Emergence of Resistance to BDQ: Considerations from a Modeling Perspective

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

David Dowdy

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BDQ Resistance: Five Considerations

1. Resistance levels will plateau.
2. BDQ resistance is emerging at a comfortable rate.
3. BDQ resistance reflects other regimen components.
4. Resistance can be lowered with effective treatment.
5. Long-term uncertainty remains high.

1. Resistance levels will plateau.

- As early as the 1960s, resistance to INH and streptomycin had stabilized in many places.
  - TB incidence in France (1968): 74 per 100,000

- Similar patterns have been seen with all other TB drugs.

Tubercle, (1972), **53**, 57

ORIGINAL ARTICLES

TRENDS IN THE PREVALENCE OF PRIMARY DRUG RESISTANCE IN PULMONARY TUBERCULOSIS IN FRANCE FROM 1962 TO 1970: A NATIONAL SURVEY

By G. Canetti, Ph. Gay and M. Le Lirzin

Table V.—Primary Resistance to the 3 Main Drugs-Isoniazid, Streptomycin and Pas in Each Year.

Year	No. of strains	Resistance to: Isoniazid No.	Isoniazid %	Streptomycin No.	Streptomycin %	PAS No.	PAS %	1 drug No.	1 drug %	2 drugs No.	2 drugs %	3 drugs No.	3 drugs %	Total resistant No.	Total resistant %
1962 + 1963	1,385	54	3·9	104	7·5	24	1·7	89	6·4	33	2·4	9	0·7	131	9·5
1964	1,325	80	6·0	117	8·4	38	2·7	97	7·3	35	2·6	22	1·7	154	11·6
1965	1,565	54	3·5	116	7·4	19	1·2	115	7·4	28	1·8	7	0·5	150	9·6
1966	1,455	58	4·0	109	7·5	13	0·9	95	6·5	33	2·3	6	0·4	134	9·2
1967	1,430	65	4·6	96	6·7	30	2·1	79	5·5	41	2·9	10	0·9	130	9·1
1968	1,570	68	4·3	126	8·0	34	2·2	120	7·6	30	1·9	16	1·0	166	10·6
1969	1,527	67	4·4	124	7·9	27	1·7	107	7·0	36	2·4	13	0·8	156	10·2
1970	1,386	55	3·9	90	6·5	15	1·1	95	6·8	25	1·8	5	0·4	125	9·0
Total	11,643	501	4·3	882	7·6	200	1·7	797	6·8	261	2·2	88	0·8	1146	9·8

1. Resistance levels will plateau.

OPEN ACCESS Freely available online

PLoS one

Quantifying the Burden and Trends of Isoniazid Resistant Tuberculosis, 1994–2009

Helen E. Jenkins[1,2*], Matteo Zignol[3], Ted Cohen[1,4]

Ou et al. Infect Dis Poverty (2021) 10:24
https://doi.org/10.1186/s40249-021-00803-w

Infectious Diseases of Poverty

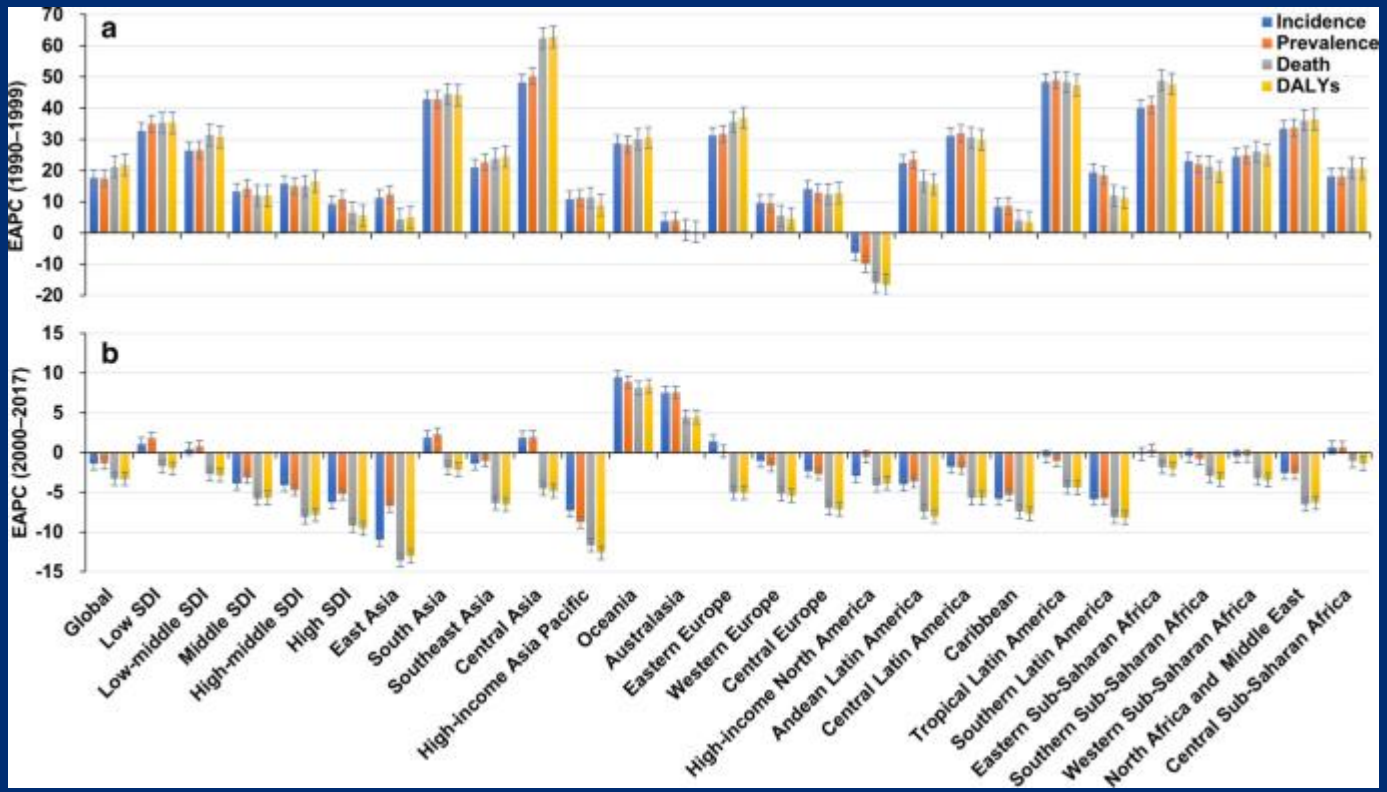
RESEARCH ARTICLE Open Access

Trends in burden of multidrug-resistant tuberculosis in countries, regions, and worldwide from 1990 to 2017: results from the Global Burden of Disease study

Ze-Jin Ou[1†], Dan-Feng Yu[2†], Yuan-Hao Liang[1], Wen-Qiao He[1], Yong-Zhi Li[1], Ya-Xian Meng[1], Hu-Sheng Xiong[1], Min-Yi Zhang[1], Huan He[1], Yu-Han Gao[1], Fei Wu[1] and Qing Chen[1*]

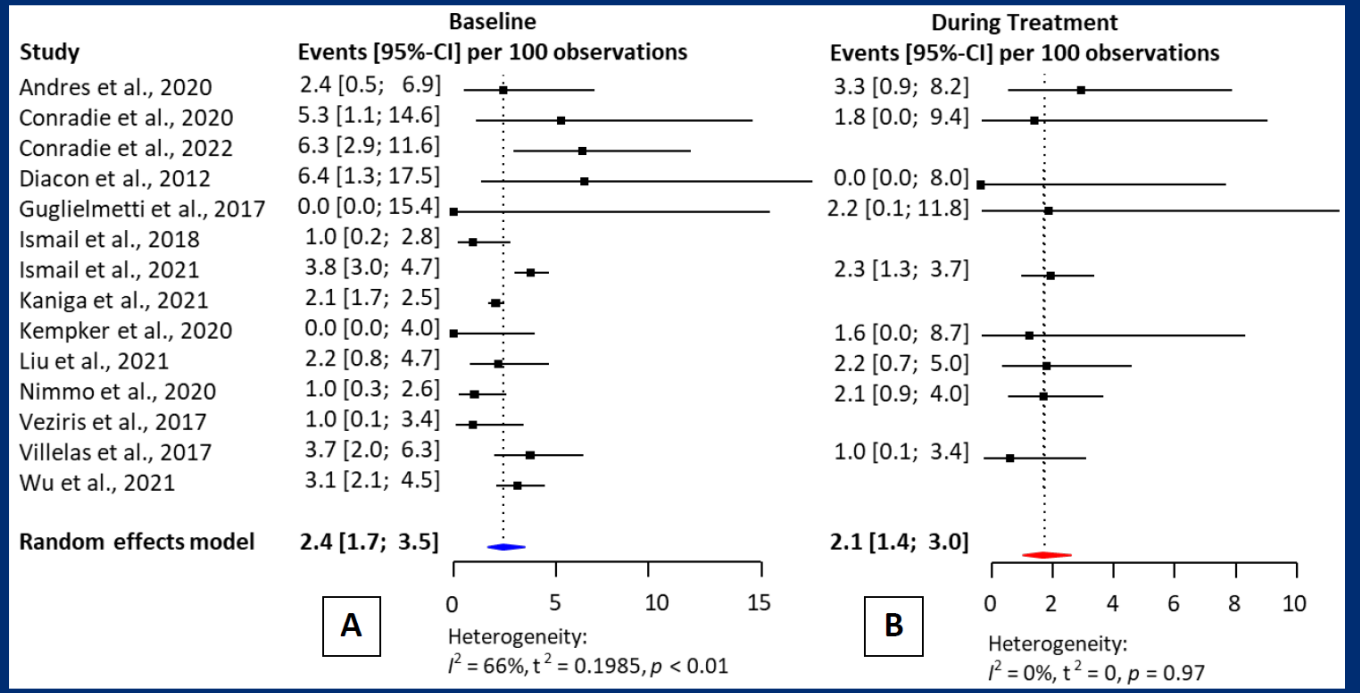
Estimated number of new TB cases with INH-R per 100,000 population

	% of new TB cases with INH-R: Down	No consistent linear trend		Up
Down		Latvia Lithuania Belgium	Denmark Portugal Slovenia	
No consistent linear trend	Hong Kong Israel	Cuba Puerto Rico Uruguay Qatar Estonia Nepal Thailand New Zealand Singapore Ivanovo Oblast – RF Andorra Bosnia and Herzegovina Croatia	Cyprus Iceland Ireland Italy Luxembourg Malta Montenegro Netherlands Norway Poland Serbia Slovakia Switzerland	Peru Canada Oman Austria Czech Republic Finland France Germany
Up		USA		Botswana Republic of Korea Arkhangelsk Oblast – RF Tomsk Oblast – RF[a] Sweden UK



2. BDQ resistance is emerging at a comfortable rate.

- Acquired BDQ resistance seen in ~2 per 100 treatments.
  - Despite being used to treat highly drug-resistant TB
- RIF: ~0.5 per 100 treatments, if treated w/ 3 effective drugs
  - ~3 per 100 if INH lost



Perumal R et al. medRxiv 2023; Eur Respir J 2023; 62:2300639
Menzies D et al. PLOS Med 2009; 6:e1000146

3. BDQ resistance reflects other regimen components.

- Across four trials including pretomanid in the regimen:
  - Only 3 cases of acquired BDQ resistance, of 859 participants (0.4-1.0 per 100)
  - Similar to levels of acquired RIF resistance with 3 effective drugs

Trial	Participant	Regimen	Acquired resistance	Outcome[1]
Nix TB	NX018	BPaL	BDQ	Unfavorable; confirmed relapse at Day 267 (83 d after last dose)
ZeNix	ZX026	$BPaL_{600x9}$	PMD	Unfavorable; withdrawn during treatment; treatment failure
	ZX079	$BPaL_{600x26}$	BDQ, PMD	Unfavorable; non-compliant patient who withdrew consent during treatment
	ZX146	$BPaL_{1200x9}$	PMD	Unfavorable; confirmed relapse at Day 539 (182 d after last dose)
SimpliciTB	ST058	6BPaMZ	BDQ, PMD	Unfavorable; withdrawn during treatment; investigator/sponsor decision prompted by patient's poor drug compliance
	ST455	6BPaMZ	PMD	Unfavorable; confirmed relapse at Day 222 (42 d after last dose)

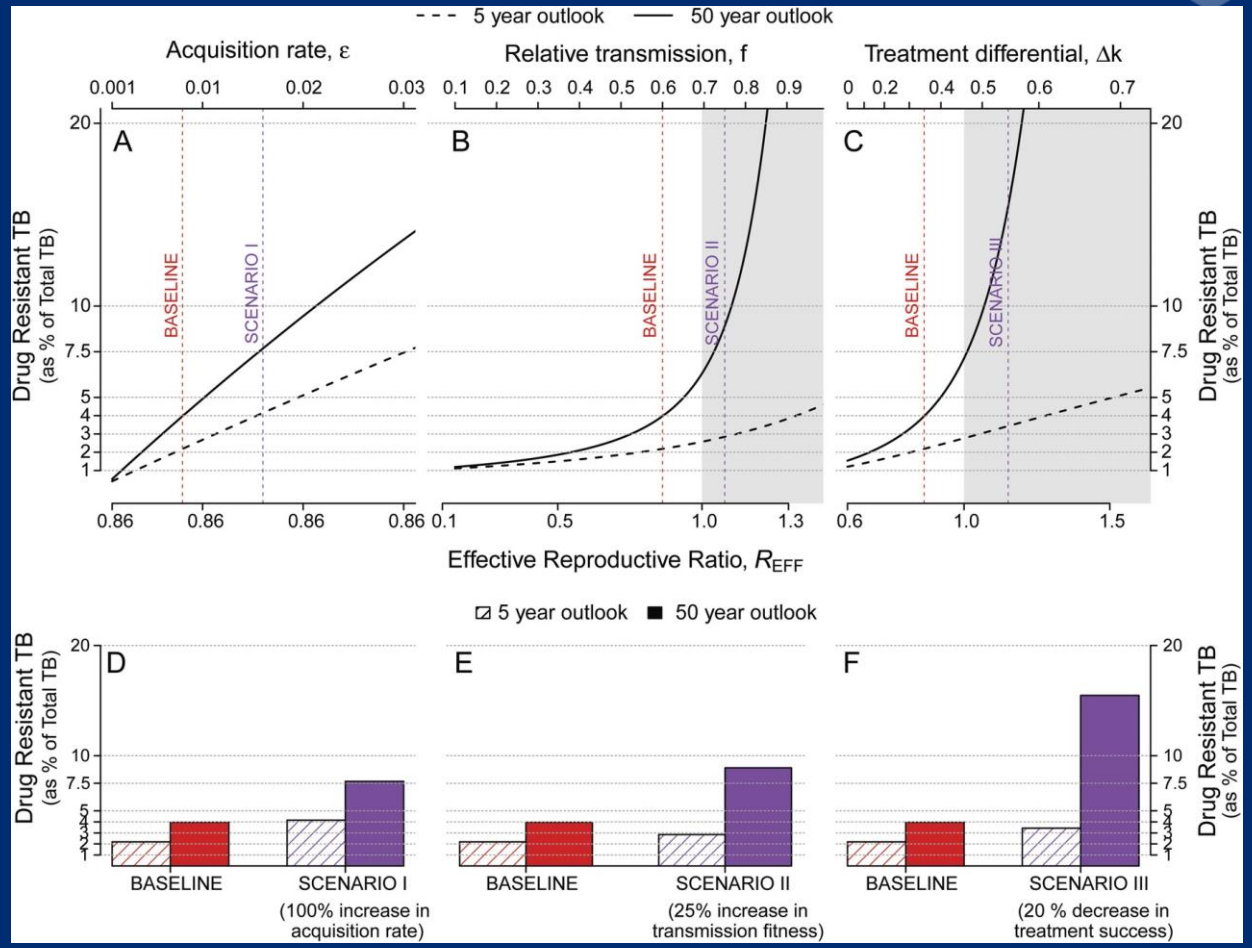
[1]Outcomes and abbreviations are as described in Table 3.

https://doi.org/10.1371/journal.pgph.0002283.t004

Timm J et al. PLOS Glob Public Health 2023; 3:e0002283

3. BDQ resistance reflects other regimen components.

- Most important long-term driver of drug resistance: <u>differential in treatment success</u>
  - BDQ-R vs BDQ-S
- Best safeguard: Use regimens that will be effective if BDQ-R.

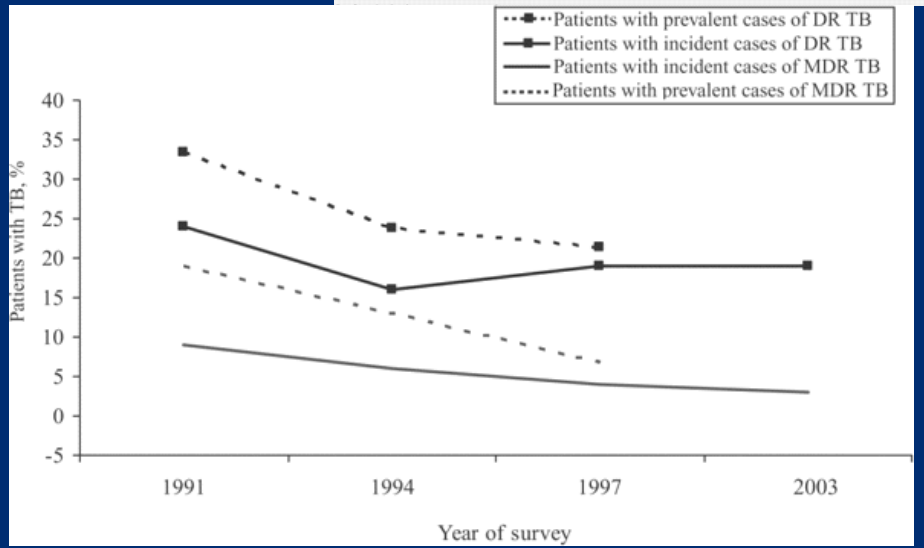


Shrestha S et al, Open Forum Infect Dis 2014; 1:ofu073

4. Resistance can be lowered with effective treatment.

- South of Vietnam, 1996-2001:
  - Any resistance: 36% → 26%
  - RR-TB: 4.5% → 2.0%
- New York City, 1991-2003:
  - Any resistance: 34% → 22%
  - MDR-TB: 19% → 7%

Drug-resistance pattern	No. (%) 1996 (*n* = 374)	2001 (*n* = 888)	*P*
Susceptible to all 4 drugs	239 (63.9)	650 (73.8)	<.01
Resistance to any drug	135 (36.1)	238 (26.3)	<.01
Any resistance to			
H	81 (21.6)	154 (16.6)	>.05
R	17 (4.5)	22 (2.0)	>.05
E	5 (1.3)	12 (1.1)	>.05
S	110 (29.4)	173 (19.4)	<.01
Monoresistance to			
H	20 (5.3)	59 (6.3)	>.05
R	3 (0.8)	1 (0.1)	>.05
E	0 (0)	0 (0)	>.05
S	50 (13.4)	82 (9.5)	>.05
Total	73 (19.5)	142 (15.9)	

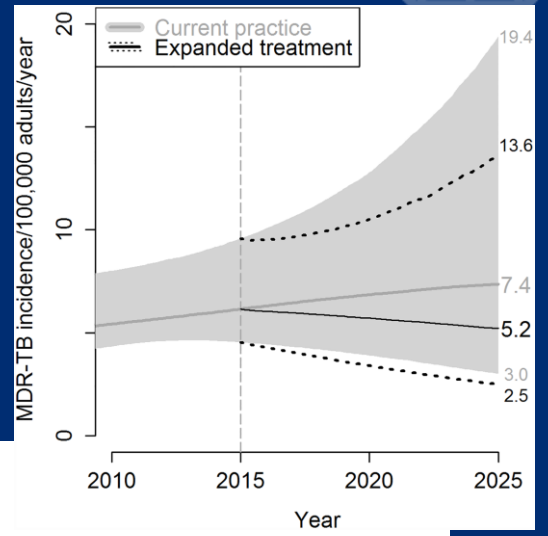


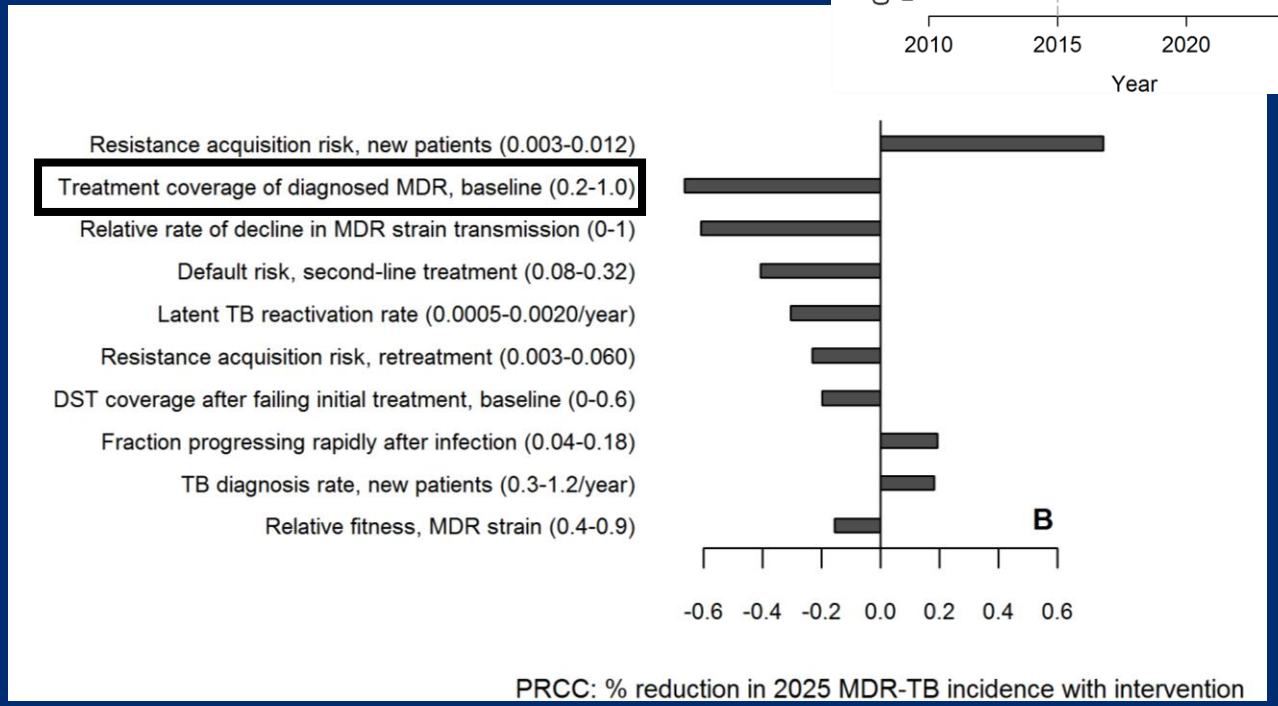
Huong NT et al, J Infect Dis 2006; 194:1226-1232
Munsiff SS et al, Clin Infect Dis 2006; 42:1702-1710

4. Resistance can be lowered with effective treatment.

- Most important determinants of MDR emergence:
  - Rate of acquired resistance
  - Treatment coverage of people with MDR-TB

- Key: Ensure that people w/ BDQ-R TB are diagnosed & treated.

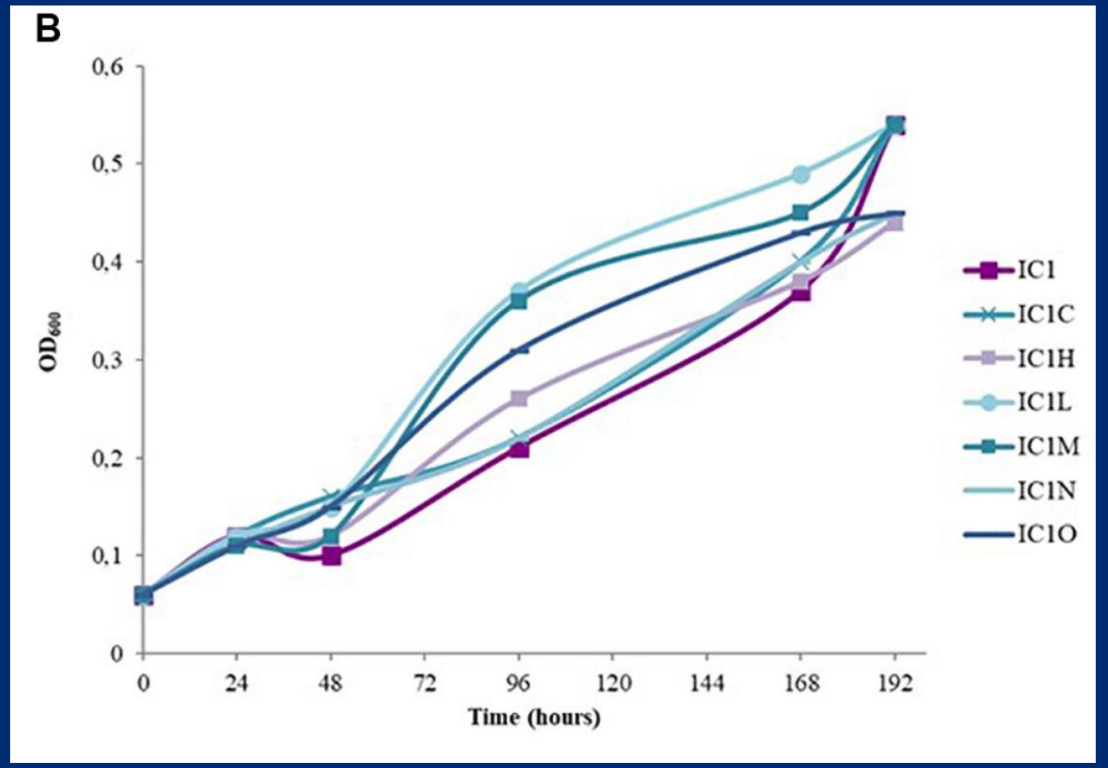




Kendall EA et al, PLOS ONE 2017; 12:e0172748

5. Long-term uncertainty remains high.

- Major outstanding questions:
  - Transmission fitness
  - Acquisition of resistance under programmatic conditions
  - Resistance to other drugs used in BDQ-containing regimens
  - Variation by location, strain, etc.



Degiacomi G et al, Front Microbiol 2020; 11:559469

Summary: A Modeler's Take on BDQ Resistance

- Short-term indications are reassuring.
- Longer-term uncertainty is high.
- Effective diagnosis and treatment of people with BDQ-R TB is a priority.
- Decisions should be driven not by fear, but by rational assessment of uncertainty.