Modeling the epidemiological impact and cost-effectiveness of improved diagnostic testing for drug-resistant TB

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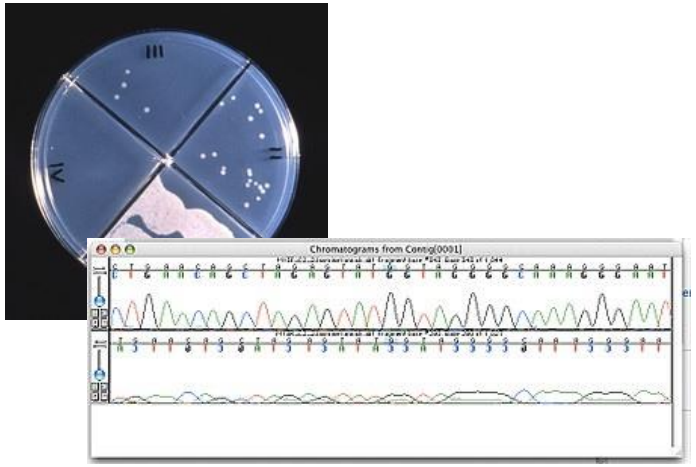
DR-TB diagnostics:
Three roles, three case studies

1) Stratifying “drug-susceptible” versus “drug-resistant” (e.g. rifampin-resistant)

2) Optimizing/individualizing DR-TB regimens



3) Implementing novel drugs and regimens

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Impact of drug-resistance testing is multi-faceted

1. Preventing morbidity and mortality in the patients evaluated

2. Preventing DR-TB transmission
   - *Reducing failure/relapse*
   - *Shortening time to effective treatment*

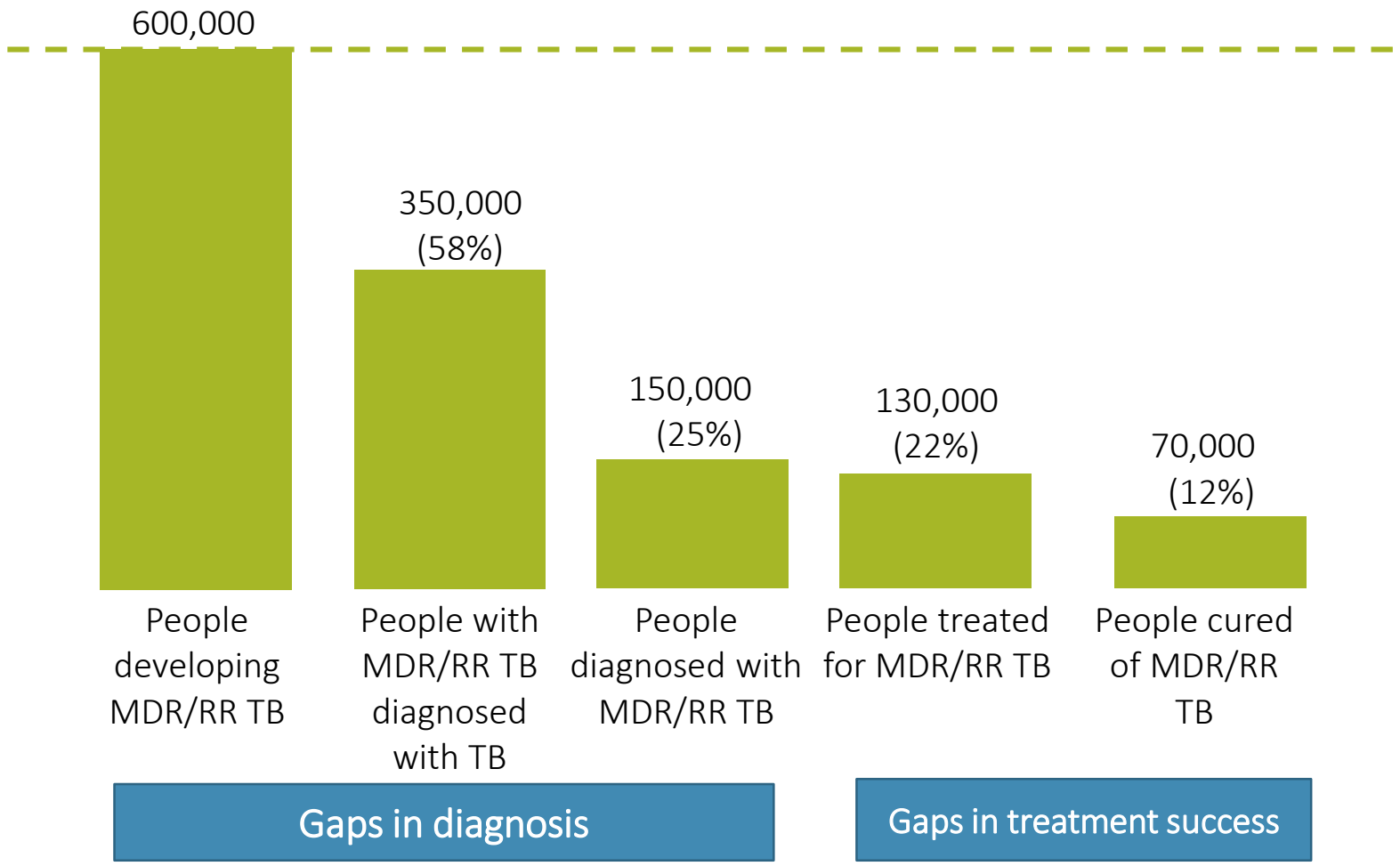
3. Preventing further acquisition of resistance (and its spread)

And multiple factors affecting cost:

- Cost of testing (providing and performing assay + infrastructure)
- Yield of testing
- Cost of acting on test results
- Future cost savings from any improved outcomes achieved
  - Prevented failure/relapse, transmission, and acquired resistance

1. Diagnostics to identify rifampin-resistant TB

The context:



Data source: WHO, Global TB Report 2017

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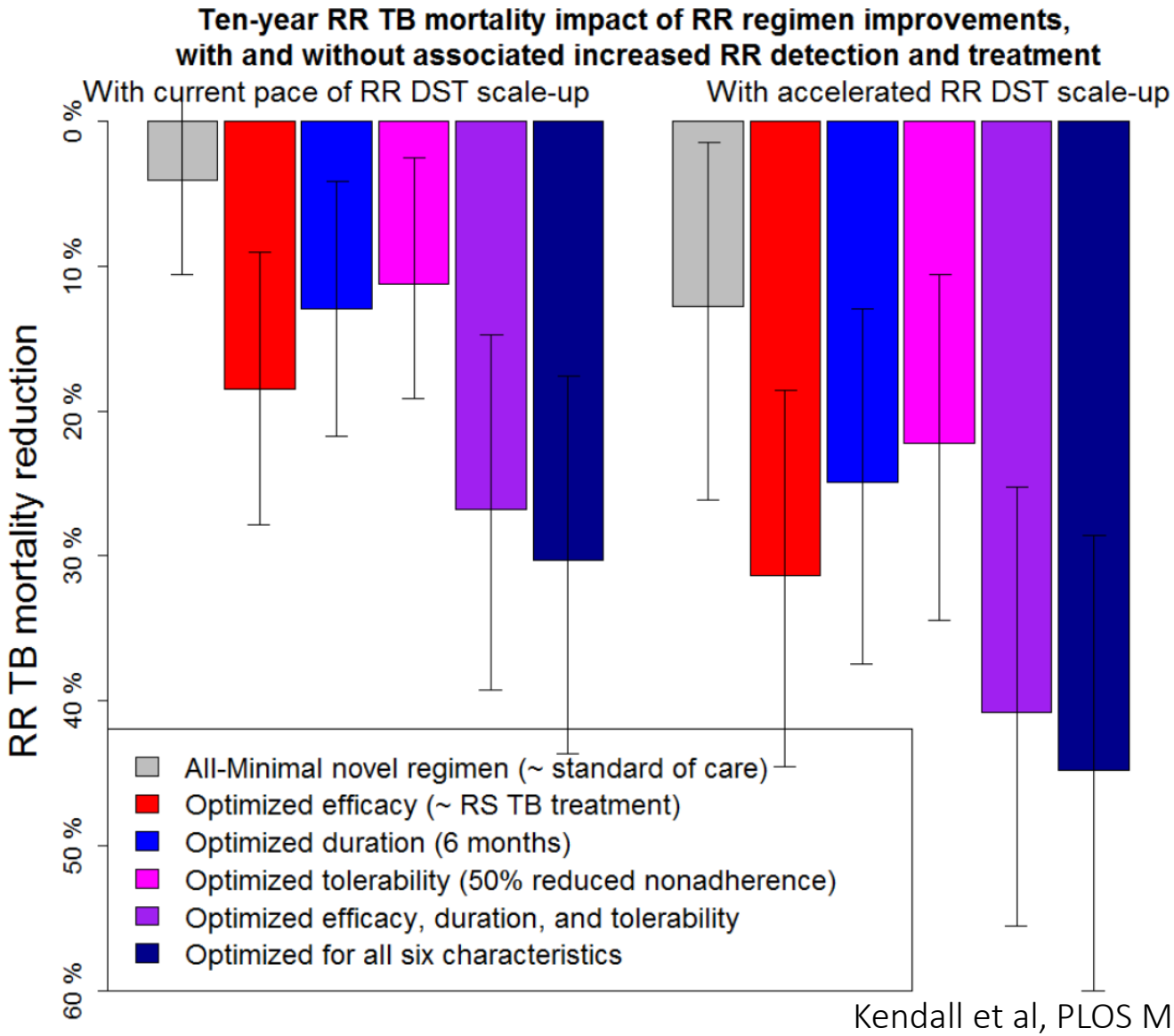
Diagnosing DR-TB can have a large impact

In models of improved DR-TB treatment regimens, better DR detection offers similar epidemiologic benefits



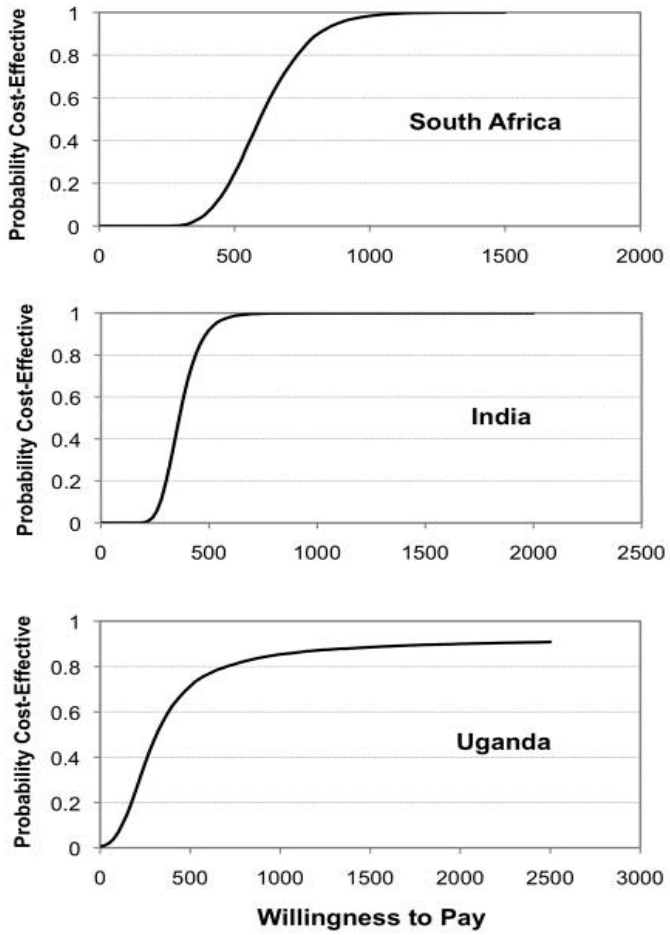
Kendall et al, PLOS Med 2017

Cost-effectiveness of RR-TB detection

Universal rifampin susceptibility testing is widely recommended.

When performed via Xpert, it appears highly cost-effective.

- Linkage to improved TB detection strengthens the epidemiologic and economic case
- Estimated US$52-$138 per DALY averted by Xpert (2011)



Vassall et al, Plos Med 2011

Looks like an easy case for universal DST?

Continued scale-up of DST may become increasingly inefficient.

- Diminishing yield among lower-risk patients and populations
- Higher costs in hard-to-test populations

  Xpert-negative patients

  Remote locations or limited health care access

There's also potential for economies of scale.

Some hard-to-reach populations may nevertheless be critical for stopping DR-TB transmission

Considerations for modelers: identifying DR-TB

Evaluation/modeling of DR-TB diagnostics needs to be incremental.

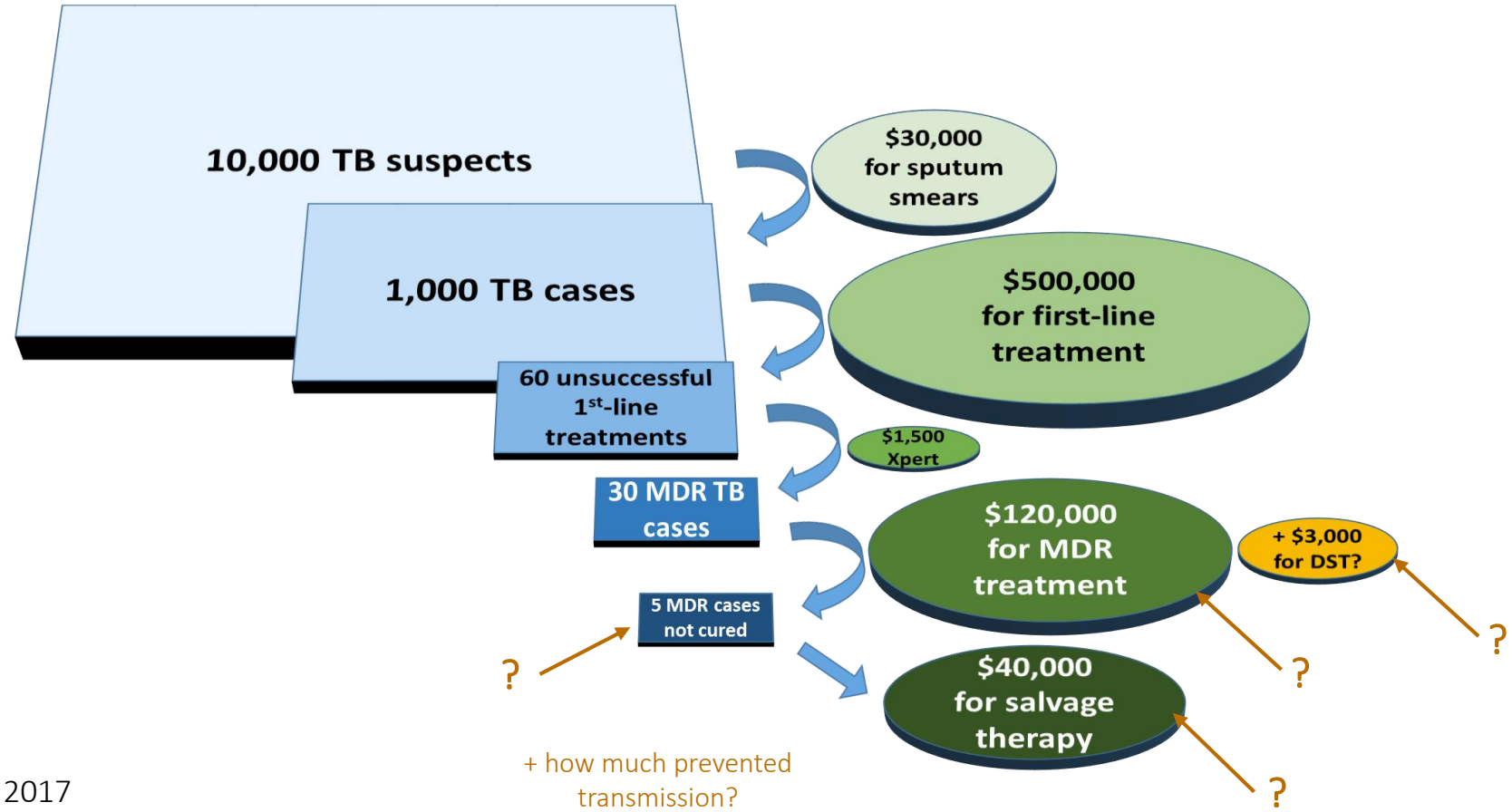
Diagnostics models may need to account for heterogeneity in epidemiology, assay performance, clinical outcomes, and testing costs.

Questions for modeling:

- **When should DST strategy shift from widening the reach of basic DST, to testing more extensively in those tested? *Where and how should DST expand next?***

2. Impact and cost of optimizing second-line regimens

Drugs and diagnostic tools for individualizing second-line treatment are improving.
When are they cost effective? ***An overly-simple assessment:***



from Kendall et al, IJID 2017

Second-line DST – Steps to achieving impact:

- Can at-risk patients access the test?
- Can we interpret the results?
- Do results reach the right people?
- Do those people have the knowledge and resources (e.g. alternative drugs) to act appropriately?
- Would they have chosen differently without the test?

- How much more effective is the DST-based regimen?

  In increasing probability of cure

  In reducing infectious time

  In preventing acquisition of additional drug resistance

- Are there adverse consequences to individualizing regimens?

  e.g. treatment delays, or limited treatment access?

Considerations for modelers: regimen optimization

Diagnostics themselves don't have an impact… until they result in better clinical decisions.

Realistic impact models must consider how diagnostics will affect practice.

We need better estimates for how host/strain/drug combinations predict cure and acquired resistance.

Roles for modelers data analysis, study design, and conceptual models

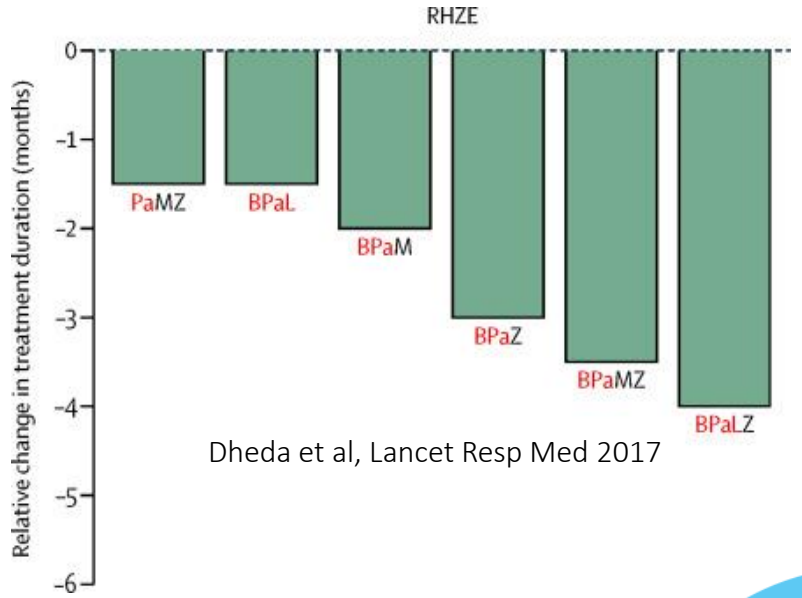
Questions for modeling:

What testing strategies and regimen selection algorithms make sense in what settings?

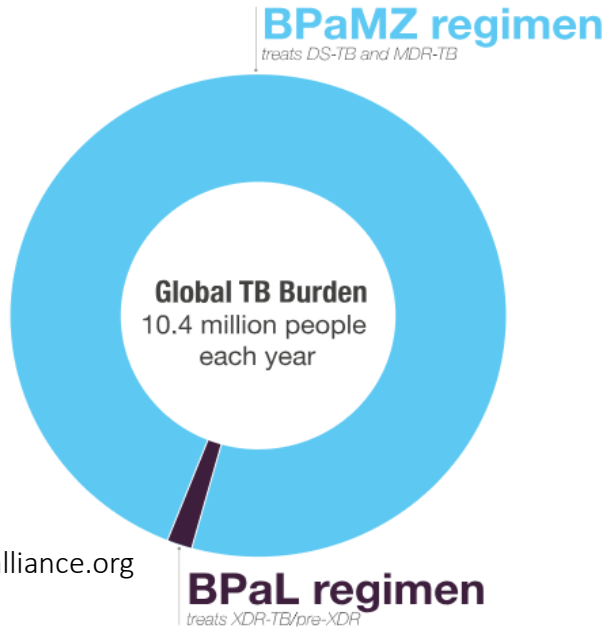
- *After accounting for drug-resistance epidemiology, treatment options, and resource constraints?*
- *Does DST as a barrier to treatment access ever outweigh its beneficial impact on those treated?*

3. Diagnostics with novel regimens: The potential regimens

Mouse data:



Dheda et al, Lancet Resp Med 2017



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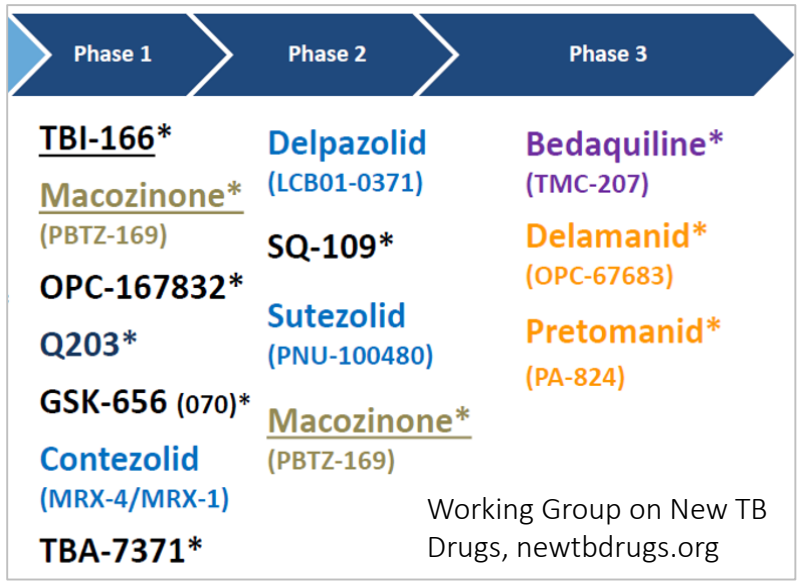


Working Group on New TB Drugs, newtbdrugs.org

TARGET REGIMEN PROFILES FOR TB TREATMENT 33

6. TARGET REGIMEN PROFILE FOR PAN-TB TREATMENT

World Health Organization

Comment

Pan-tuberculosis regimens: an argument for

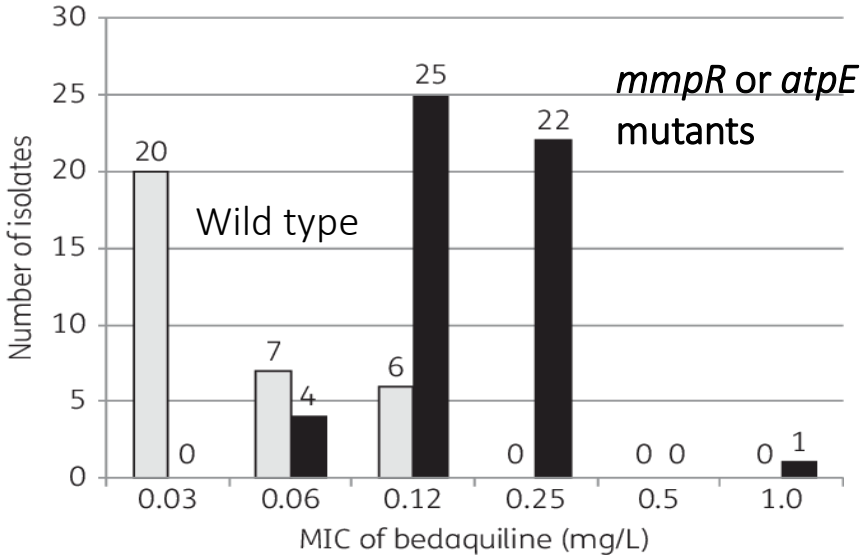
3. Diagnostics with novel regimens: The potential resistance

	Azerbaijan	Bangladesh	Belarus (Minsk city)	Pakistan	South Africa (Gauteng)	South Africa (KwaZulu Natal)
0·5 µg/mL						
Rifampicin susceptible	618, 0·5% (0·0–1·1)	873, 3·9% (2·4–5·3)	99, 2·7% (0·0–5·9)	1401, 7·7% (6·1–9·3)	910, 0·5% (0·0–1·1)	621, 0·3% (0·0–0·8)
Rifampicin resistant	130, 17·9% (11·2–24·5)	60, 12·2% (3·7–20·7)	97, 26·8% (18·0–35·7)	102, 13·8% (6·3–21·4)	41, 8·4% (0·0–18·4)	33, 12·2% (2·2–22·2)

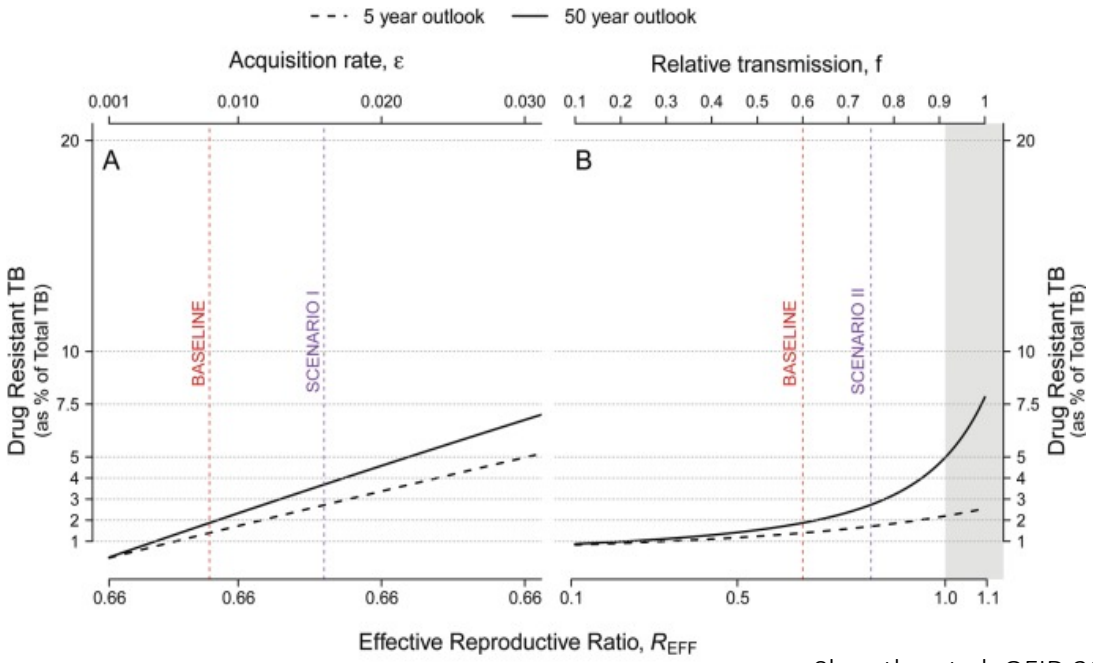
Data are number tested, % resistant (95% CI) or p value.

Table 4: Moxifloxacin 0·5 µg/mL susceptibility testing results

Zignol et al, Lancet Inf Dis 2016



Zimenkov et al, JAC 2017



Shrestha et al, OFID 2014

Considerations for modelers: novel regimens

Novel and universal regimens won't eliminate the need for smart diagnostic strategy.

Questions for modeling:

- Under what circumstances should we use a regimen "universally"?
- How should we approach fluoroquinolone (and/or pyrazinamide) resistance testing with new regimens that contain them?
- How important is DST for novel drugs?
- What monitoring for emergence of resistance would all-novel universal regimens require?

Summary

Drug resistance diagnostics can help prevent (1) poor treatment outcomes, (2) DR-TB transmission, and (3) additional drug resistance.

Implementation decisions are incremental –

- Modelers can help identify which next DST investment or expansion will be most impactful and efficient in a given context.

Diagnostics achieve impact by fostering better clinical decisions –

- Models must consider implementation realities when evaluating drug-resistance testing strategies and regimen selection algorithms.

Novel drugs won't replace the need for smart choices –

- Modelers may help guide implementation of novel regimens alongside appropriate diagnostic strategies.