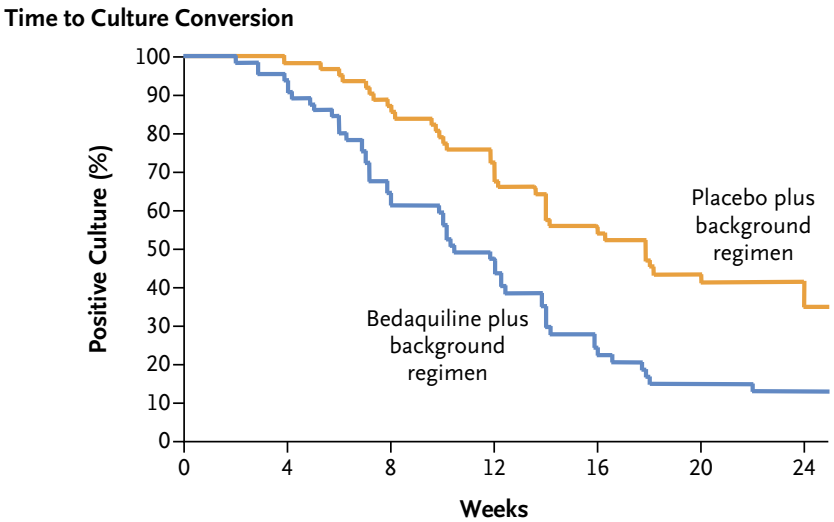
Kunkel, A., Cobelens, F.G., & Cohen, T. (2016). Tradeoffs in introduction policies for the anti-tuberculosis drug bedaquiline: a model based analysis. *Plos Med 13*(10):e1002142.

Tradeoffs in new anti-tuberculosis drug introduction policies

Amber Kunkel

TB Modelling and Analysis Consortium

Bedaquiline Background



No. at Risk						
Bedaquiline	58	37	25	12	7	3
Placebo	61	53	40	30	22	5

WARNINGS:

- An increased risk of death was seen in the SIRTURO™ treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO™ when an effective treatment regimen cannot otherwise be provided.
- QT prolongation can occur with SIRTURO™. Use with drugs that prolong the QT interval may cause additive QT prolongation.

Diacon et al (2014)

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  - XDR: resistance to ≥1 FQ AND ≥1 2LI
- What are the potential effects on transmission?

Current Thinking

- Interim WHO Guidelines (2013)
  - Based on expert assessment of bedaquiline safety and efficacy
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- Recommendations focus on operational issues
  - Pharmacovigilance
  - Informed consent
- No rational framework to address population-level implications of bedaquiline eligibility criteria
  - Fear of losing first new TB drug in >40 years, generating "untreatable" TB
  - "Never add a single drug to a failing regimen"

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- Policies: Should bedaquiline be provided to
  - All patients with MDR TB
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- Approach: Markov cohort model of patients initiating treatment for MDR TB

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- Population:
  - HIV-negative, European men
  - 30 years old at baseline
  - Combination of MDR, pre-XDR, and XDR TB patients
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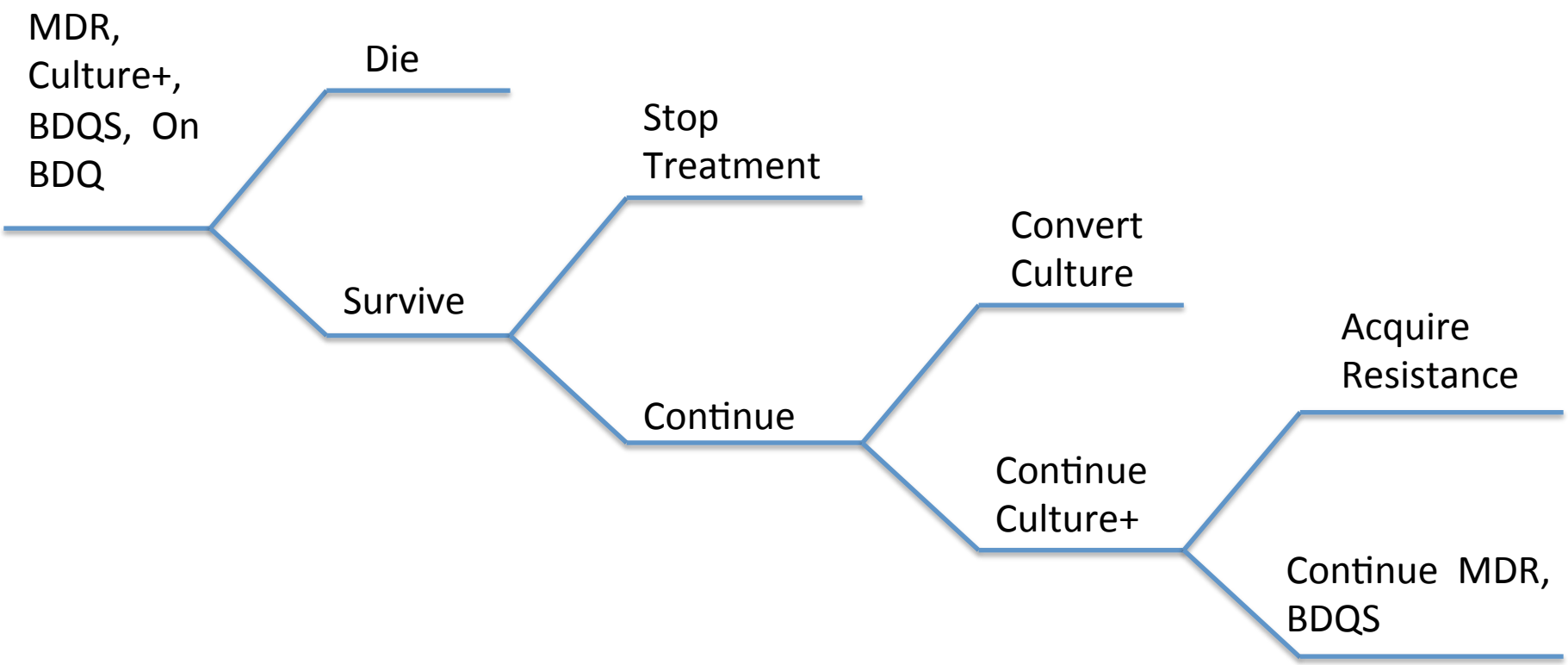
- States based on:
  - Culture status (+/-)
  - Risk of relapse after treatment end (high/low risk)
  - Regimen (BR, BR+bedaquiline, or no treatment)
  - Resistance (MDR, pre-XDR, and XDR +/- bedaquiline resistance)

Transitions



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- We assume the parameters not related to bedaquiline use are known with certainty; we assign conservatively wide uniform distributions to bedaquiline related parameters

Primary Results

Policy	Outcome of Interest					
BDQ Available for	Maximize Health	Minimize Acquired Resistance			Minimize Secondary Cases	
	Life Expectancy	XDR	BDQR	XDR+BDQR	Total Number	Life Years Lost To
None	22.6%	0.0%	100.0%	100.0%	0.0%	*0.0%
XDR Only	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%
PreXDR+XDR	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%
All MDR	76.8%	100.0%	0.0%	0.0%	100.0%	100.0%

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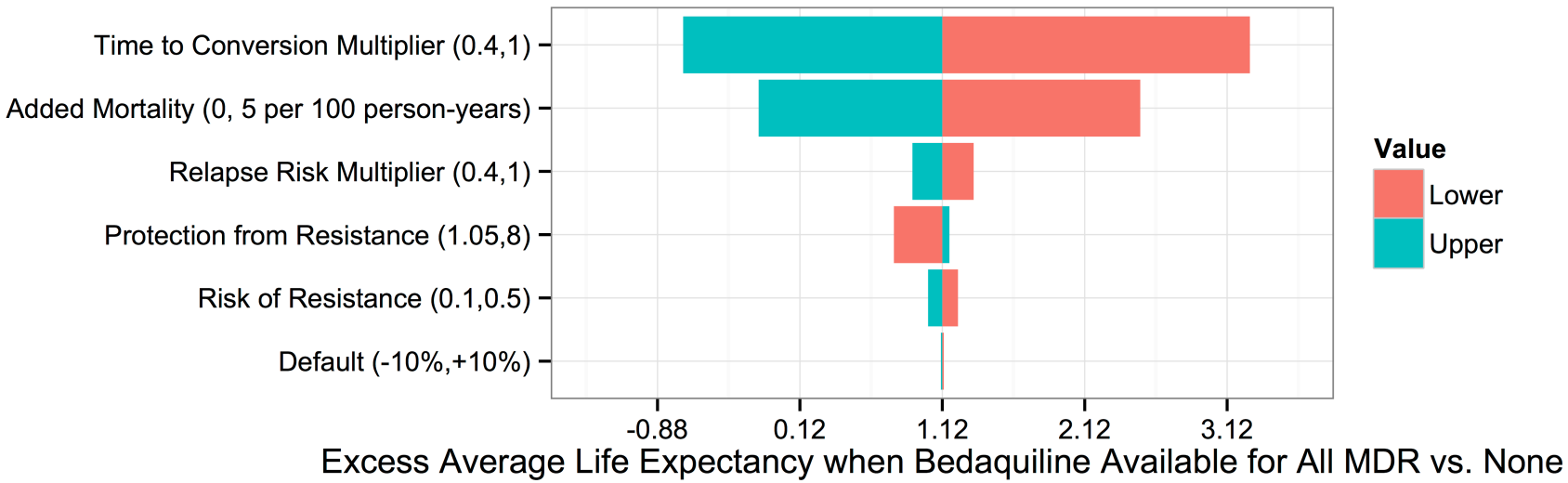
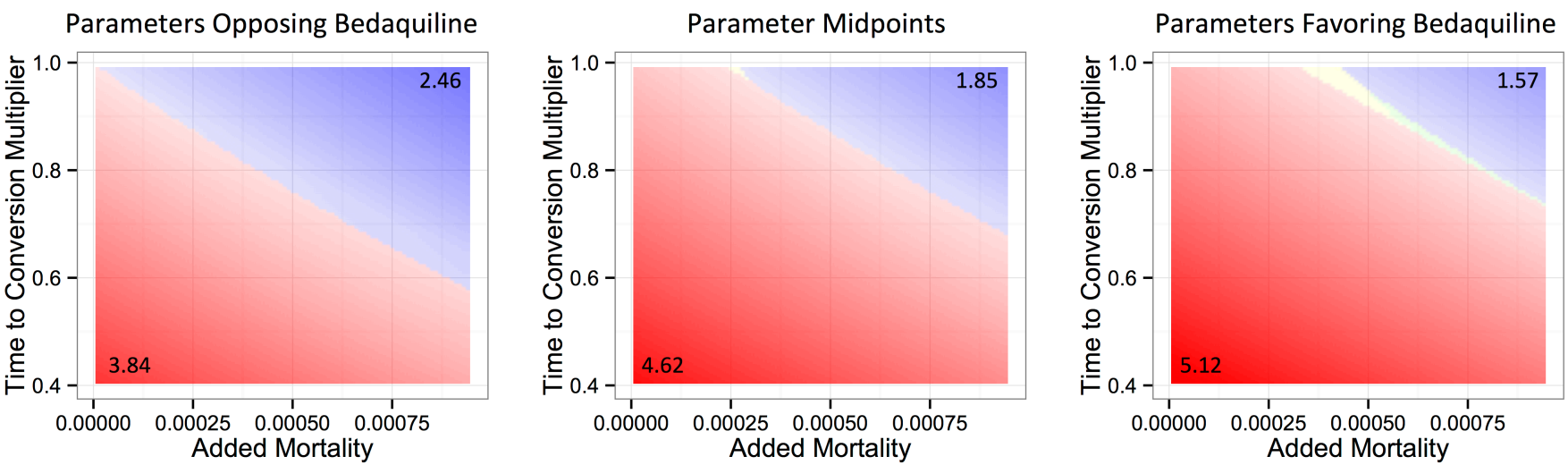
Life Expectancy Sensitivity





Primary Results – Excluding "No Bedaquiline"

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	Life Expectancy	XDR	BDQR	XDR+BDQR	Total Number	Life Years Lost To
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PreXDR+XDR	1.1%	0.0%	0.0%	85.6%	0.0%	0.0%
All MDR	78.1%	100.0%	0.0%	3.6%	100.0%	100.0%

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PreXDR+XDR	1.1%	0.0%	0.0%	85.6%	0.0%	0.0%
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- More liberal bedaquiline use policies would lead to greater resistance to bedaquiline, less resistance to other drugs
  - Appears that an intermediate strategy would minimize the "untreatable" combination XDR+bedaquiline resistance, but effect sizes are small
- More widespread bedaquiline use would likely decrease transmission and extend the life expectancy of potential secondary cases

Acknowledgements

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