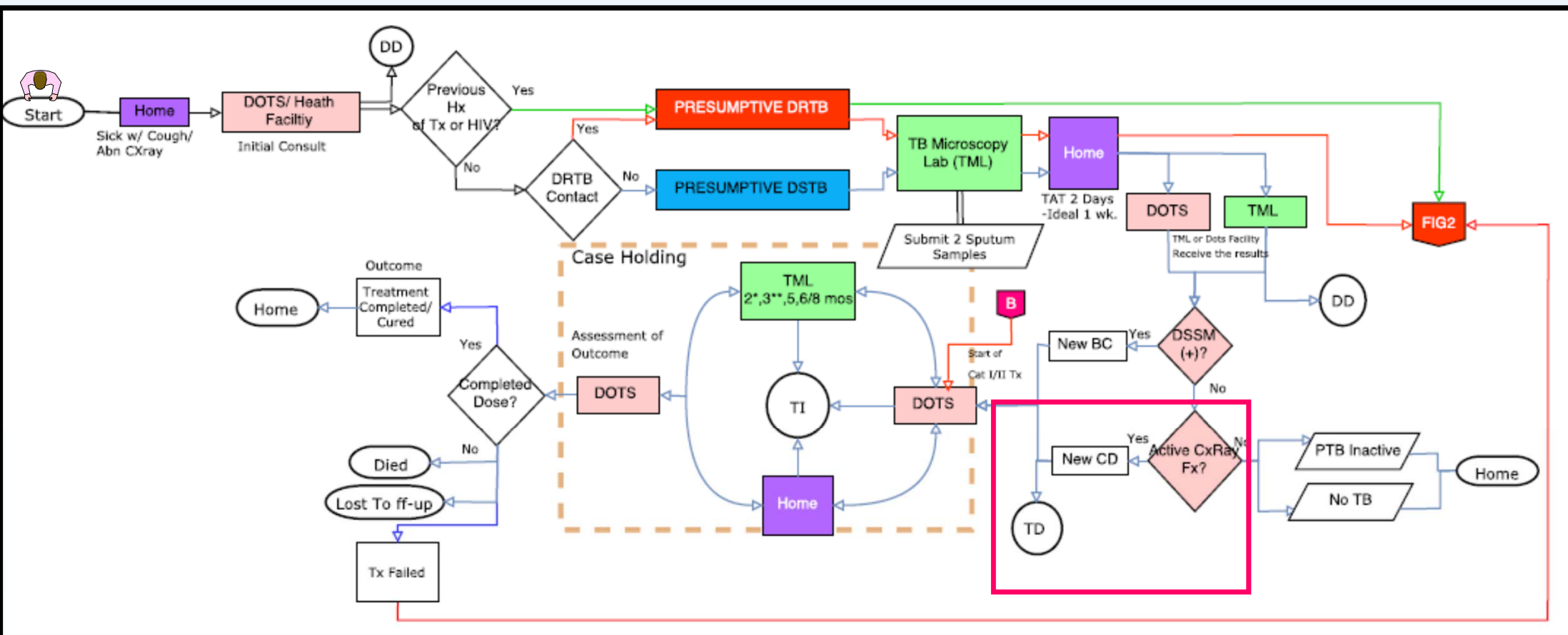# Impact assessment framework (Langley, Squire *et al,* 2015)

**Layer 1 –Effectiveness**
- How well does new tool work in terms of accuracy?
- How many additional cases will be identified?
- How many additional cases will start treatment?

**Layer 2 –Patient Analysis**
- Patient pathway impacts?
- Incremental cost/saving to the patients in relation to poverty status/income?
- Impact on time to start treatment?

**Equity**
- Who benefits from new tool? (e.g. poor, adults/children)
- Why do these benefits accrue?

**Layer 3 –Health System Analysis**
- Human resource implications?
- Infrastructure implications?
- Laboratory and drug impacts?
- What is the incremental cost to the Health System?

**Layer 4 – Scale-Up Analysis**
- What are the effects of going to scale? e.g.
a) Number of cures
b) Cost effectiveness analysis
c) Health system impacts
- How to phase roll-out?

**Layer 5 – Horizon Scanning**
- What other similar technologies are available or likely to become available?
- How do similar existing or emerging technologies compare?

# Impact of triage prior to seeking a tuberculosis diagnosis in the context of Brazil (Langley *et al,* Pending)



B. Projected impact of implementing triage approaches **with X-ray** before Xpert for TB diagnosis compared to using microscopy without triage **(TB prevalence 15.8%)**

The area of the circle is proportional to the annual benefit in TB patients starting treatment shown also as a number in or adjacent to the circle
ANN - Artificial Neural Network approach[21]
TPP - Target Product Profile[23]

52-T3 Cough>3wks
114-T5 ANN
137 No Triage
114-T4 Clinical Score
132-T2 Cough for 1 wk
128-T7 Minimal TPP
116-T6 Optimal TPP

Additional annual cost per additional TB patient starting treatment (US$)
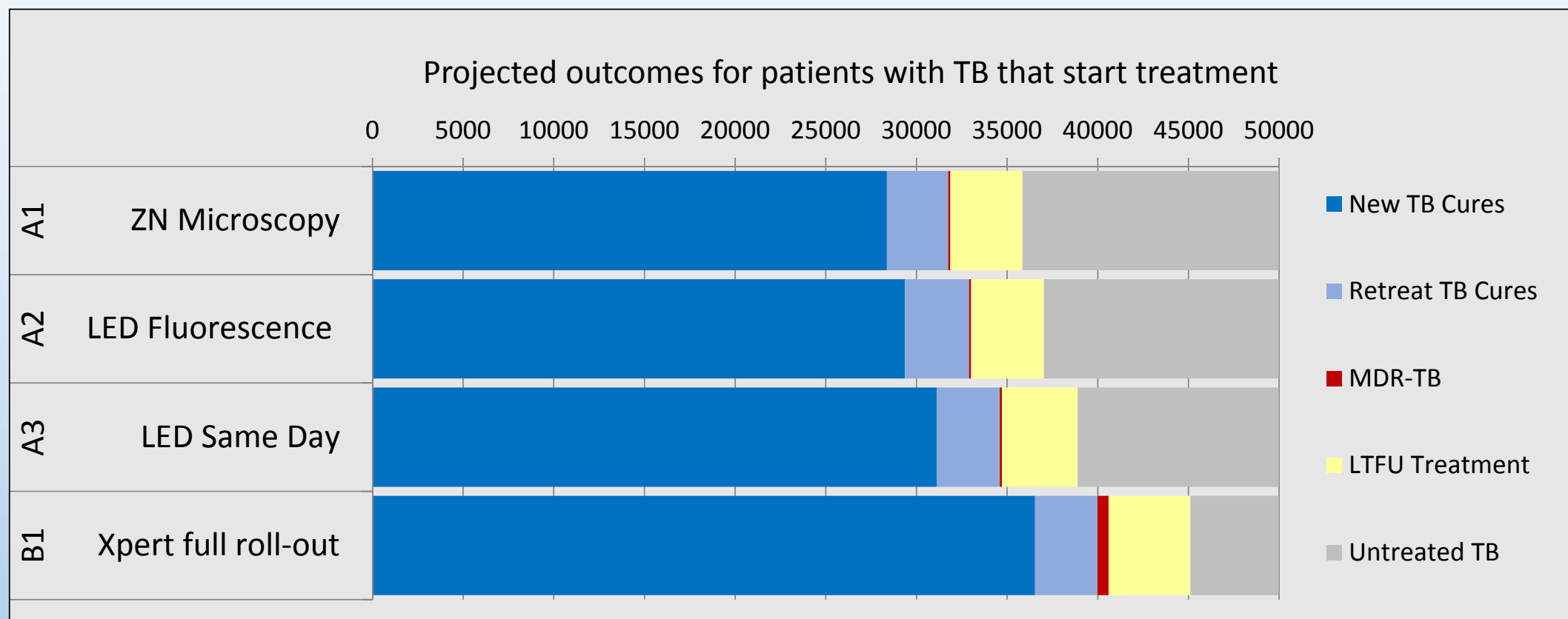
Additional annual health system cost ($US 000s)

Langley I, Rahman A, Galliez R, Kritski A, Tomeny E, Squire SB. Modelling the use and impact of triage prior to seeking a tuberculosis diagnosis in the context of Brazil (2017)

# Diagnostic Patient Pathways in Philippines

# Assessment of effects of Xpert and alternative diagnostics in Tanzania (Langley, Lin *et al*, 2014)



Projected outcomes for patients with TB that start treatment

Legend: New TB Cures, Retreat TB Cures, MDR-TB, LTFU Treatment, Untreated TB

Rows: A1 ZN Microscopy, A2 LED Fluorescence, A3 LED Same Day, B1 Xpert full roll-out

# Summary observations from modelling in Philippines

## OPTION 2 - Xpert MTB/RIF as replacement for microscopy

1. DRUG SENSITIVE TB CASES correctly treated
   - Bacteriologically Confirmed would rise by **35-45%**
   - Clinically diagnosed TB cases are likely to fall by **67-77%**
   - Overall minimum change
2. MDR-TB CASES correctly treated
   - Would rise by **43-53%**
3. Highly cost-effective
4. Overall numbers on drug sensitive TB treatment would fall due to reduced clinical diagnosis
5. ULTRA cartridge provides a further improvement (MDR-TB **+5%**)

# Observations from modelling in Philippines (cont.)

## OPTIONS 3 and 4 – targeted use of Xpert MTB/RIF

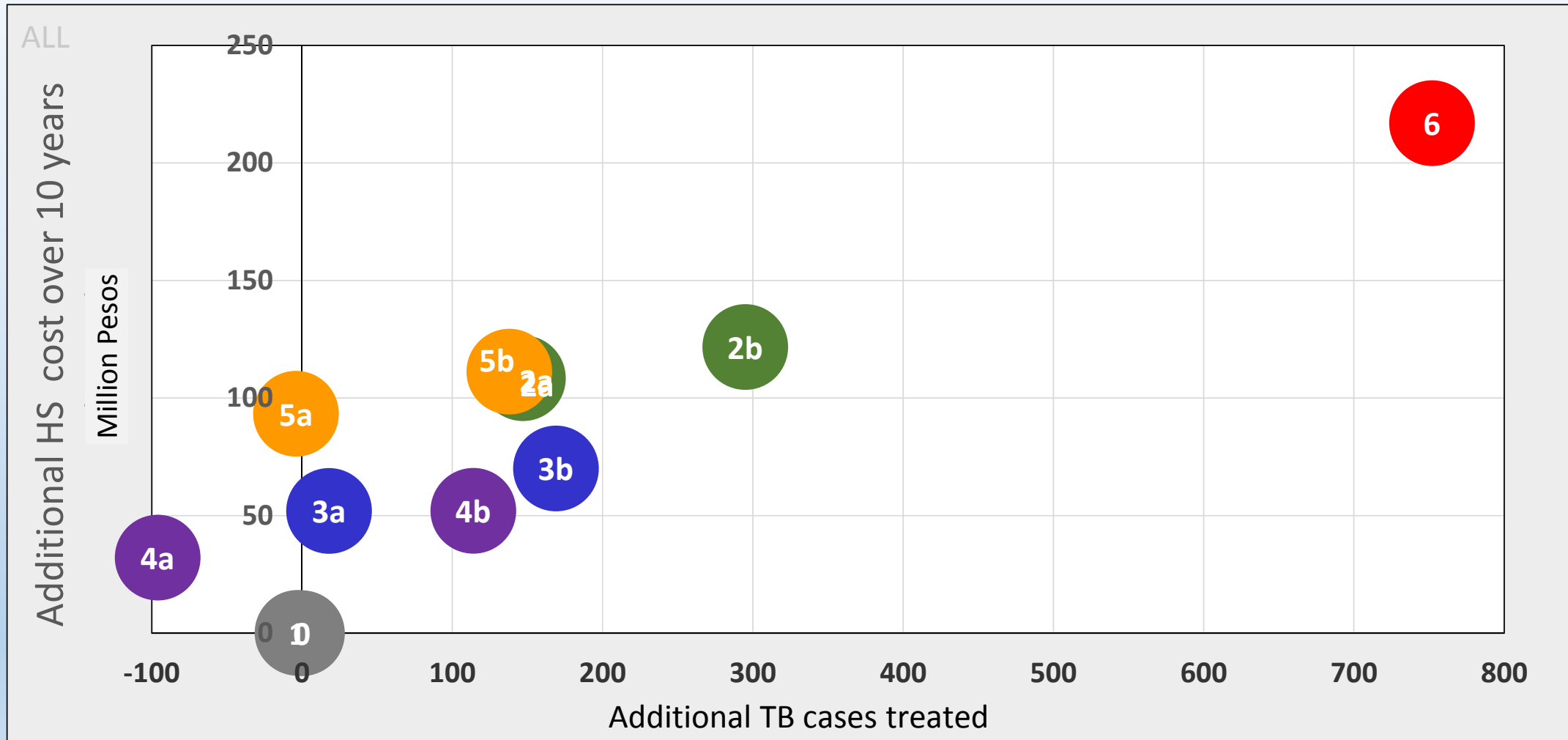- Cost effective alternatives to Option 2 with reduced benefits at reduced cost.

## OPTION 5 – X-ray as triage prior to Xpert test replacing microscopy

- Requires ULTRA cartridge to provide a benefit – highly dependant on sensitivity of Chest X-ray
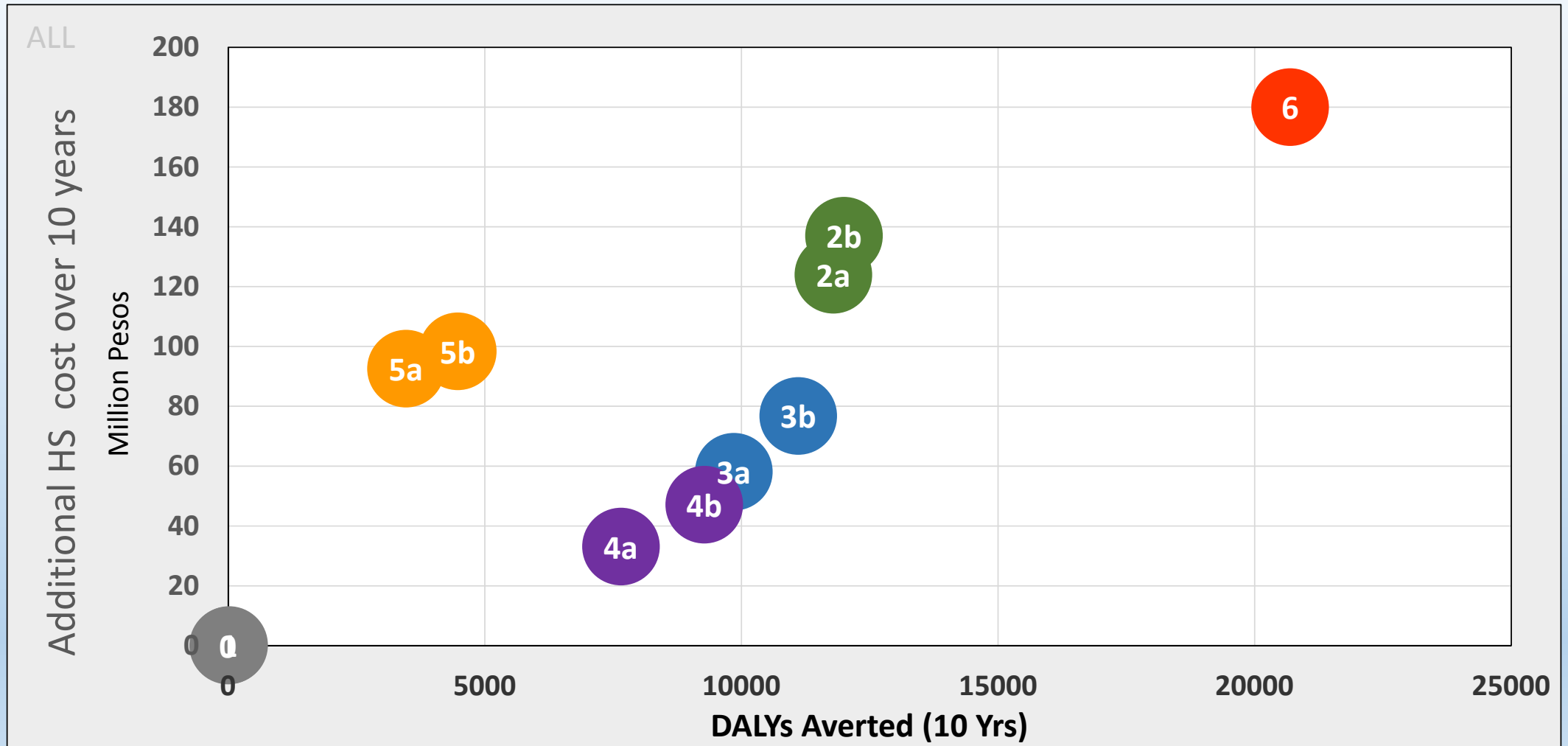
## OPTION 6 – OMNI with ULTRA cartridge

- When available as Point of Care test would be the best option as is likely to reduce lost to follow up and will therefore increase case detection for DS-TB and MDR-TB.

# Incremental **cost-effectiveness** analysis (Health System costs)



ALL

Additional HS cost over 10 years

Million Pesos

250
200
150
100
50
0

6

5b
2a
2b
5a
3a
3b
4b
4a
0
1

-100    0    100    200    300    400    500    600    700    800

Additional TB cases treated

NOTE: Based on the 6 sites modelled in Cavite province over 10 years

Incremental **cost-effectiveness** analysis (**DALYs averted**)

NOTE: Based on the 6 sites modelled in Cavite province over 10 years