Considering population level impact in prioritizing profiles of novel TB drugs

Emily A Kendall, MD PhD

Assistant Professor, Division of Infectious Diseases, Johns Hopkins University

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2018 Global New TB Drug Pipeline [1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP/ GLP Tox. → Phase 1 → Phase 2 → Phase 3

Diarylthiazoles

DprE1 Inhibitors

InhA Inhibitor

Macrolides

Mycobacterial Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, Clp, PKS13

Oxazolidinones

Pyrimidines

Squaramides

CPZEN-45*

Spectinamide - 1810*

SPR-720 (pVXc-486)*

TB-47*

DC-159a

BTZ-043*

TBAJ-587

TBI-223

GSK-286*

TBI-166*

Macozinone* (PBTZ-169)

OPC-167832*

Q203*

GSK-656 (070)*

Contezolid (MRX-4/MRX-1)

TBA-7371*

Delpazolid (LCB01-0371)

SQ-109*

Sutezolid (PNU-100480)

Macozinone* (PBTZ-169)

Bedaquiline* (TMC-207)

Delamanid* (OPC-67683)

Pretomanid* (PA-824)

Underline = new to Phase since October 2017

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

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www.newtbdrugs.org

Updated: March 2018

2018 Global TB Drug and Regimen Clinical Research [1]

Ongoing Clinical Development Research: Strategy/Optimization/Regimen Development

Phase 2

Bedaquiline-Delamanid (ACTG 5343)

Bedaquiline - Pretomanid - Pyrazinamide (BPaZ) (NC-005)

Bedaquiline - Pretomanid – Moxifloxacin - Pyrazinamide (BPaMZ) (NC-005)

Levofloxacin with OBR for MDR-TB (OPTI-Q)

Linezolid Dose-Ranging

Nitazoxanide

Beta-Lactams

High Dose Rifampicin (PANACEA)

TB PRACTECAL - regimens with Bedaquiline-Pretomanid-Linezolid

Phase 3 Regimens

Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)

Bedaquiline-Pretomanid-Linezolid (NiX-TB)

Delamanid with OBR for MDR-TB

High Dose Rifampicin for DS-TB (RIFASHORT)

Rifapentine - Moxifloxacin for DS-TB (CDC TBTC 31)

Pretomanid-Moxifloxacin-Pyrazinamide (STAND)

Optimization/Post Market

Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

endTB 5-Regimen Trial for MDR TB

PredictTB – PET/CT, biomarkers DS-TB, 4 mo

Clofazimine - formulation development

Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

[1] Strategy trials, regimen development, open label, repurposed drug studies. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

[2] OBR = Optimized Background Regimen

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Which drugs should be prioritized for development? What can population-level modeling tell us?

Drugs for TB treatment

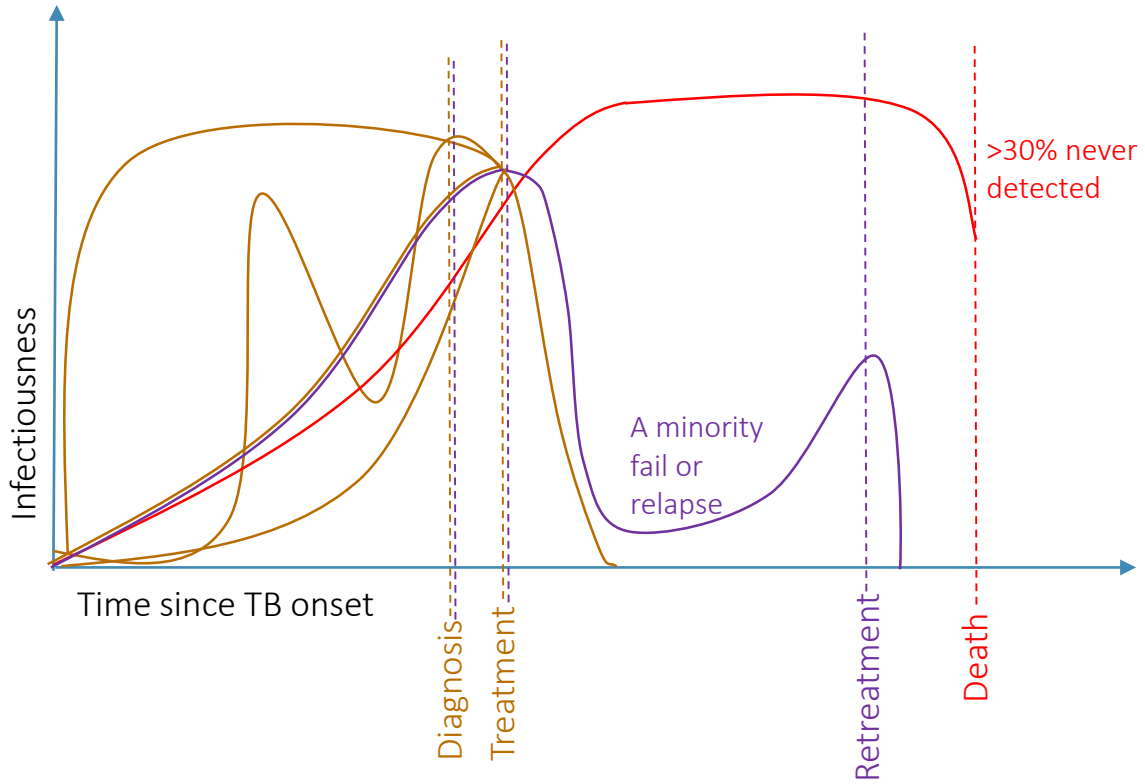
- What population-level impact can they have?
- What characteristics matter?

How could drugs achieve greater impact?

- Drugs and product profiles for prevention
- Can drugs help transform treatment delivery?

What population level impact can better TB treatment have?

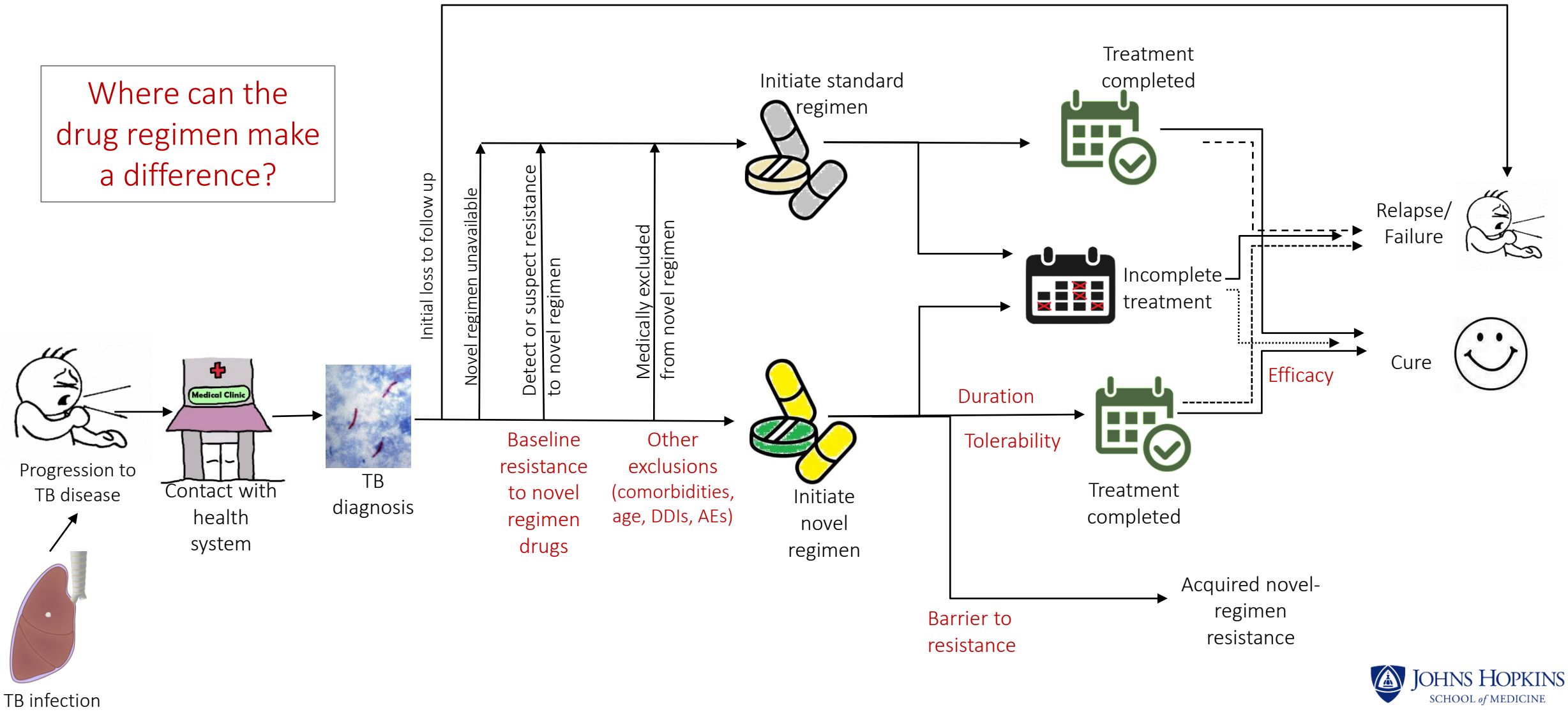
How much of all TB morbidity, mortality, or transmission are from people who have started treatment?



- In simple transmission models, ideal first-line regimens reduce TB incidence <10% (e.g. Kendall et al, Plos Med 2017)
- Impact of DR-TB regimens is greater, but also plateaus

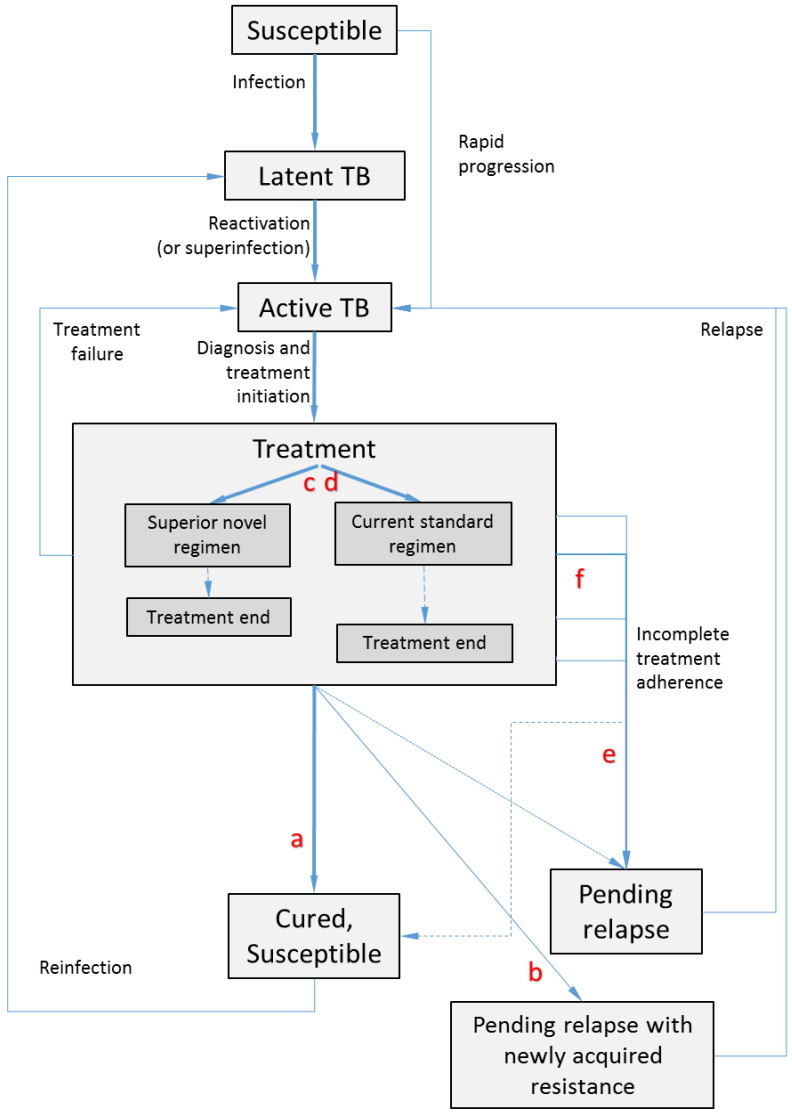
But which drug/regimen characteristics matter most?

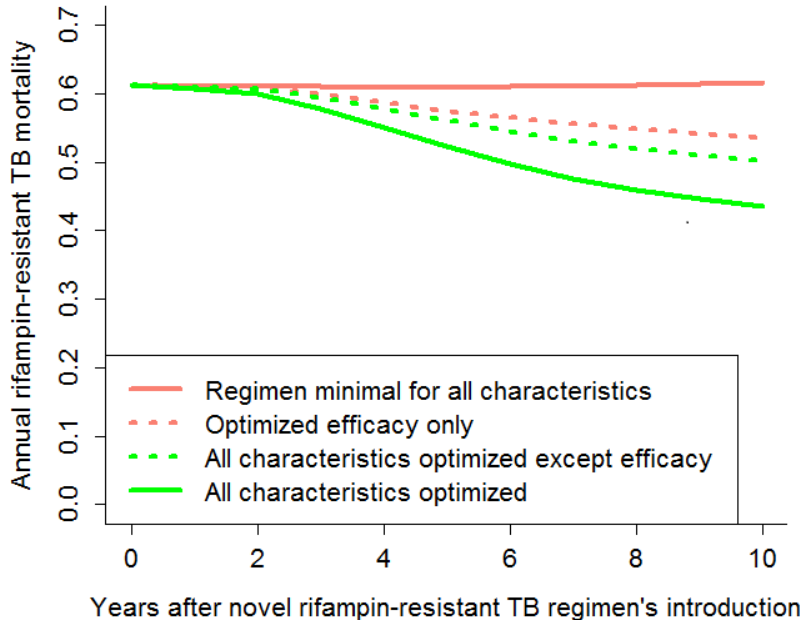
Where can the drug regimen make a difference?



Methods: Regimen characteristics and transmission model

Regimen characteristic	Values in **Novel RS-TB regimen**	Values in **Novel RR-TB regimen**
a. **Efficacy** (% cured if susceptible and completed tx)	94% 97% 99%	76% 88% 94%
b. New drug **resistance acquisition**	1 in 20 1 in 125 ~0	1 in 10 1 in 20 1 in 125
c. **Baseline resistance** to regimen	10% 3% 0%	15% 5% 0%
d. Other **exclusions** from regimen eligibility	11% 5% 0%	11% 5% 0%
e. **Duration** of treatment	6mo 4mo 2mo	20mo 9mo 6mo
f. **Tolerability**/ Improved Adherence	0% 25% 50%	0% 25% 50%





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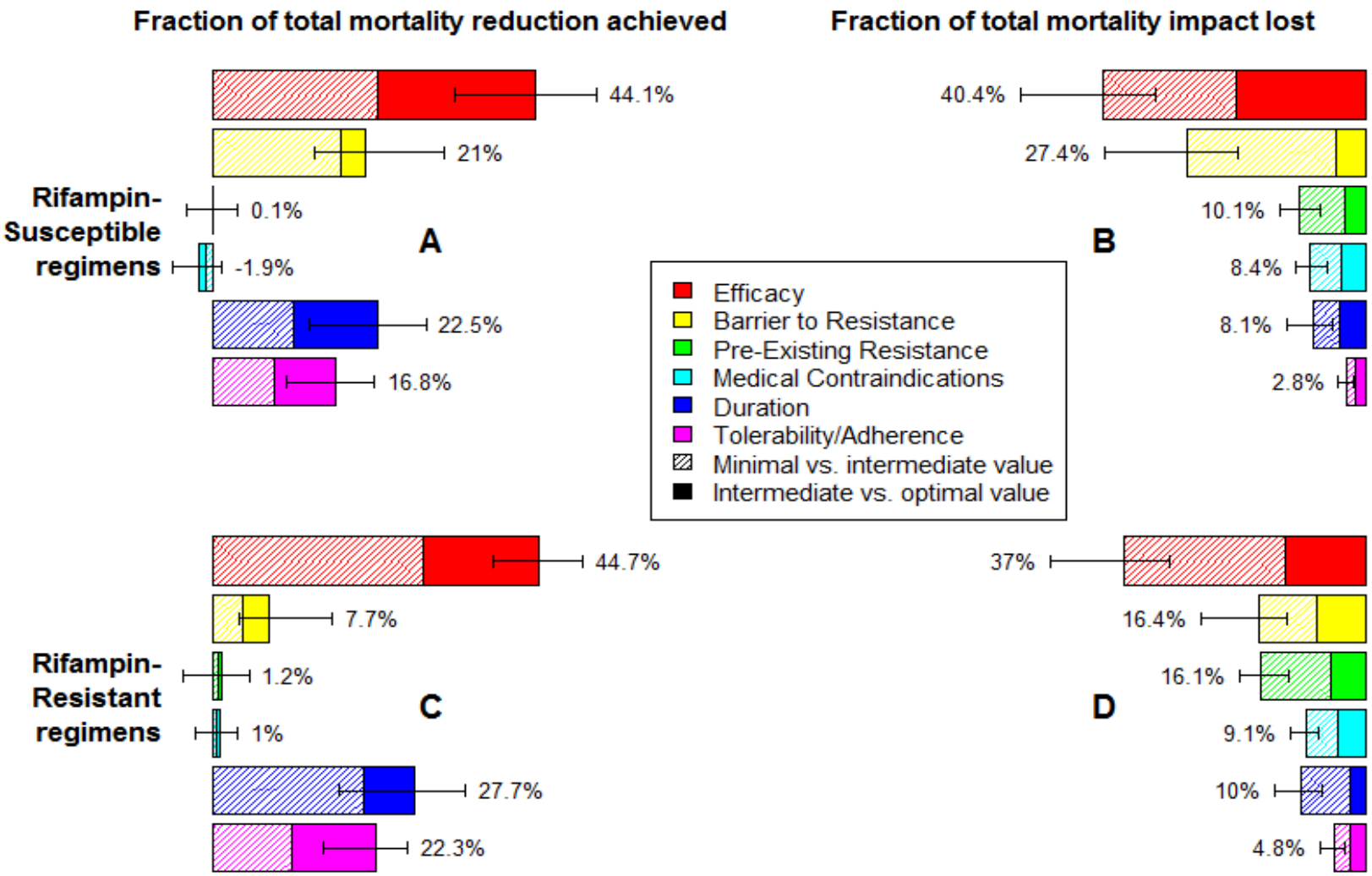
Results



Implication: Novel regimen efficacy is key – Even when the differences are too small to feasibly measure.

Limitations:

- Assumption of constant infectiousness
- Consideration of only "direct" effects (no resource reallocation)

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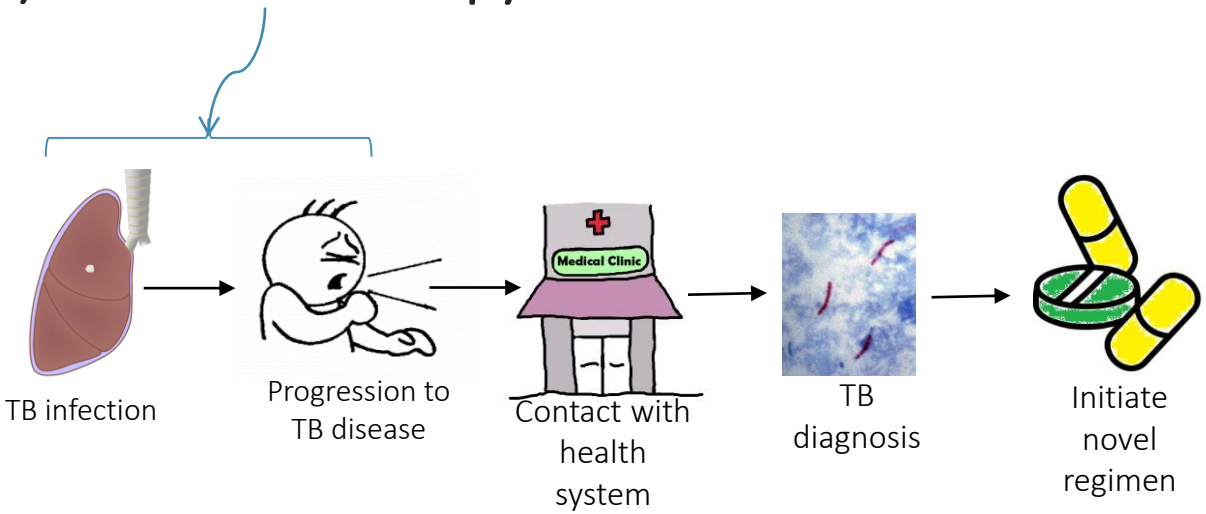
How could drugs achieve greater impact?

For drugs to have a transformative impact on TB epidemics, their reach must expand.

1) Preventive therapy



Prioritizing target profiles of preventive therapy

What characteristics would we evaluate and model?

1) Operational characteristics

- Duration
- Ease of administration and adherence
- Breadth of eligibility

2) Efficacy – e.g. reduction in incident TB risk as measured in clinical trials

- Also, different mechanisms of the same measured efficacy?

Teasing out components of preventive therapy efficacy

The same measured effect size can have multiple mechanisms:

		Type of effect	
		On pre-existing latent infection	On new TB exposure
Duration of effect	Short	Temporary suppression of reactivation	Brief drug activity (e.g. potent one-time dose)
	Long	Durable/permanent cure of LTBI	Persistent drug activity (e.g. injectable/implantable/long-half-life drug)

Relevant to generalizability of efficacy between settings

Important where rate of re-infection is high

Relevant to decisions about treatment duration e.g. continuous IPT

Important over longer follow up

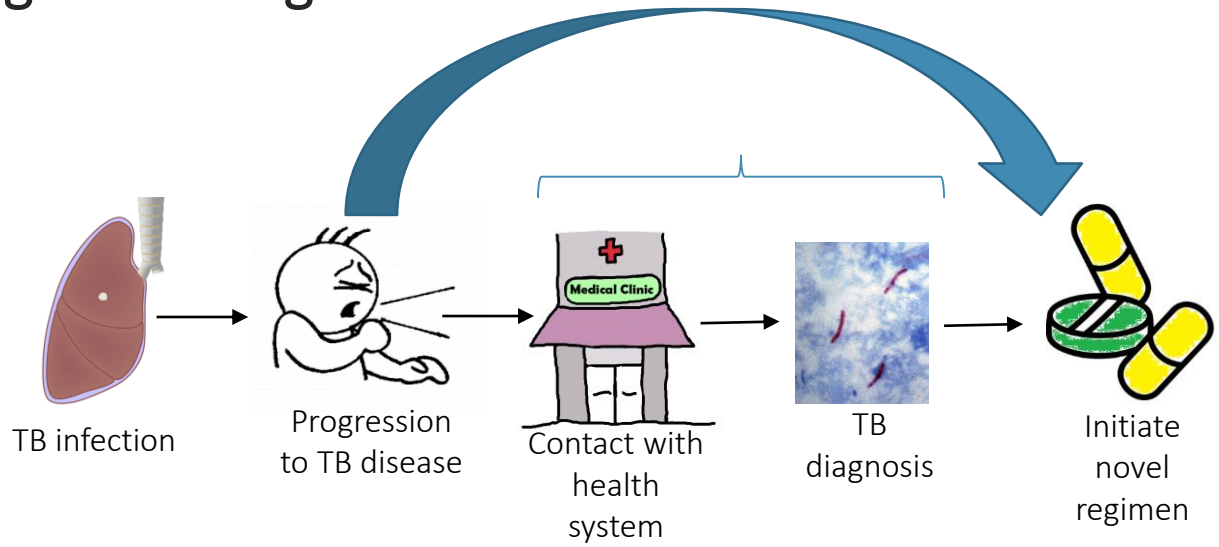
Distinguishing and prioritizing these contributions will involve both modeling and empirical study.

How could drugs achieve greater impact?

For drugs to have a transformative impact on TB epidemics, their reach must expand.

1) Preventive therapy

2) Operational game-changers



What regimen characteristics could allow for wider and earlier treatment?

Safe

Easy

Short

Cheap

Universal

Could better drugs facilitate massive shifting of resources to active case finding and immediate treatment?

Summary

Models of population-level impact can help set priorities for TB drug development.

For treatment regimens, efficacy appears critical to impact.

But the maximum impact of better treatment regimens is limited by late diagnosis.

Modeling could also help set priorities for development of preventive therapies.
Distinguishing mechanisms of observed effects may be important here.

Future modeling should also consider indirect effects – Could drugs with certain characteristics help facilitate earlier diagnosis and wider reach of treatment?