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Will better diagnosis of TB drug resistance translate into better clinical outcomes?

Considerations for modellers

TB-MAC Meeting
14 September 2018

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Fakulteit Geneeskunde en Gesondheidswetenskappe
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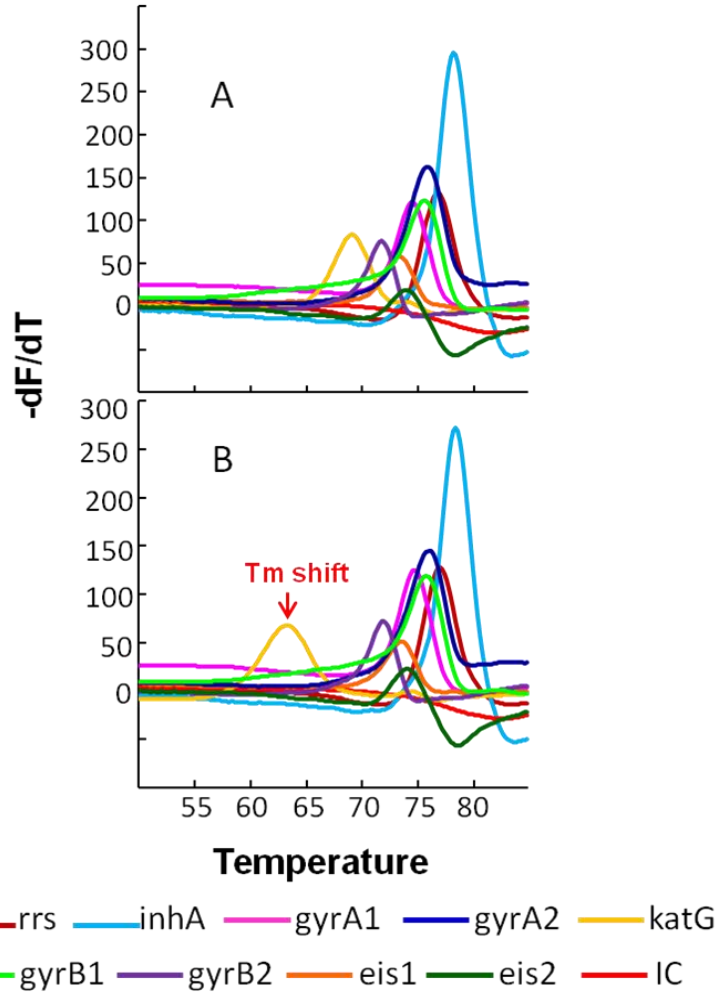
What's in the drug-resistant diagnostic pipeline?

- Xpert XDR
- Hain Fluorotype suite
- Direct targeted (deep?) sequencing
- Whole genome sequencing

Short term DST challenges for key drugs in new regimens:

- PZA
- EMB
- ETHI
- BDQ
- DLM



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis

Y.L. Xie, S. Chakravorty, D.T. Armstrong, S.L. Hall, L.E. Via, T. Song, X. Yuan, X. Mo, H. Zhu, P. Xu, Q. Gao, M. Lee, J. Lee, L.E. Smith, R.Y. Chen, J.S. Joh, Y.S. Cho, X. Liu, X. Ruan, L. Liang, N. Dharan, S.-N. Cho, C.E. Barry III, J.J. Ellner, S.E. Dorman, and D. Alland

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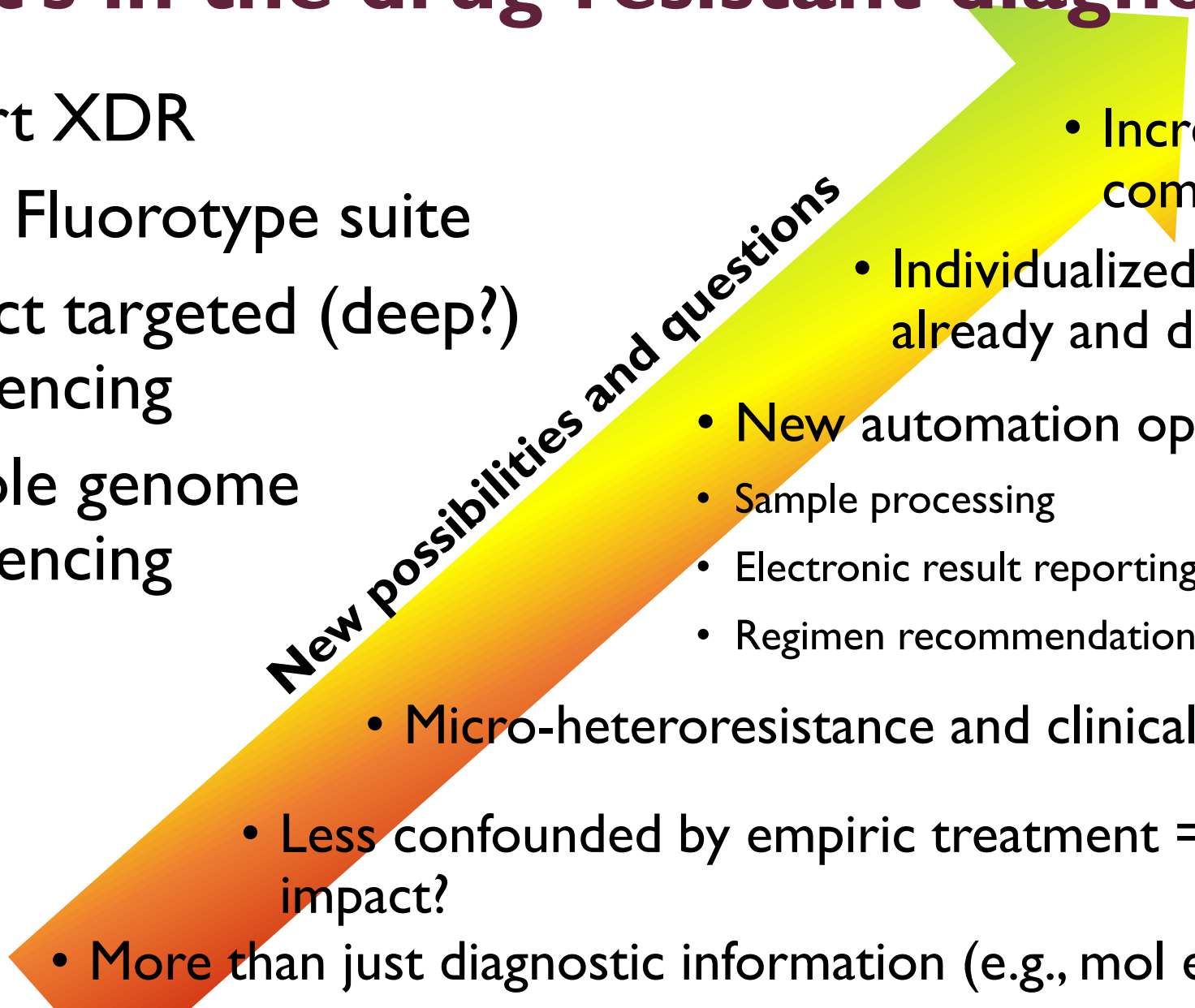
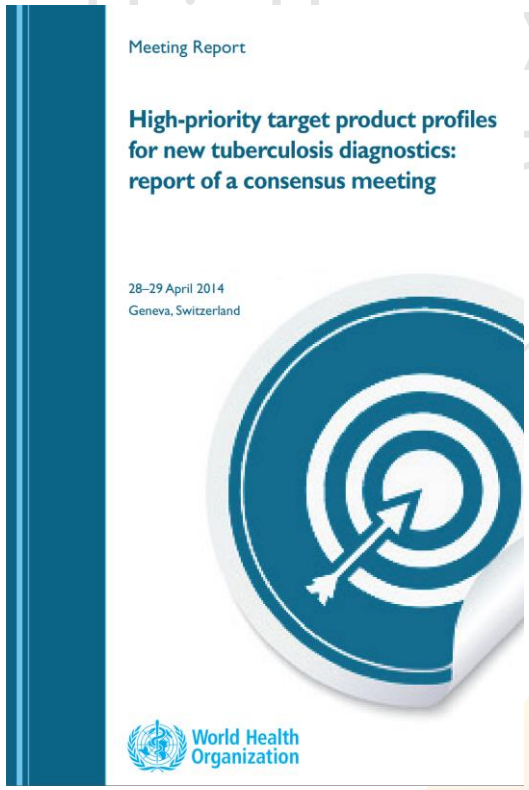


- Increasing internal technical complexity
- Individualized regimens (could do already and don't… MTBDR*sl*, Ultra)
- New automation opportunities
  - Sample processing
  - Electronic result reporting
  - Regimen recommendations when added to clinical data
- Micro-heteroresistance and clinical significance?
- Less confounded by empiric treatment = more incremental impact?
- More than just diagnostic information (e.g., mol epi)

What's in the drug-resistant diagnostic pipeline?

- Xpert XDR



Lots of ongoing innovation for non-sputum based TB tests

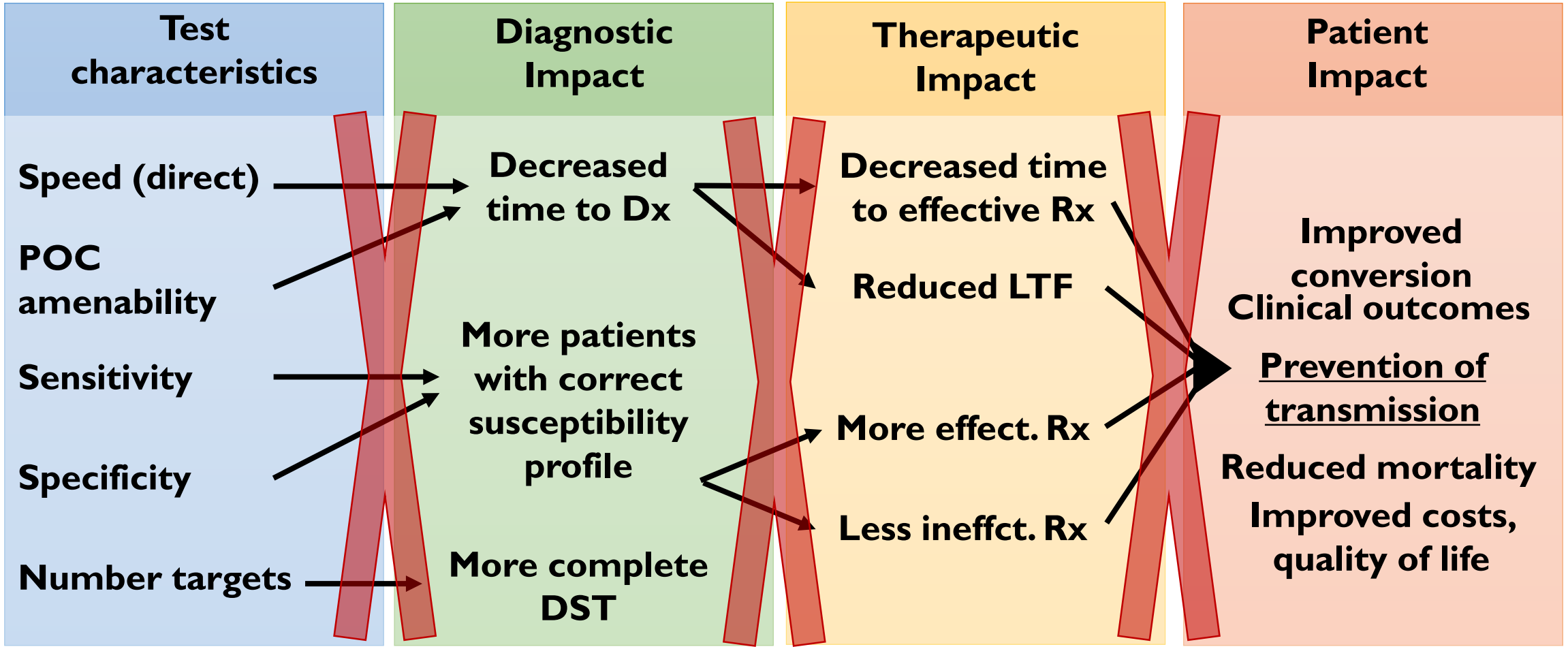
- Promisingly high predictive values
- But sputum induction facilities often not available
- Will these advances jeopardise DST coverage? What is the impact of this?

- Increasing internal technical complexity
- Less confounding by empiric treatment = more incremental impact?
- More than just diagnostic information (e.g., mol epi)

A big assumption

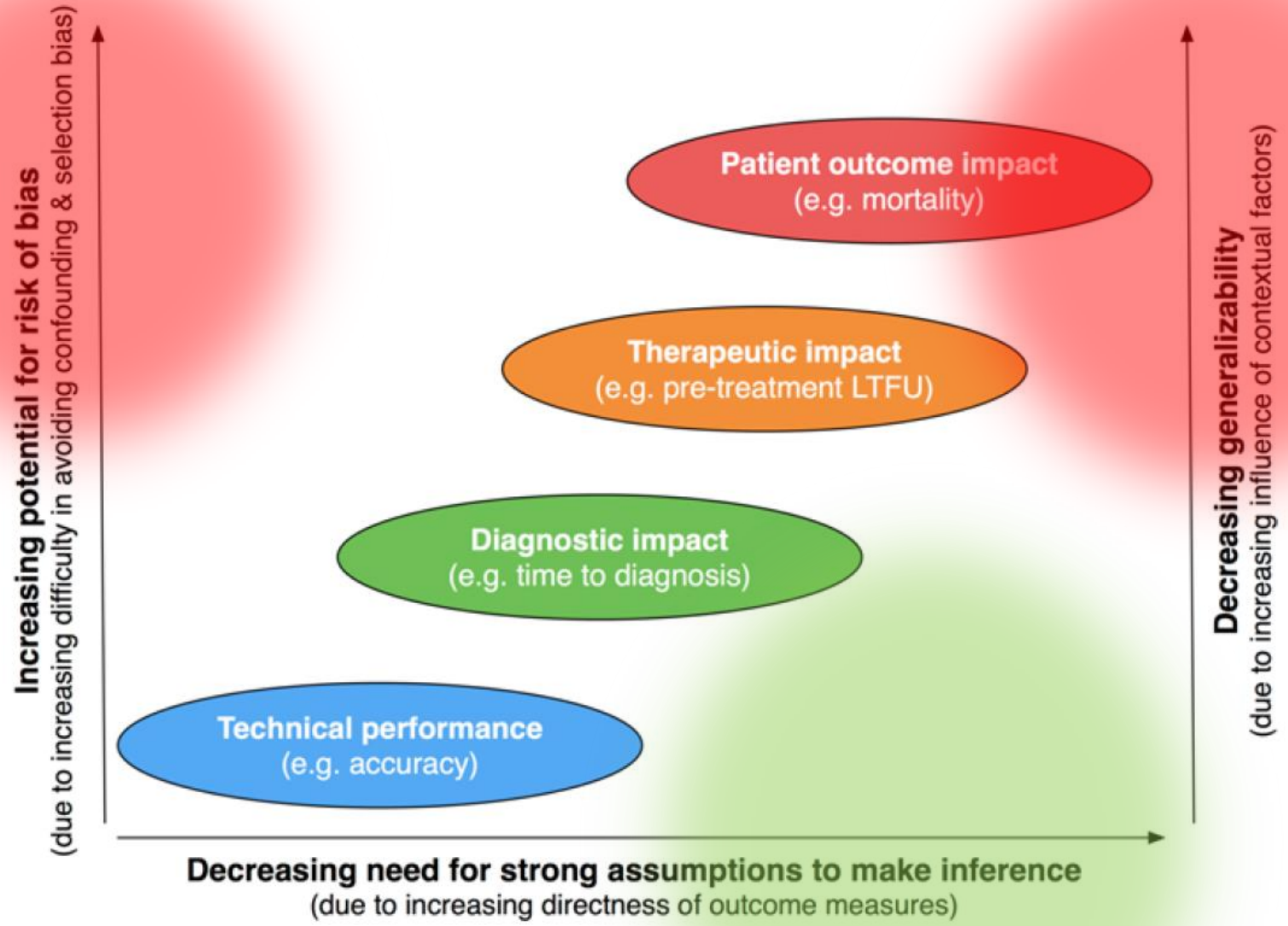
Accurate and rapid tests for key TB drugs exist

Conceptual framework



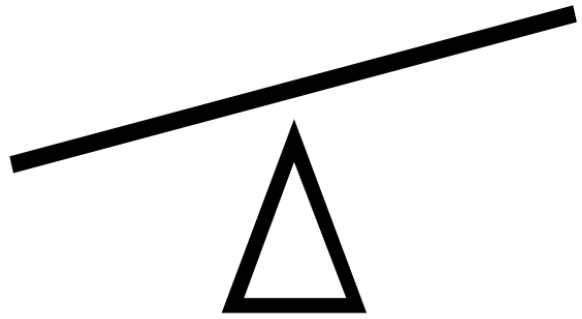
Adapted from Schumacher *et al*, PLOS One, 2016 10.1371/journal.pone.0151073

Is it really ever just about the test?

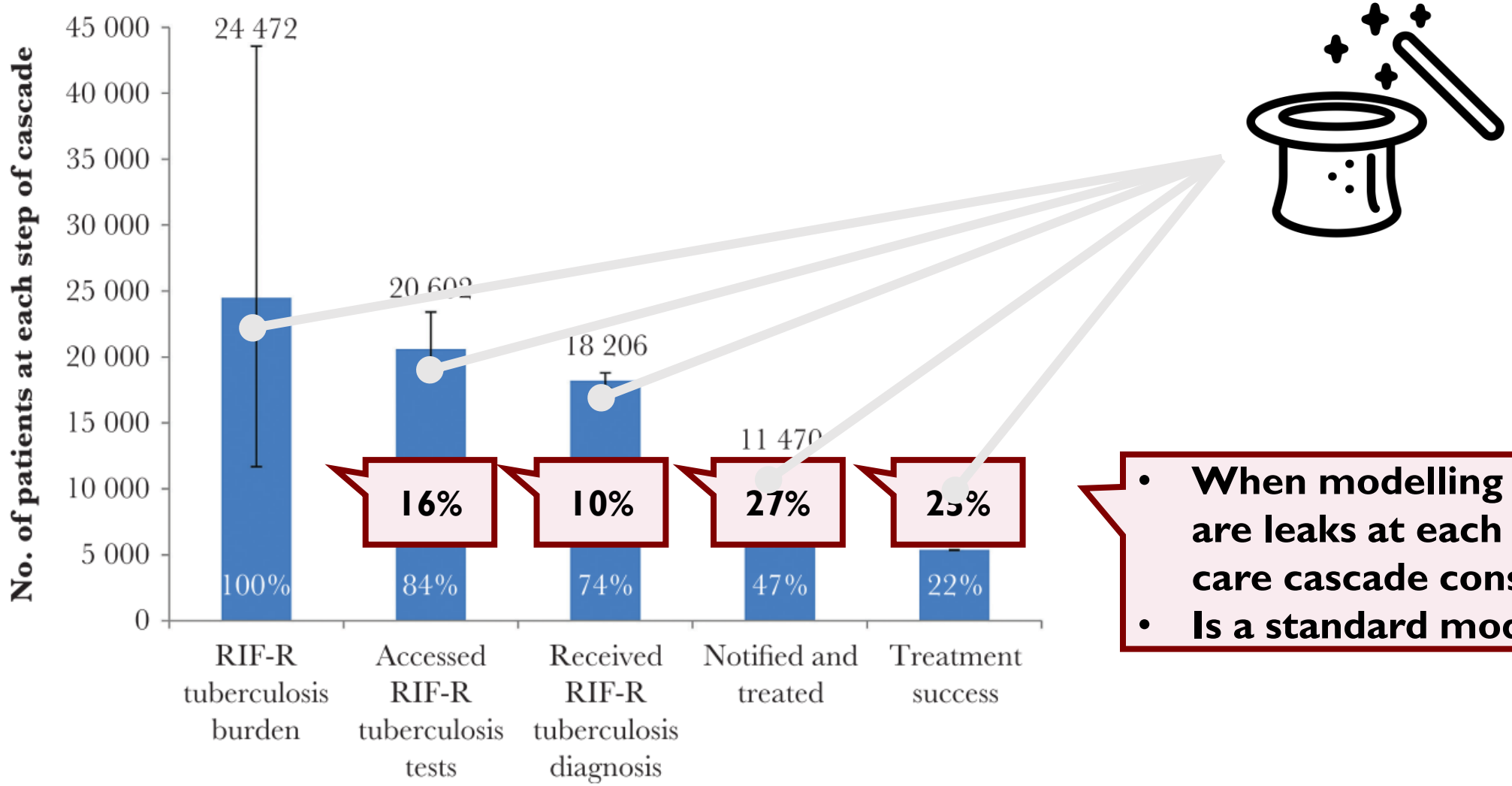


Schumacher *et al*, PLOS One, 2016 10.1371/journal.pone.0151073

Do we overvalue patient outcome data?



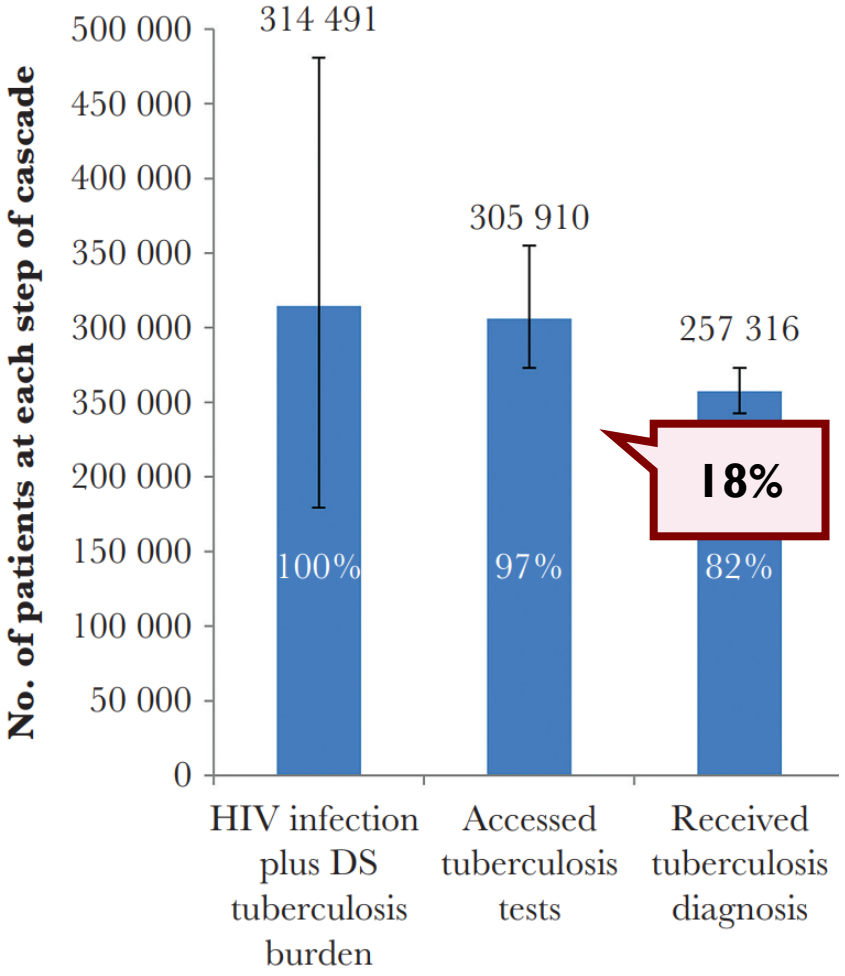
South African rifampicin-resistant TB cascade

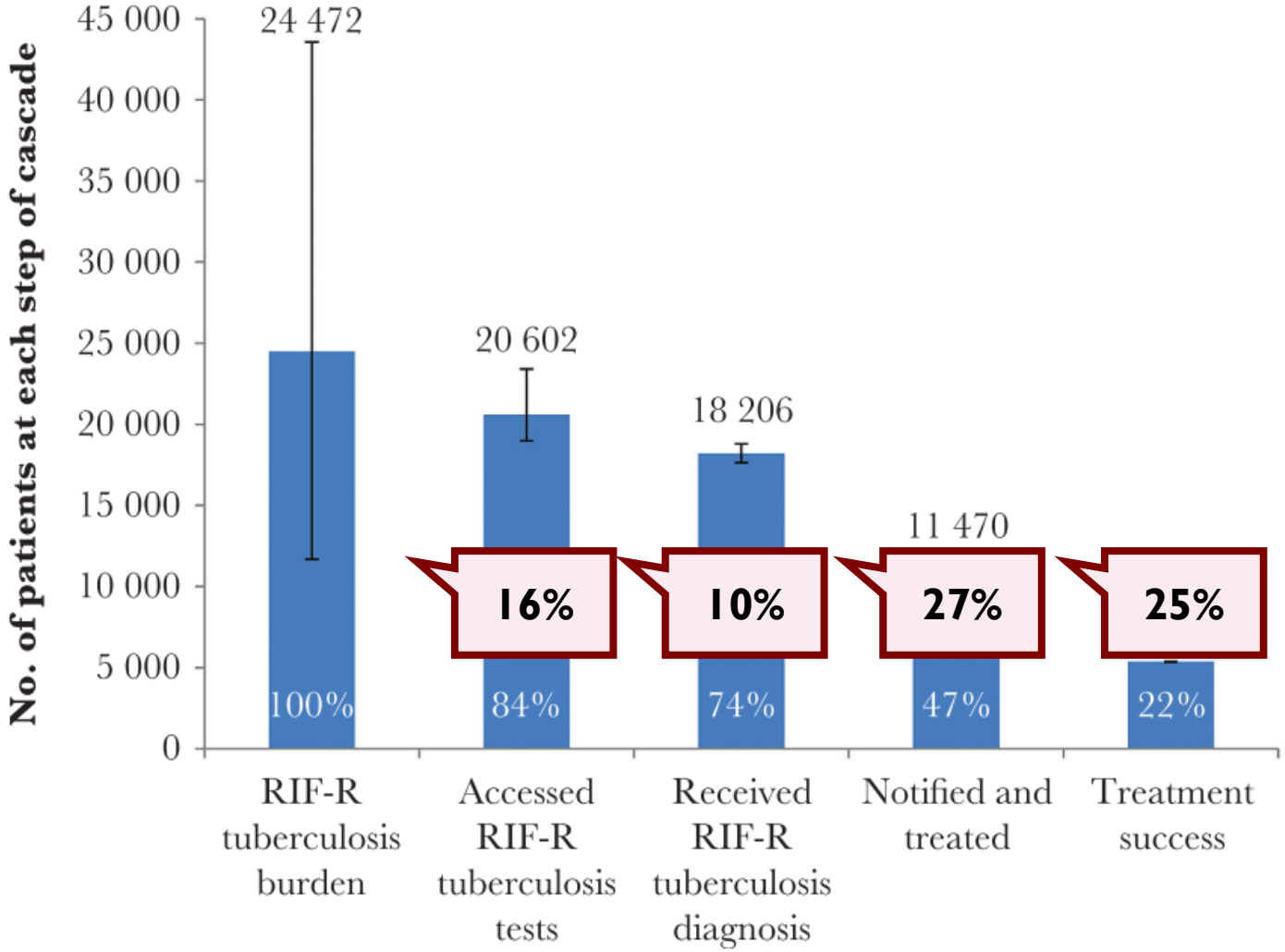


- **When modelling impact, how are leaks at each stage of the care cascade considered?**
- **Is a standard model needed?**

Naidoo *et al*, JID, 2017 10.1093/infdis/jix335

South African rifampicin-resistant TB cascade





Naidoo *et al*, JID, 2017 10.1093/infdis/jix335

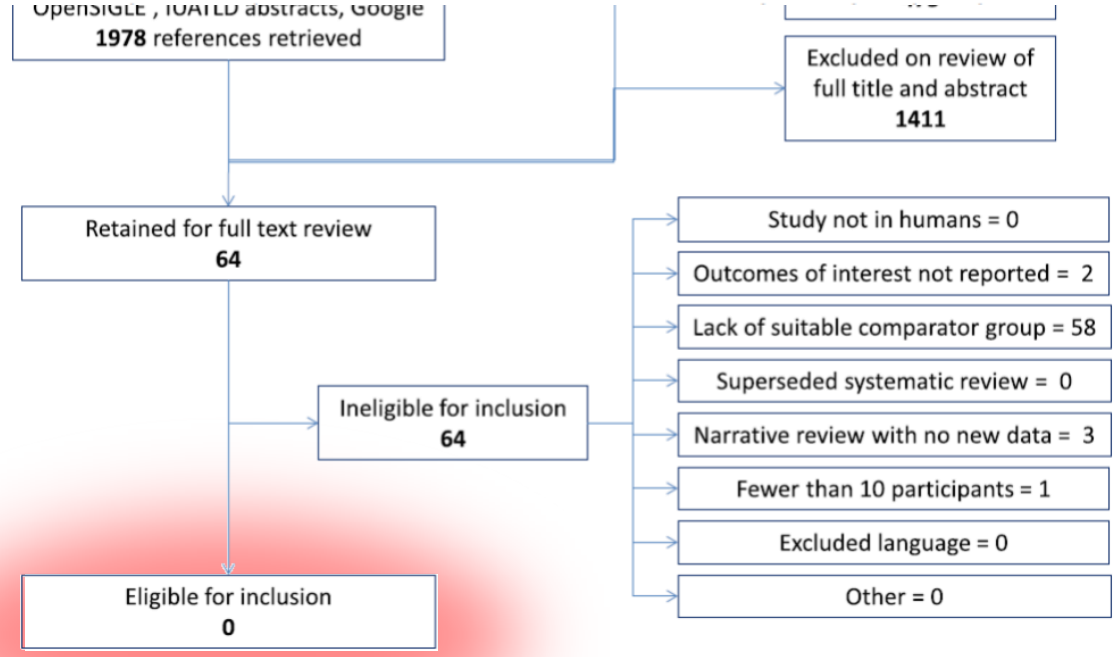
Simple steps to reduce some of these drug-resistant cascade links

- If you suspect TB, suspect drug-resistance (including in ACF)
- Get multiple specimens at the first encounter
- Local epidemiology can inform DST and regimens but usually doesn't
- Punitive interventions at poor performing clinics (e.g., high treatment LTF) disincentivise honest reporting
- Embrace e-Health

RESEARCH ARTICLE Open Access

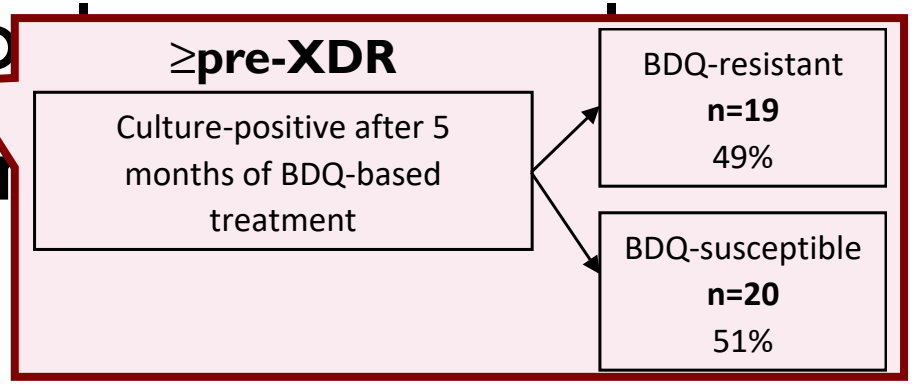
The effect of early versus late treatment initiation after diagnosis on the outcomes of patients treated for multidrug-resistant tuberculosis: a systematic review

Conclusions: Whilst there is an inherent logic in the theory that treatment delay will lead to poorer treatment outcomes, no published evidence was identified in this systematic review to support this hypothesis. Reports of programmatic changes leading to reductions in treatment delay exist in the literature, but attribution of differences in outcomes specifically to treatment delay is confounded by other contemporaneous changes.



Drug-resistant diagnostician's wish list from modellers

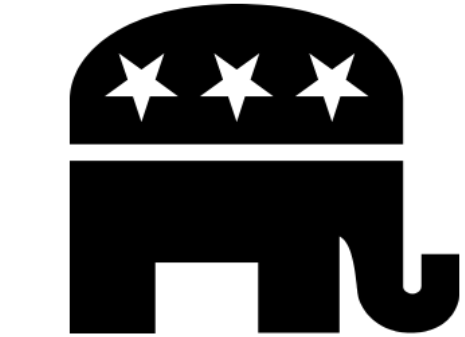
- How much DR-TB is there, what type, and where?
- How can the way we design and evaluate tests help?
- Don't expect a shiny new test to solve a complex health systems problem – the package should be modelled
- Impact of better using existing to
- Drugs go hand-in-hand with diagn
  roll one out without the other
- One more thing…

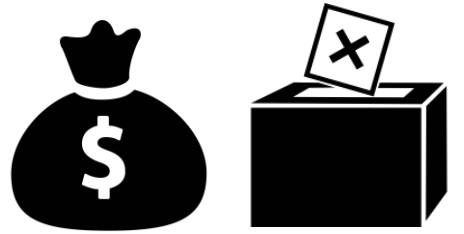


Can we control (or model) the elephant in the room?

IZINDABA

Eastern Cape treatment dysfunction boosts virulent new XDR-TB strain





…zookas' will help fight TB says M…

Kerry Cullinan
and Dipuo Sedibe

THE health department has bought 30 multi-million rand machines that can diagnose drug-resistant tuberculosis within two hours rather than the usual four weeks.

Health minister Aaron Motsoaledi unveiled the biggest of these GeneXpert machines, which can process 48 TB tests in a two-hour session, at Prince Mshiyeni Hospital in Durban during a World TB Day function yesterday.

South Africa is the first African

'REVOLUTION': Health Minister Aaron Motsoaledi

TB was first discovered.

Motsoaled… described machines as a "revolution", sa… that these were the "bazookas… the war against TB.

The GeneXpert machines… easy to use and 98 percent accu… The machines have all been link… to the National Health Laboratory Service's central computers, which can monitor whether they are being used properly.

One in five South African TB patients has drug-resistant TB, thanks to years of inadequate monitoring and control of TB patients.

Motsoaled… machines as a "revo… that these were the… the war against TB…

However, Motsoaledi warned that technology alone could not win the war against TB. For this reason, he also launched a campaign involving house visits to homes of TB patients in areas where there is a high TB rate.

"We need to change the practice…

…TB susceptibility," said Motsoaledi.

By next TB Day, countrywide teams aim to visit 200 000 homes.

"This is not a once-off cam…

SOUTH AFRICA

Health department announces international first in the fight against TB

18 June 2018 - 18:03

BY TANYA FARBER

Known unknowns (1/2)

- It's never really just about the test… (can a test's impact alone even be accurately measured?)
- Individualised regimens probably saves lives and are increasingly possible. Where should this be prioritised?
- Can modelling identify implementation bottlenecks to capitalise on new tests?
  - NTPs don't follow algorithms well
  - How do we model fidelity of implementation and algorithm adherence, which are poor?
- Personal clinical benefit vs. population benefit

Known unknowns (2/2)

- If we improve treatment, how do we link this to DR-TB transmission?
  - Is this different to DS-TB?
  - Are "reduced fitness costs" offset by diagnostic delay?
- If DR-TB diagnosis is far worse than TB diagnosis, is there more of an opportunity to make a difference?
- Impact of better DR-TB diagnostics on patient costs
- Role for DST in universal TB regimens is unclear
- If intuitive and logical that faster effective treatment initiation is good, do we need even need empirical data on this?
  - If not, how do we project impact?

Acknowledgements and thanks

TB-MAC organisers and colleagues

CLIME

Clinical Mycobacteriology and Epidemiology Group

CBTBR DST/NRF

saMRC advancinglife