Modelling the impact of novel drugs and drug treatment in populations: the example of tuberculosis

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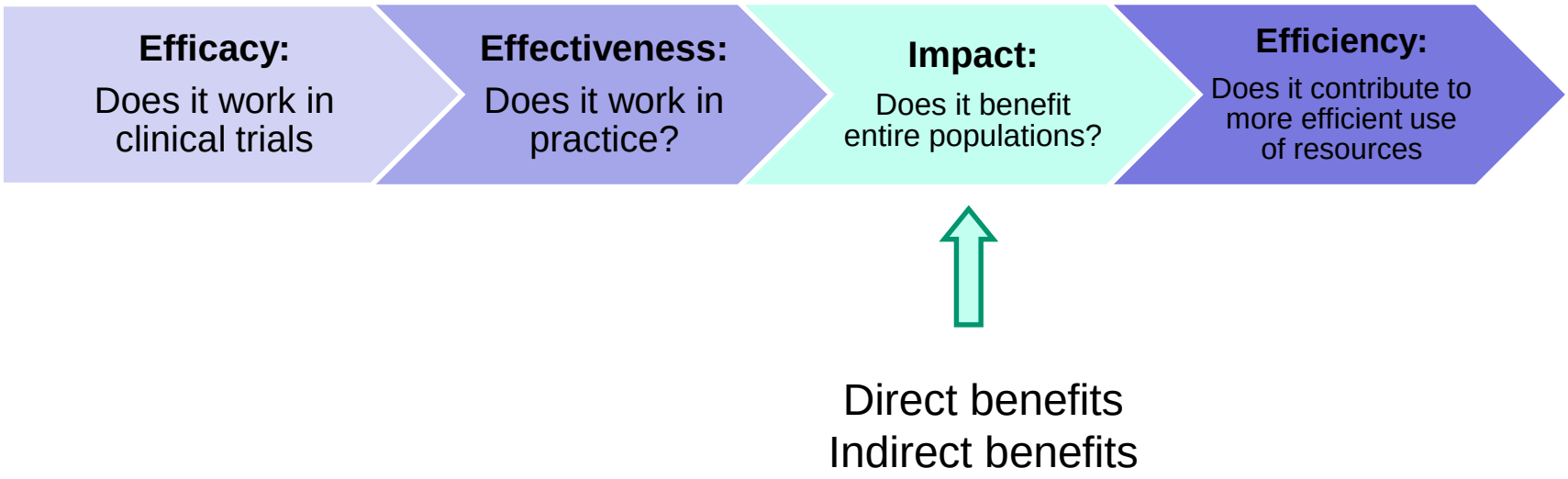
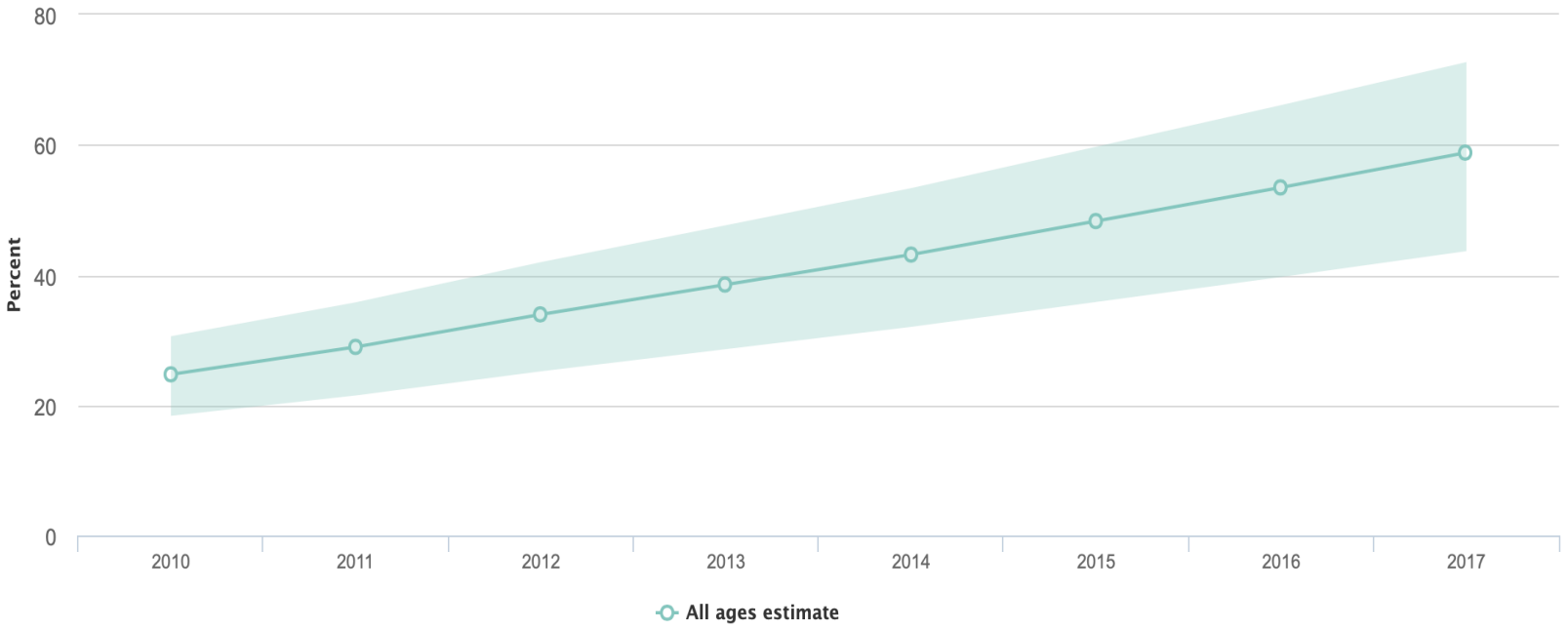
Overview

- Beyond clinical trials: novel drugs and drug treatments as part of larger health programmes
- The case of tuberculosis
- Modeling the impact of novel TB drugs and treatment programmes: 3 examples
- Conclusions

Beyond clinical trails: effective and efficient use of novel drugs and drug regimens in populations

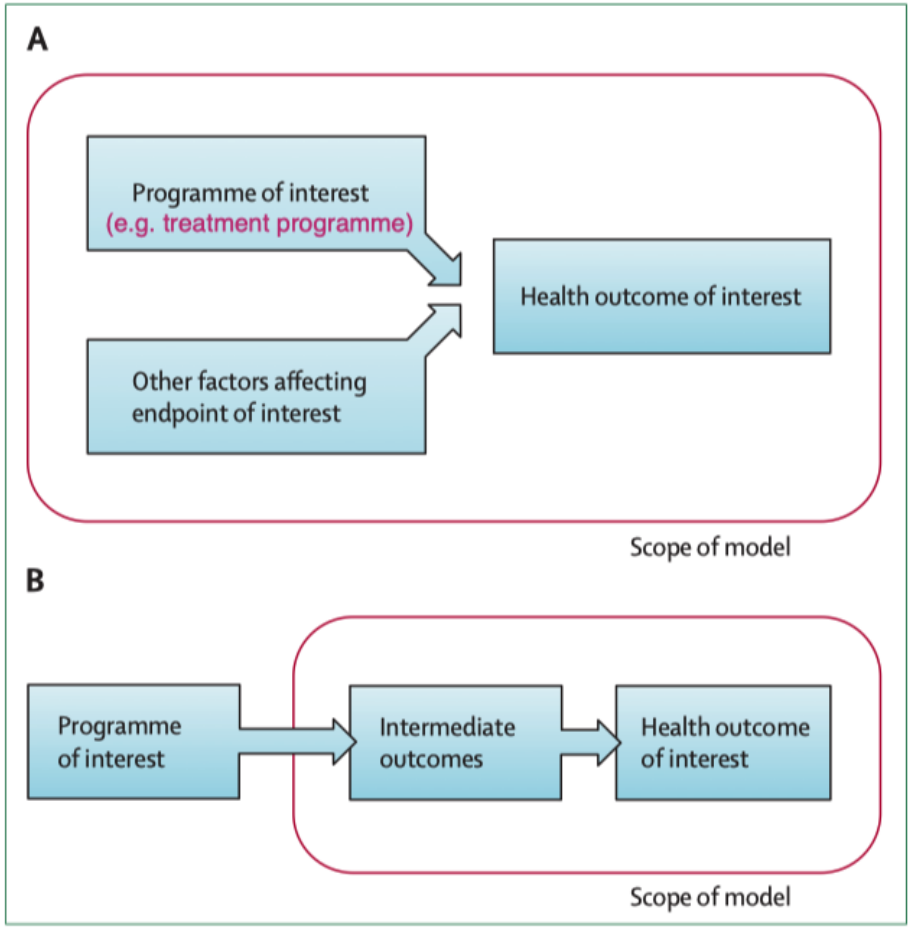


Global coverage of antiretroviral therapy among people living with HIV



Source: UNAIDS 2018 estimates; Global AIDS Monitoring 2018

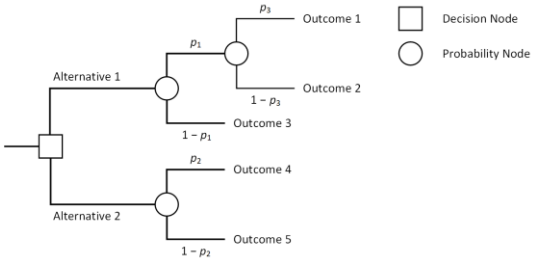
Mathematical models in the evaluation of treatment and health programmes



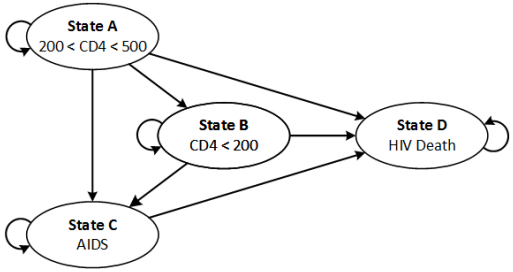
Garnet et al., The Lancet, 2011 (adapted)

Impact of drug treatment in populations – Types of mathematical models commonly used

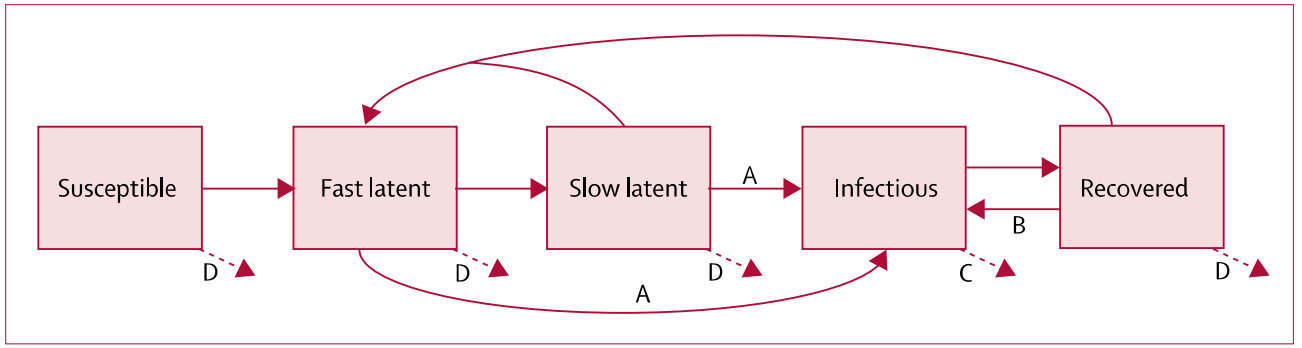
- Decision tree models



- Markov models

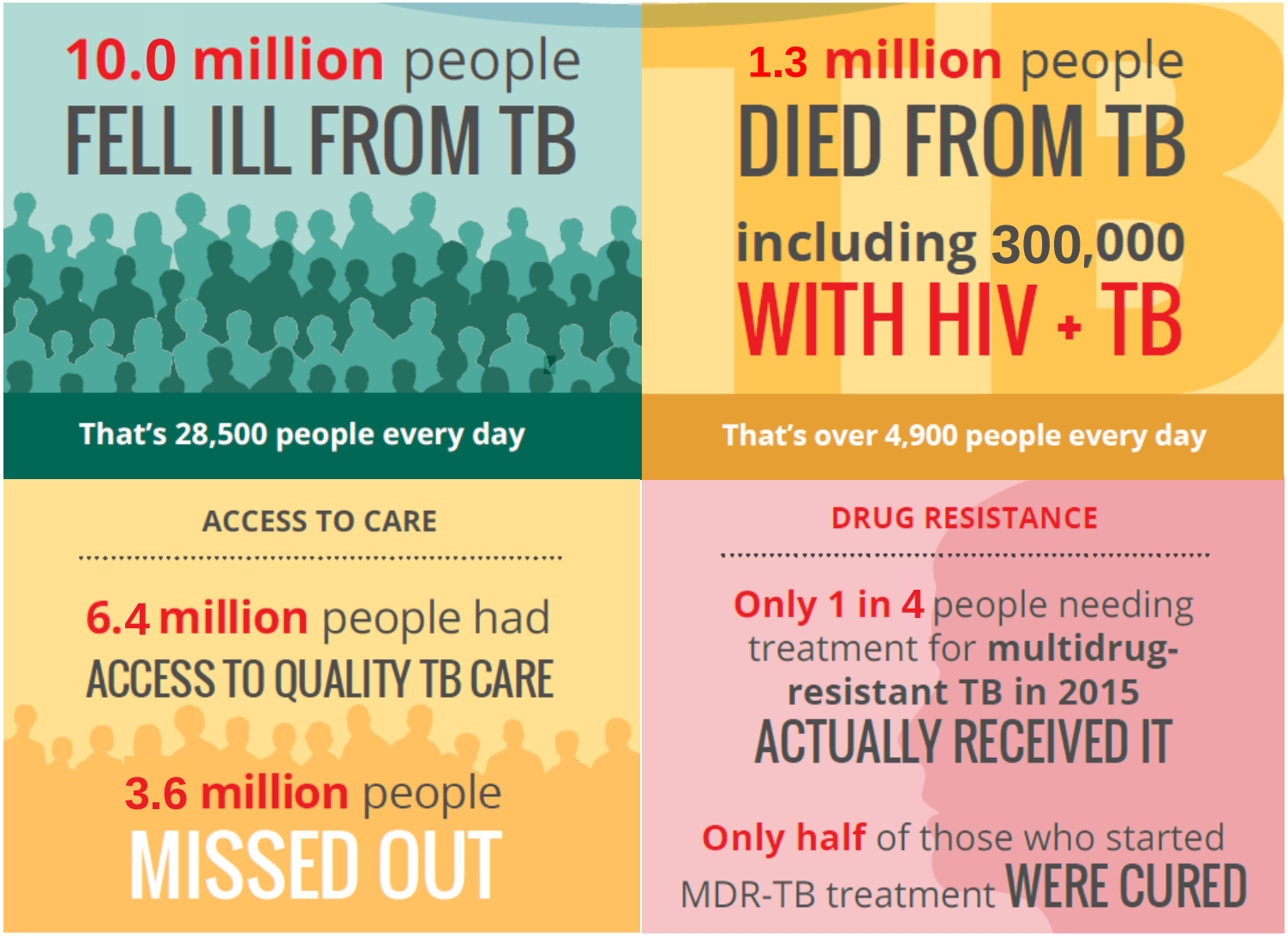


- Population-based, transmission-dynamic models



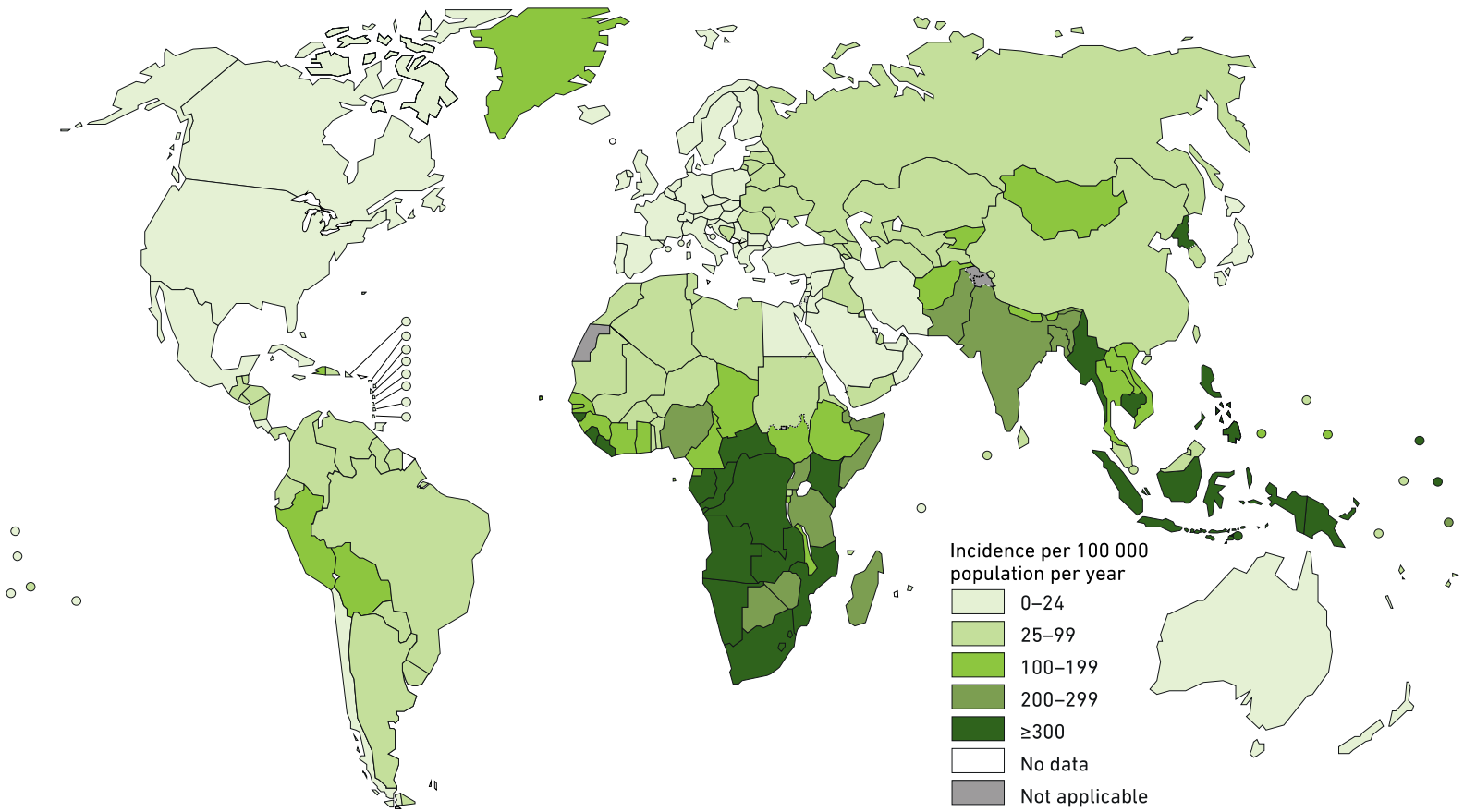
Pan et al., Lancet Diab Endocr, 2015

Tuberculosis worldwide (2017)



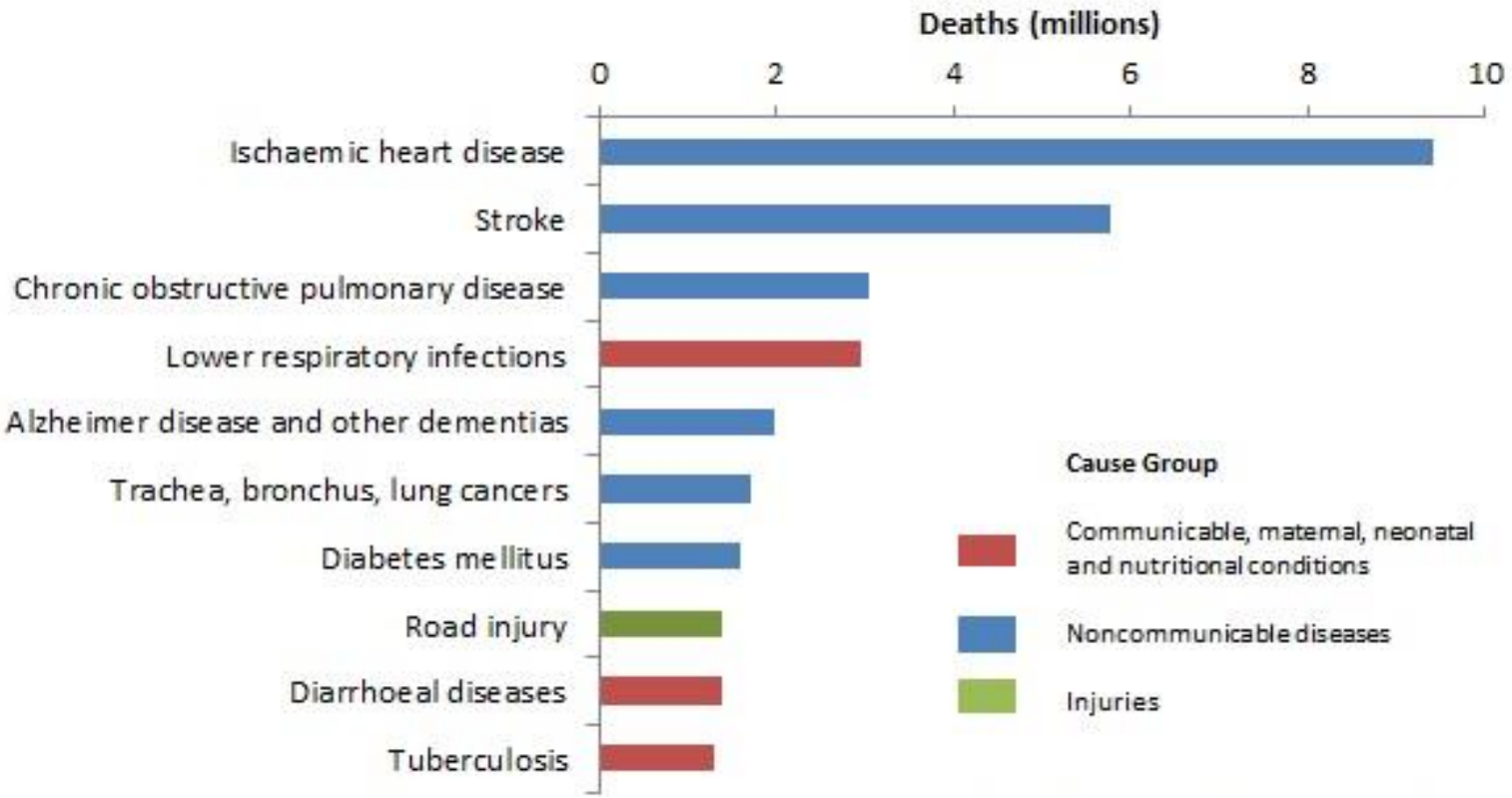
(Source: WHO)

Estimated incident TB cases per 100,000 population



WHO Global TB Report, 2018

Top 10 global causes of deaths, 2016

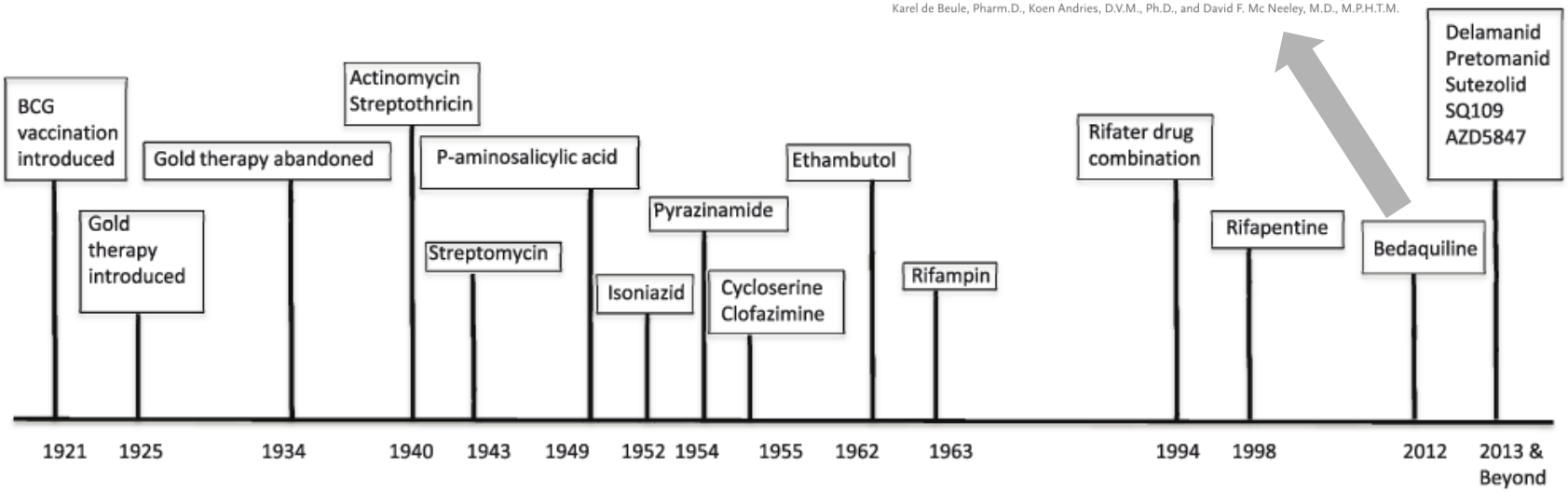


Source: WHO

Timeline for tuberculosis drug development

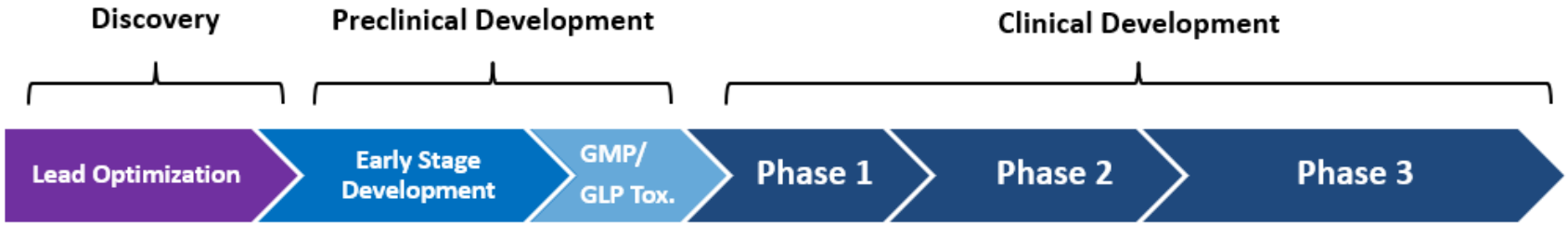
The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.&H., Ramonde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pistorius, M.D., Rene Krause, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.Tech.(Micro), Jenny Allen, B.Sc., Juan Carlos Palomino, Ph.D., Tine De Marez, Ph.D., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Johan Verbeeck, D.V.M., Ph.D., Wim Parys, M.D., Karel de Beule, Pharm.D., Koen Andries, D.V.M., Ph.D., and David F. Mc Neeley, M.D., M.P.H.T.M.



Podany & Swindells, F100Res, 2016

2018 Global New TB Drug Pipeline [1]



Lead Optimization

- Diarylthiazoles
- DprE1 Inhibitors
- InhA Inhibitor
- Mtb energy metabolism
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, Clp, PKS13
- Oxazolidinones
- Squaramides

Early Stage Development

- CPZEN-45*
- Spectinamide - 1810*
- SPR720*
- TB-47*

GMP/ GLP Tox.

- TBAJ-587
- TBAJ-876
- GSK-286*
- TBI-223
- Sanfetrinem
- S-004992*

Phase 1

- BTZ-043*
- TBI-166
- Macozinone* (PBTZ-169)
- GSK-656* (070)
- TBA-7371*
- Contezolid (MRX-4/MRX-1)

Phase 2

- OPC-167832*
- Telacebec (Q203*)
- Delpazolid (LCB01-0371)
- Sutezolid
- SQ-109*
- Macozinone*

Phase 3

- Bedaquiline* (TMC-207)
- Delamanid* (OPC-67683)
- Pretomanid* (PA-824)

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

[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: http://www.newtbdrugs.org/pipeline/discovery

Underline = new to Phase since March 2018

WORKING GROUP ON NEW TB DRUGS

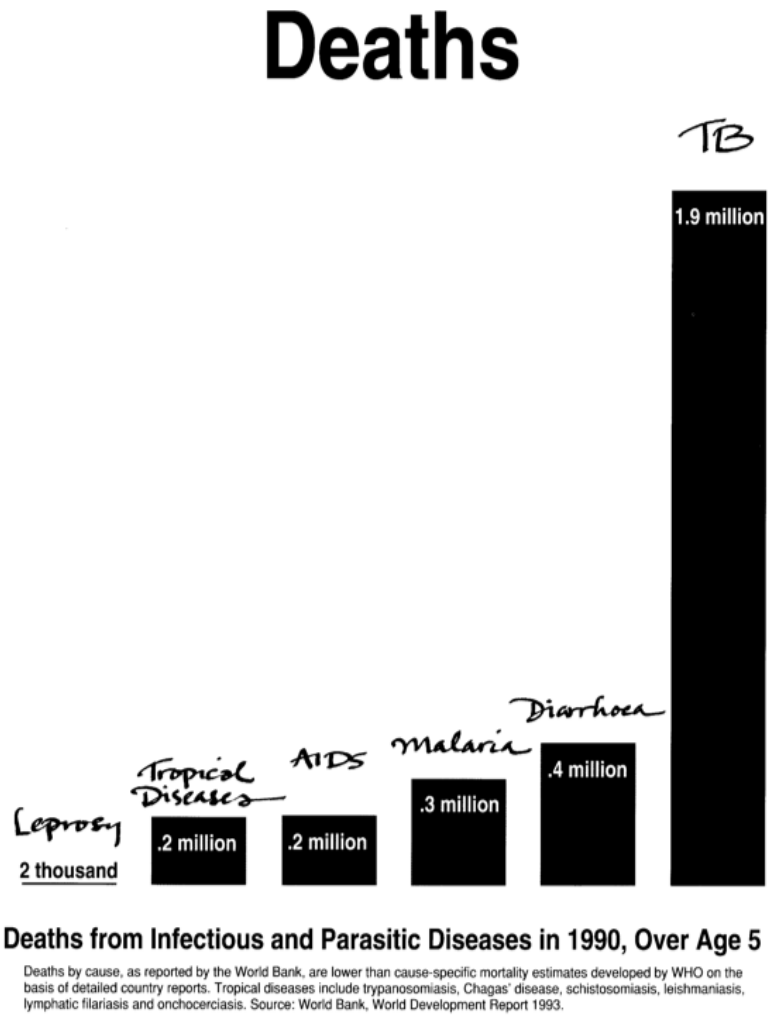
www.newtbdrugs.org

Updated: October 2018

Overview of examples

Author	Year	Title
Dye et al.	1998	Prospects for worldwide tuberculosis control under the WHO DOTS strategy
Kendall et al.	2017	Priority-Setting for Novel Drug Regimens to Treat Tuberculosis: An Epidemiologic Model
Kunkel et al.	2016	Benefits of continuous isoniazid preventive therapy may outweigh resistance risks in a declining tuberculosis/HIV co-epidemic

WHO declares TB a global emergency in 1994



Deaths from Infectious and Parasitic Diseases in 1990, Over Age 5

Deaths by cause, as reported by the World Bank, are lower than cause-specific mortality estimates developed by WHO on the basis of detailed country reports. Tropical diseases include trypanosomiasis, Chagas' disease, schistosomiasis, leishmaniasis, lymphatic filariasis and onchocerciasis. Source: World Bank, World Development Report 1993.

WHO's DOTS strategy, 1995

- "Direct Observed Treatment Short-course" strategy
- Aim: to provide high-quality TB treatment globally
- 5 elements:
  - Political commitment
  - Case detection through bacteriology
  - Standardized treatment, with supervision and patient support
  - Effective drug supply system
  - Monitoring and impact evaluation

Global TB control targets for 2010:

70% Case detection under DOTS, 85% Treatment success

Prospects for worldwide tuberculosis control under the WHO DOTS strategy

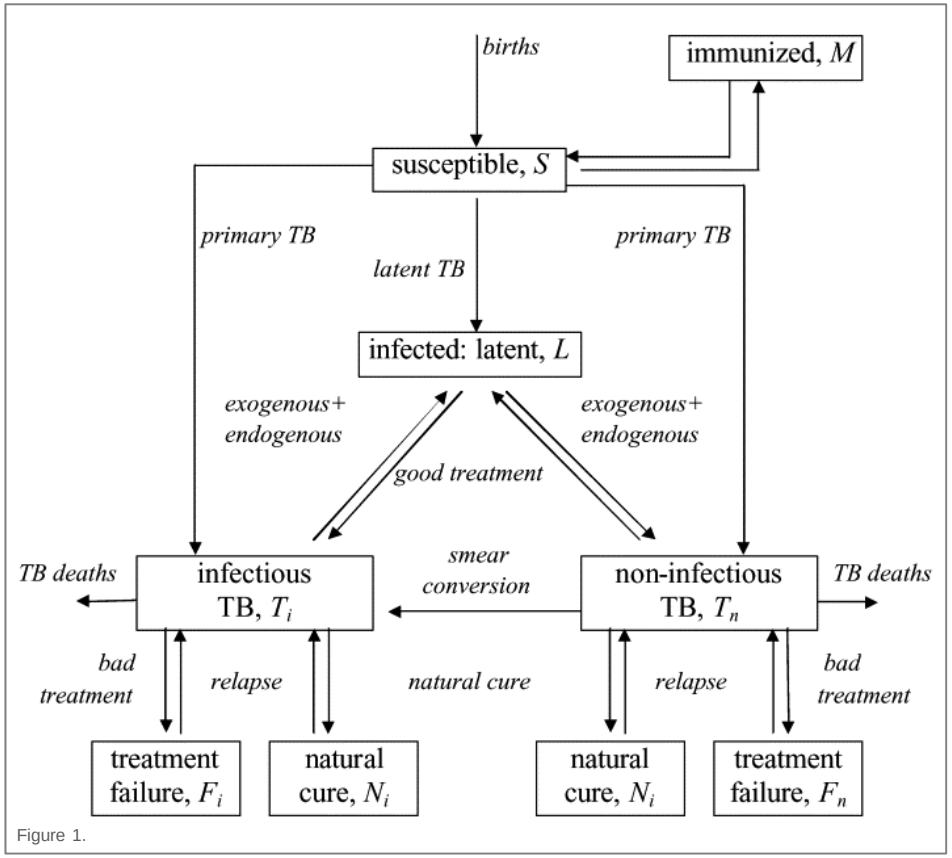
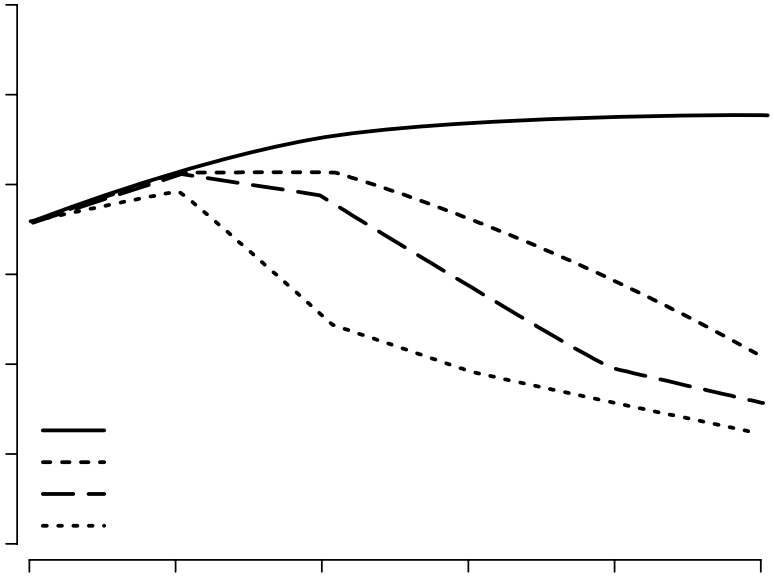


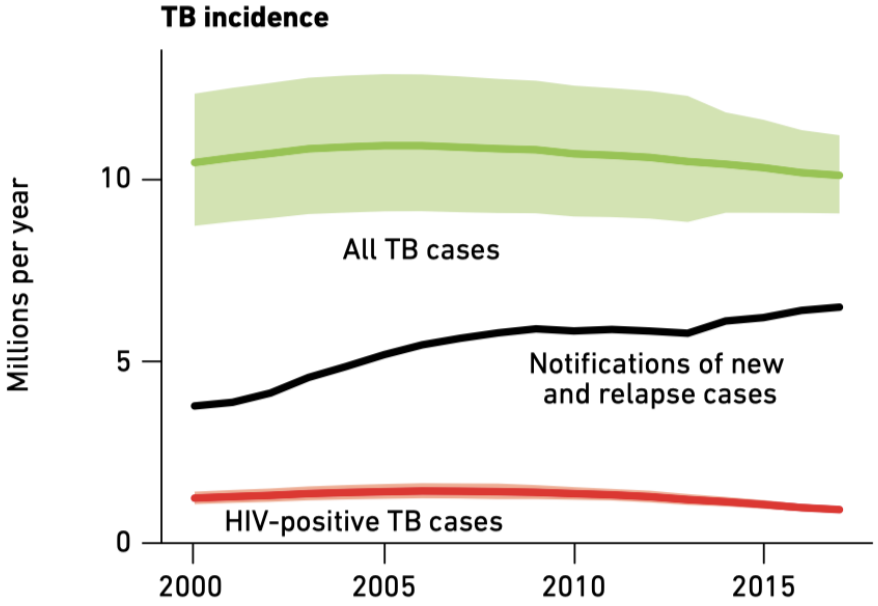
Figure 1.

Population-based transmission-dynamic model

Dye et al., The Lancet, 1998

Projected TB incidence when meeting the targets for DOTS





WHO estimates 2018

Dye et al., The Lancet, 1998

Modeling to inform priority setting for novel TB drugs

- Different characteristics of treatment matter for reducing TB deaths and new cases:
  - Efficacy
  - Duration
  - Ease of adherence
  - Medical contraindications
  - Barrier to resistance
  - Baseline prevalence of resistance

- Modeling can help understand the impact that these characteristics have when implementing novel drug regimens

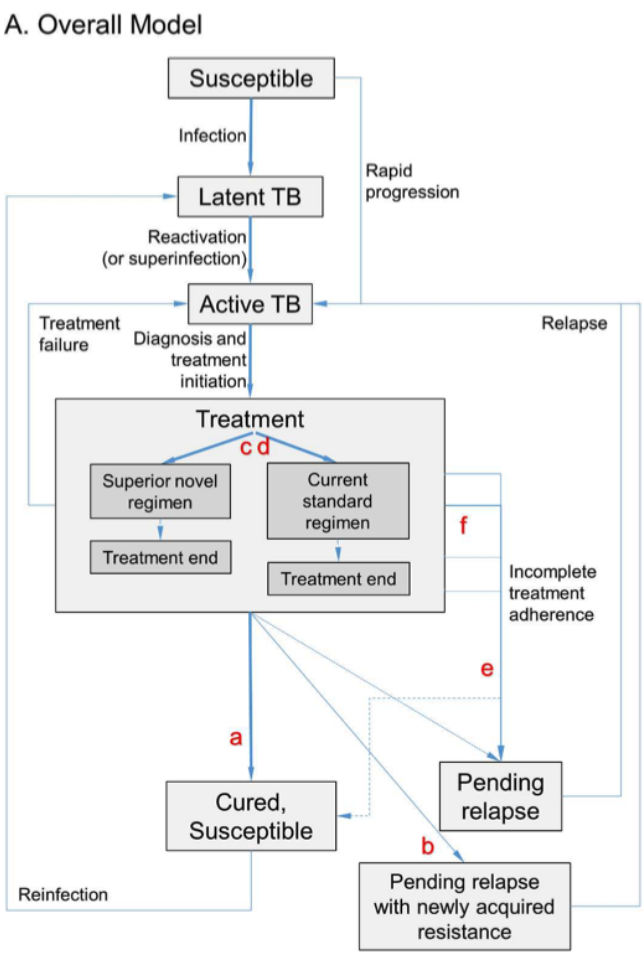
Kendall et al., PLoS Med, 2017

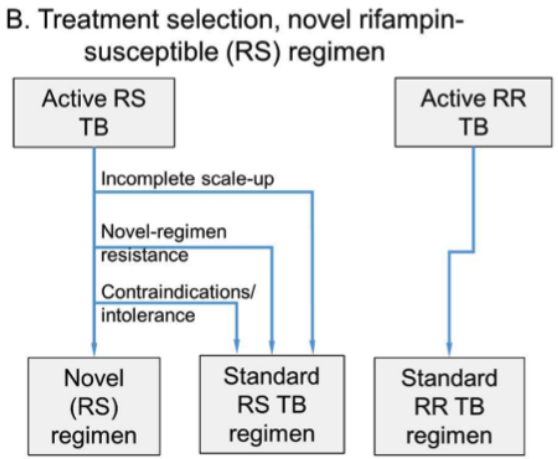
PLOS | MEDICINE

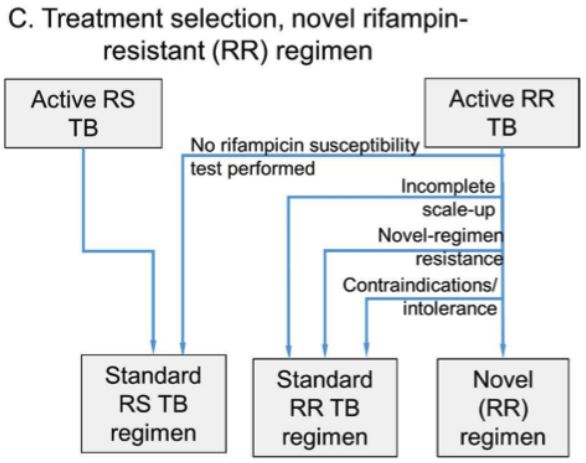
RESEARCH ARTICLE

Priority-Setting for Novel Drug Regimens to Treat Tuberculosis: An Epidemiologic Model

Emily A. Kendall[1]*, Sourya Shrestha[2], Ted Cohen[3], Eric Nuermberger[1], Kelly E. Dooley[1,4], Lice Gonzalez-Angulo[5], Gavin J. Churchyard[6], Payam Nahid[7], Michael L. Rich[8,9], Cathy Bansbach[10], Thomas Forissier[10], Christian Lienhardt[5], David W. Dowdy[2]

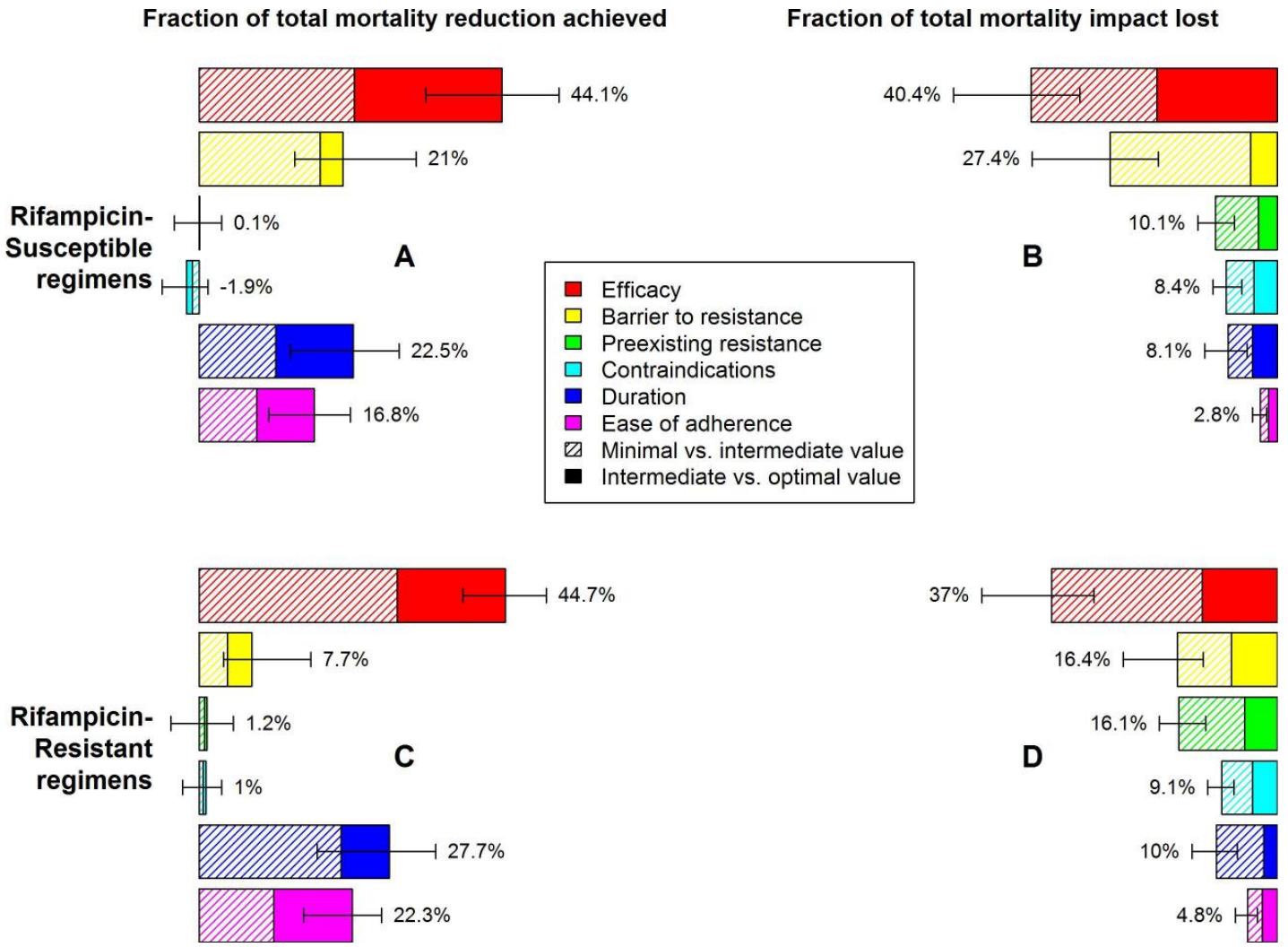






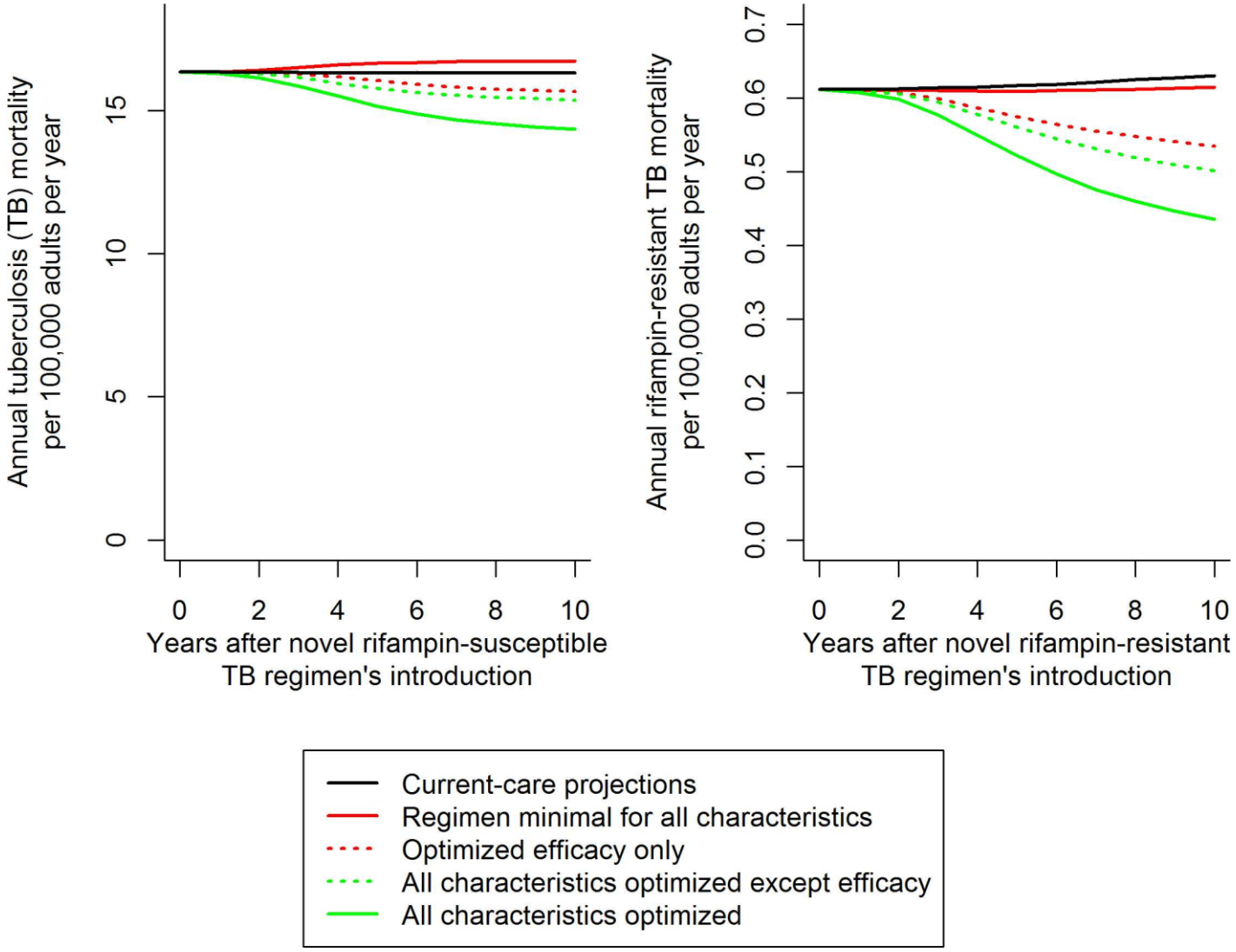
Kendall et al., PLoS Med, 2017

Impact of different characteristics on TB mortality



Kendall et al., PLoS Med, 2017

Impact of different characteristics on TB mortality



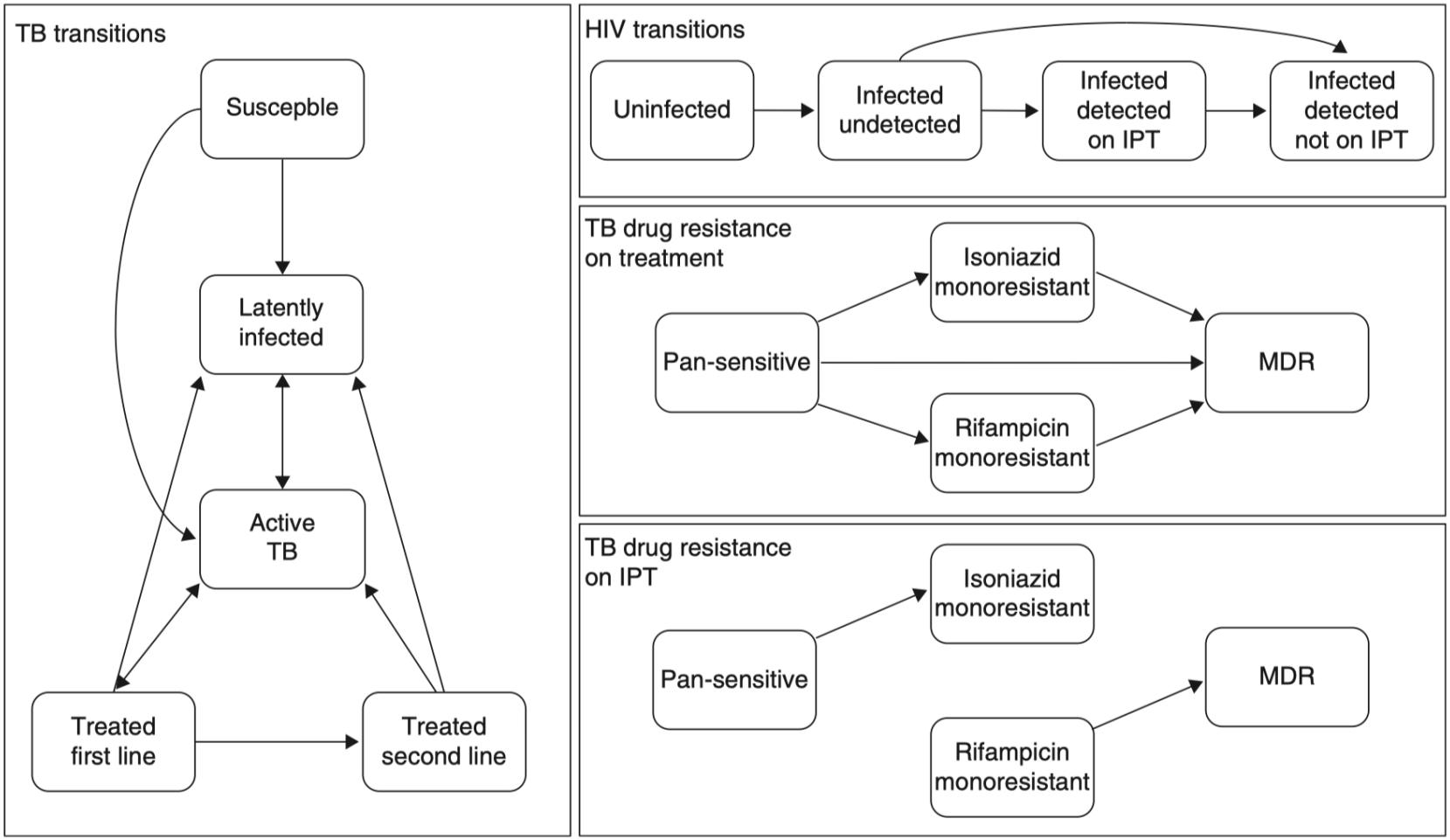
Kendall et al., PLoS Med, 2017

Benefits vs. resistance risk of extending isoniazid preventive therapy in Botswana

- Isoniazid recommended for TB preventive therapy among HIV-infected people
- Among people living with HIV, longer durations of IPT may increase effectiveness but increase selective pressure for drug resistance
- Aim of model: to determine the relative importance of these two effects

Kunkel et al., AIDS, 2016

Transmission-dynamic model of continuous vs. 6-months IPT among HIV-infected people

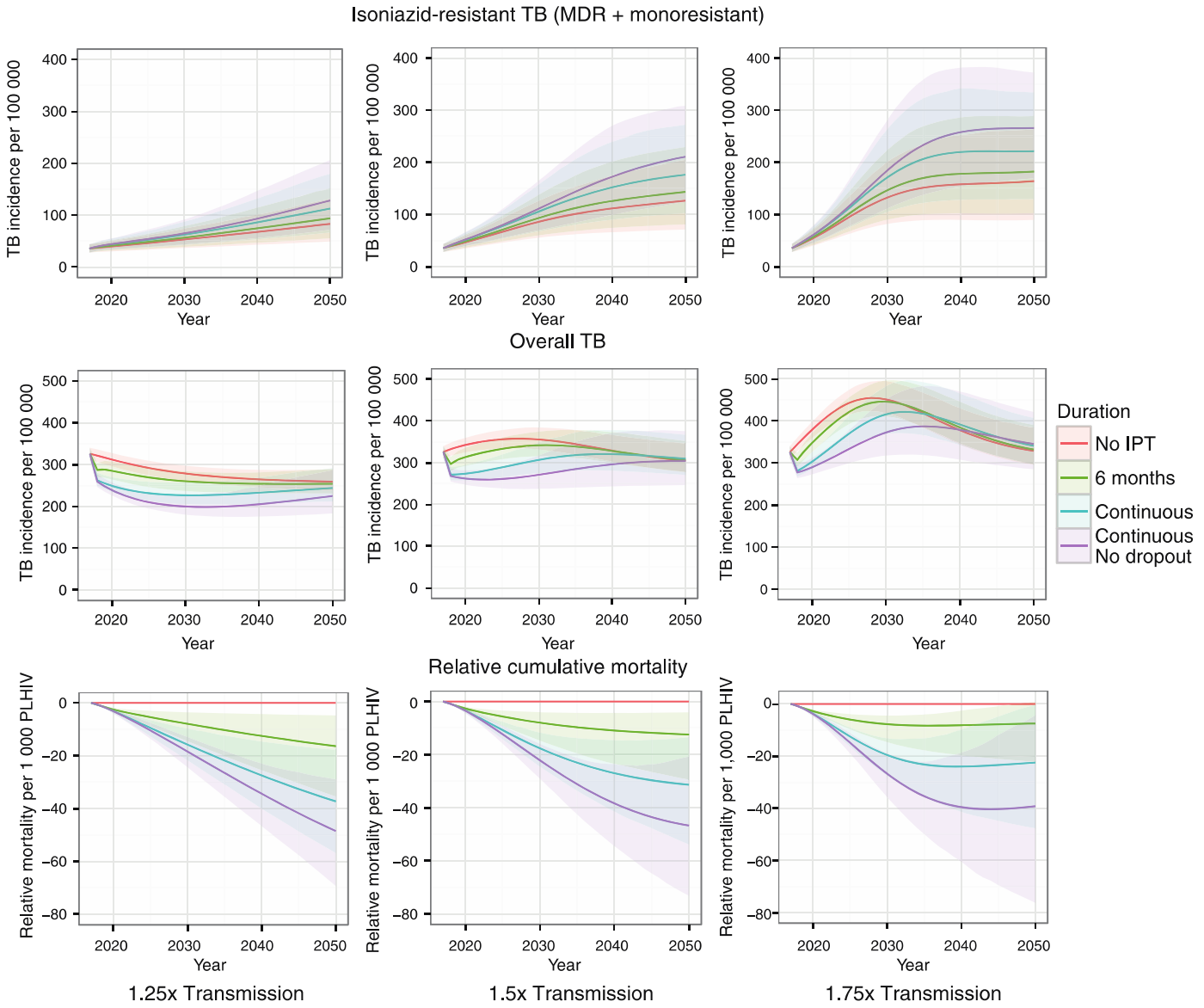


Kunkel et al., AIDS, 2016

Key findings

- in a declining TB epidemic (Botswana), the benefits of continuous IPT outweigh resistance risks
- in a scenario of increased transmission, the benefits of longer IPT may be eroded by increasing drug resistance
- the benefits of IPT may outweigh any increase in resistance when coupled with strong TB and HIV case-finding and treatment programs, and robust drug-resistance surveillance

Kunkel et al., AIDS, 2016



Kunkel et al., AIDS, 2016

Conclusions

- Increasing use of mathematical modelling to inform the impact of novel TB drugs and drug treatment

- Mathematical models can be helpful to guide decision making beyond clinical trials, specifically for:
  - Evaluating the impact of treatment programmes
  - Setting priorities for drug development
  - Projecting beneficial vs. adverse effects (drug resistance)

SACEMA - DTTC

Tuberculosis Modelling Partnership and Research Programme

Working Group Data Analysis & Modelling

WGDAM

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Thank you!

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(Florian Marx)

SACEMA
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Every breath counts