LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Modelling the impact of shortened TB treatment: why such variation?

Gwen Knight

Overview

- What drives the impact of a shorter-course regimen?
- Example of a 4 month regimen (“REMox”)
- Variation across modelling results
- Implications

Why me?

- TB Alliance funded project
  - Explore potential impact of REMox as trial went along
  - Modelling of impact on transmission
  - Cost-effectiveness modelling of REMox using patient data from trial sites

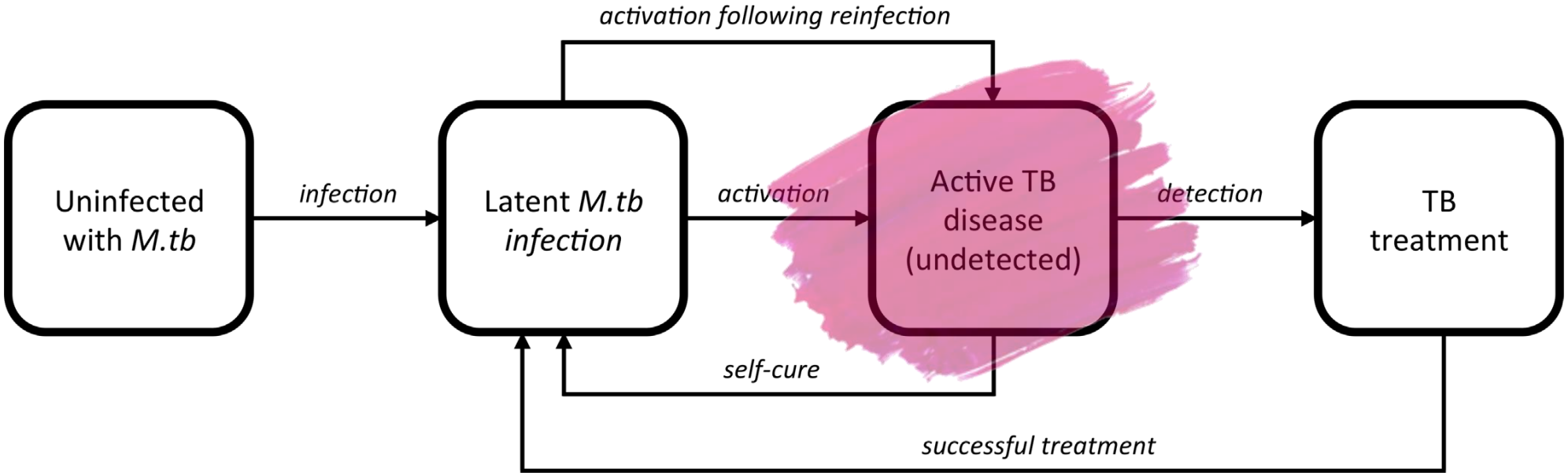
- Transmission modelling suggested:
  - Impact on cases / deaths of 4mo regimen (2015-2035): < 3%

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

(Knight et al., PLoS One, 2015)

Modelling TB spread

- Dynamic TB models = more TB if more people with infectious TB
- People on treatment = non-infectious

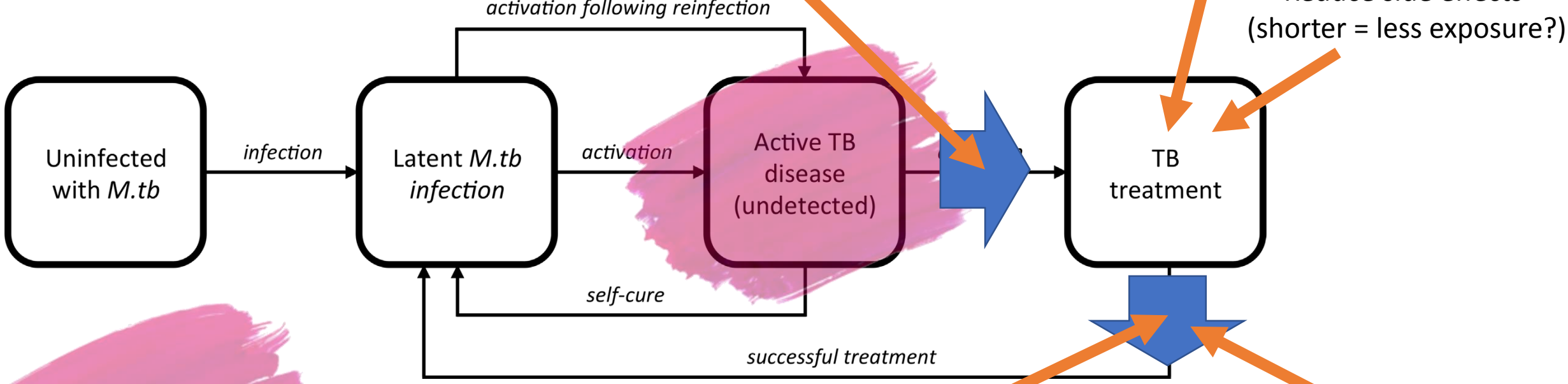


Impact of “shorter-course” regimen

Improve uptake of treatment
(shorter = easier / less burden)

Reduce patient
burden and costs

Reduce side effects
(shorter = less exposure?)



Only one reduces active TB disease

Improve completion rates
(better adherence as shorter?)

Improve “cure” rates
(better drugs?)

What might a new shorter-course regimen do?

DEFINITELY

- Reduce patient burden and costs

MAY

- Improve “cure” rates
- Improve completion rates
- Improve uptake of treatment
- Reduce side effects (shorter = less exposure?)

What might a new shorter-course regimen do?

DEFINITELY

- ~~Reduce patient burden and costs~~

MAY

- Improve “cure” rates
- Improve completion rates
- Improve uptake of treatment
- ~~Reduce side effects (shorter = less exposure?)~~

What might a new shorter-course regimen do?

DEFINITELY

- ~~Reduce patient burden and costs~~

MAY

- Improve "cure" rates *(more who finish, cured)*
- Improve completion rates *(more finish)*
- Improve uptake of treatment *(more start)*

Unknown size

- ~~Reduce side effects (shorter = less exposure?)~~

(Knight *et al.*, 2015)

Impact: 4month regimen, total cases over 20yrs = < 3%

Model duration of treatment completed

"REMox"

(Knight et al, PLoS One, 2015)

What might a new shorter-course regimen do?

DEFINITELY

- ~~Reduce patient burden and costs~~

Unknown size

MAY

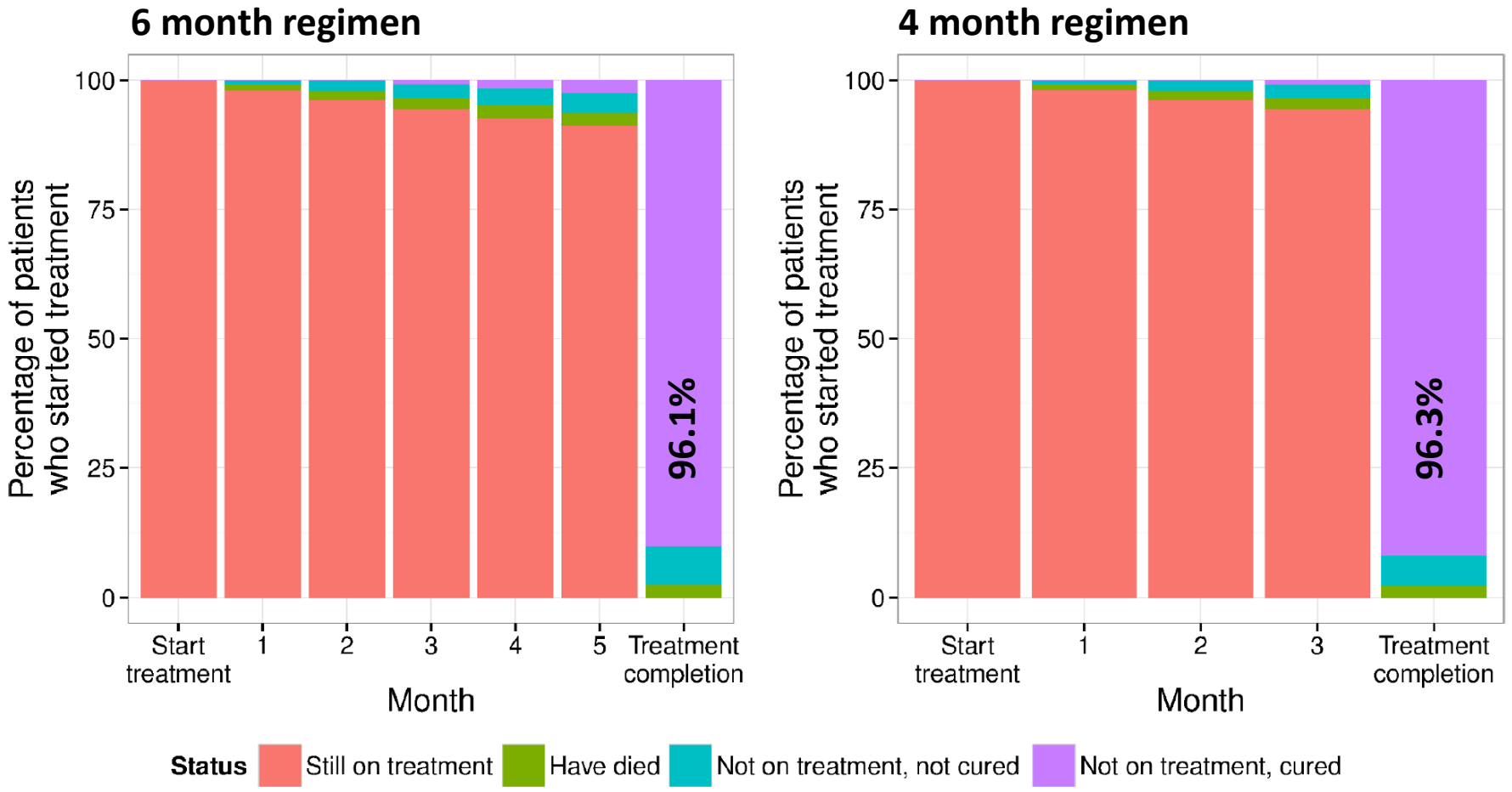
- Improve "cure" rates
- Improve completion rates
- Improve uptake of treatment
- ~~Reduce side effects (shorter = less exposure?)~~

Assumed:
SC same efficacy but divided over 4 not 6mo

Assumed:
SC prevents defaulters at mo 5/6 (but no deaths in months 5/6)

Impact: 4month regimen, total cases over 20yrs = < 3%

(Knight *et al.*, 2015)



Short course assumed to:

(1) Have same efficacy, but over 4mo not 6mo

(2) Increase proportion completing treatment ("saves" those that default at mo5/6)

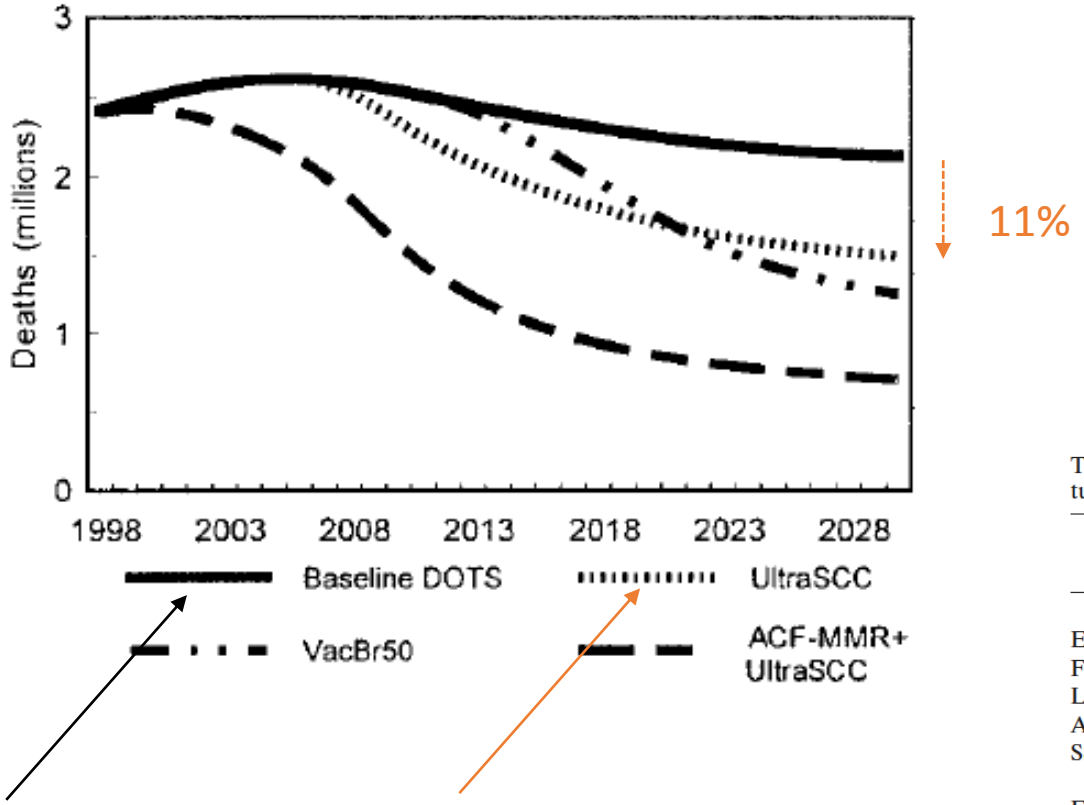
- "Non-inferior" assumptions
- Assumed scale-up of treatment and continuing background improvements in TB control

97% cured if complete, 1.5% default rate

(Knight et al, PLoS One, 2015)

Impact: Single dose, total cases over 32yrs = 11%

(Murray & Salomon, 1998)



DOTS-M = baseline (existing "medium HIV projections and BCG efficacy)

Single dose treatment

Short course assumed to:
(1) Increase cure rates to 95% within 10 years

Table 1. Case-detection and cure rates for new smear-positive tuberculosis cases in three DOTS scenarios, 1995 and 2020

Region	1995 rate, %	2020 rate, %		
		DOTS-H	DOTS-M	DOTS-L
		Smear-positive case-detection rate		
EME	91	96	95	94
FSE	70	96	90	81
LAC/MEC	64	83	80	78
Asia	50	70	62	56
SSA	35	70	50	45
		Smear-positive cure rate		
EME	86	98	95	93
FSE	70	95	90	85
LAC/MEC	67	88	85	82
Asia	50	80	62	56
SSA	50	80	75	68

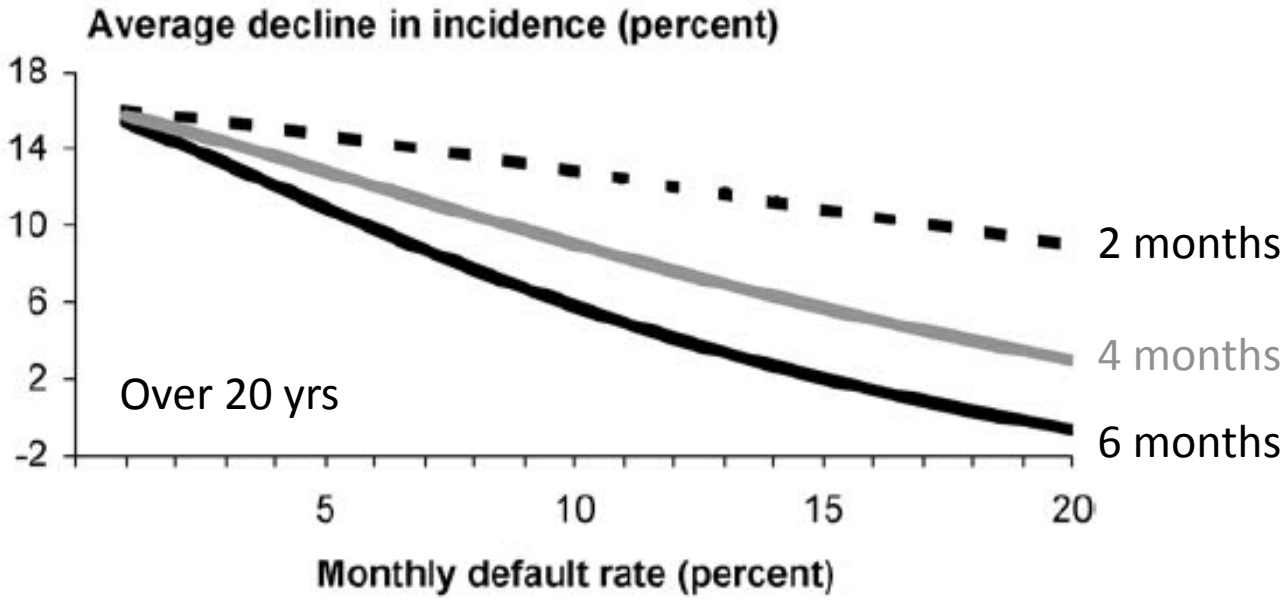
DOTS-H, high uptake; DOTS-M, medium uptake; DOTS-L, low uptake.

Baseline cure rate ranges from
50 – 86% in 1995
56 – 98% in 2020

(Murray & Salomon, PNAS, 1998)

Impact: 2month regimen, incidence at 18yrs = 40% [23-51%]

(Salomon *et al.*, 2006)



Impact greater when default higher
(compare distance between lines)

Short course assumed to:

(1) Increase cure rates (by not having the default and death at later months: assumed same default rates per month and same failure rates at end)

Cure probabilities

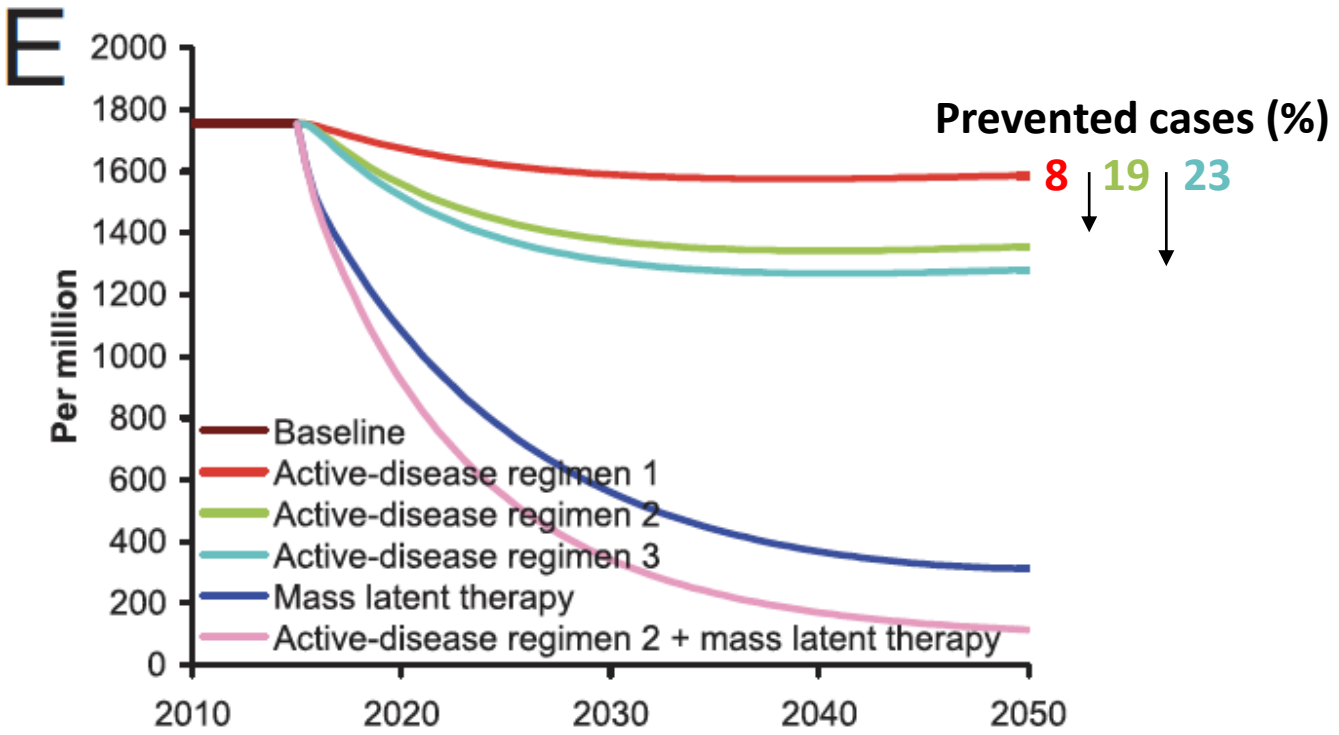
(same default / mortality / cure at end rates)

	Standard	**Shorter (2mo)**
DOTS program	85%	93%
Non-DOTS program	50%	80%

(Salomon, PLoS Med, 2006)

(Abu-Raddad *et al.*, 2009)

Impact: 4month regimen, total cases over 35yrs = 8%
[2month regimen + DR impact, total cases over 35yrs = 19%
10 days + DR impact, total cases over 35yrs = 23%]



Active disease treatment regimens

1. 4 months
2. 2 months + 90% efficacy against drug-resistant strains
3. 10 days + 90% efficacy against drug-resistant strains

Short course assumed to:
(1) Increase treatment success proportion

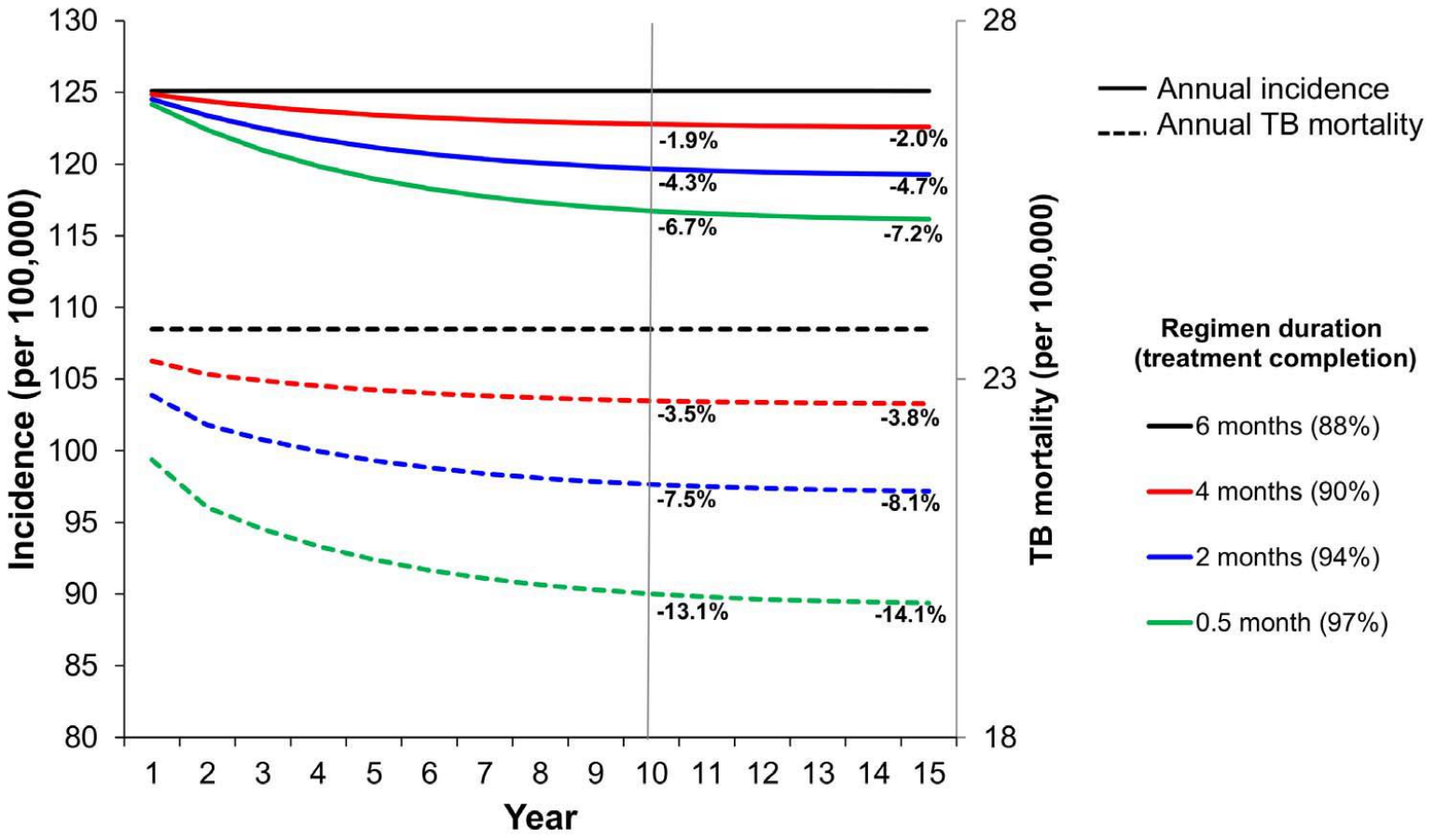
Factor = relative shortening = relative reduction in treatment failure

(Abu-Raddad, PNAS, 2009)

(Fofana *et al.*, 2014)

Impact: 4month regimen, incidence at 10yrs = 2%
2month regimen, incidence at 10yrs = 4%
0.5 month, incidence at 10yrs = 7%

Model duration of treatment completed



Short course assumed to:

(1) Increase treatment completion *(REMox)*

(2) Same efficacy by completion of stage of treatment = greater proportion of total treatment *(REMox)*

(3) Avert mortality in later months of therapy (not in *REMox*)

(Fofana, PLoS One, 2014)

Summary

* Improved uptake of treatment not modelled

Reference
(1) Murray, 1998
(4) Fofana, 2014
(2) Salomon, 2006
(4) Fofana, 2014
(3) Abu-Raddad, 2009
(4) Fofana, 2014
(5) Knight, 2015

Implications

- Impact of shorter course higher when default rates higher

  (if assume shorter course avoids later default)
  - Explored in Salomon, Fofana, Knight
  - Explains big difference in Fofana vs. Salomon (latter has higher default)

- Treatment success proportion important
  - e.g. Abu-raddad 84% vs. 89%, Knight: 96.1% vs. 96.3%

Conclusions

- If “on treatment” non-infectious, then unlikely that a shorter-course regimen would have effect on transmission
  - Unless default rates high
  - Unless treatment success / cure rates much higher for shorter-course

=> “Just” improve adherence / success of current regimens?

- Impact of shorter-course on uptake not taken into account in models so far
- Variation in impact due to
  - Outcome indicator
  - Time frames
  - Uncertainty in effect & effect size of shorter-course regimen

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- “REMox” modelling team: Anna Vassall, Richard White, Gaby Gomez, Frank Cobelens, David Dowdy, Alice Zwerling
- Pete Dodd
- TB Alliance (then), USAID (now): William Wells

Salomon vs Fofana

Salomon

Cure probabilities		
	Standard	**Short**
DOTS program	85%	93%
Non-DOTS program	50%	80%

Monthly default rates : 1.5% (DOTS), 7.5% (non-DOTS)
Failure probabilities at finish: 3% (DOTS), 6% (non-DOTS)
constant

Different levels of DOTS / non-DOTS included over time

Fofana

Table 1. Model inputs for TB treatment outcomes, by treatment phase.

Outcome	Treatment phase					Reference(s)
	Week 0–2	*Week 3–8*	*Month 3–4*	*Month 5–6*	*Total*	
Duration	2 weeks	6 weeks	2 months	2 months	2 weeks-6 months	
Percentage defaulting (sensitivity analysis range)	0.2% (0–1.0%)	1.9% (0–4.1%)	2.7% (0–5.7%)	2.2% (0–4.8%)	7.0% (2–15%)	[1,6]
Percentage dying (sensitivity analysis range)	1.1% (0.5–2.1%)	1.3% (0.6–2.5%)	0.8% (0.4–1.7%)	0.8% (0.4–1.7%)	4.0%	[1,28–30]
Percentage completing treatment period	98.7%	96.8%	96.5%	96.9%	-	
Cumulative percentage remaining in therapy	98.7%	95.0%	92.1%	89.0%	89.0%	

98% probability of cure if finish

By time of impact measurement