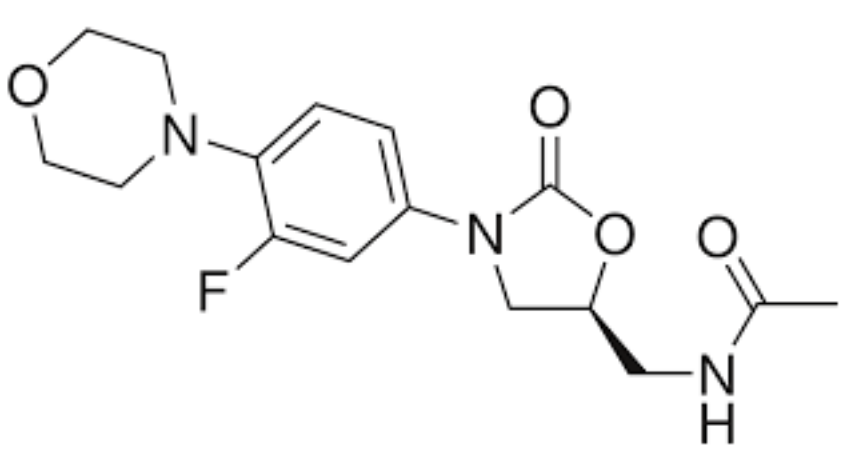
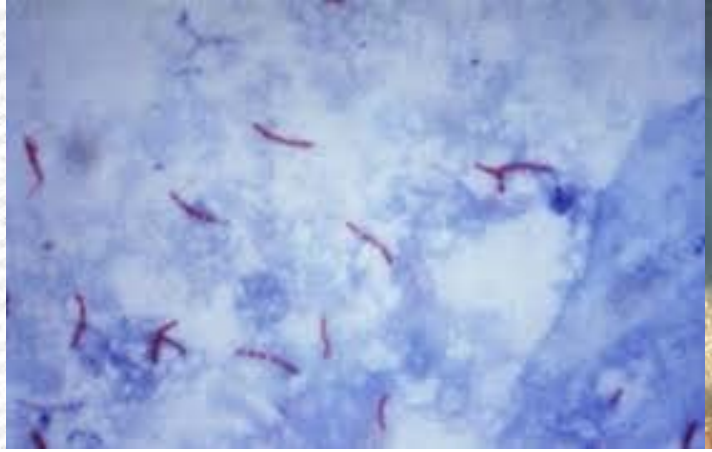





Linezolid for TB

MRC C2HTB Symposium 2017

Sean Wasserman

UCT

“Confronted with such an astronomical computation of distress, it is clear that tuberculosis is very far from being defeated…Indeed, in underdeveloped countries it is often said that little can be done until the standard of living is raised. One can hardly accept that”

John Crofton

Royal College of Physicians lecture, 1960

Multiple trials of new DR-TB regimens

Trial	Phase	Patients	Design	Primary end point
NExT (NCT02454205)	Phase 2 to 3	MDR-TB, adults *n* = 300	Open-label RCT of an injection-free regimen including linezolid[a] and bedaquiline (plus standard drugs without kanamycin) for 6–9 months compared with WHO standard regimen	Favorable outcome at 24 months
Nix-TB (NCT02333799)	Phase 3	MDR- and XDR-TB, adults *n* = 200	Open-label, single-arm evaluation of bedaquiline and pretomanid plus linezolid[b] for 6–9 months	Bacteriologic or clinical failure at 24 months
endTB (NCT02754765)	Phase 3	MDR-TB, adults *n* = 750	Open-label RCT of five all-oral experimental regimens compared with standard of care. Experimental regimens contain bedaquiline and/or delamanid together with four companion drugs, including linezolid[c]	Favorable outcome at 18 months
TB-PRACTECAL (NCT02589782)	Phase 2 to 3	MDR-TB, adults *n* = 630	Open-label RCT comparing three novel regimens including bedaquiline, pretomanid, and linezolid[d], plus moxifloxacin or clofazimine for 6 months with WHO standard of care	Culture conversion and discontinuation/death at 8 weeks, unfavorable outcome at 72 weeks
MDR-END (NCT02619994)	Phase 3	MDR-TB, adults *n* = 238	Open-label RCT comparing a 9–12-month regimen of delamanid, linezolid[e], levofloxacin, and pyrazinamide with WHO standard or care	Treatment success at 24 months

LZD in clinical practice

- When do you use it?

We don’t really know

- What is the optimal dose and dosing interval?

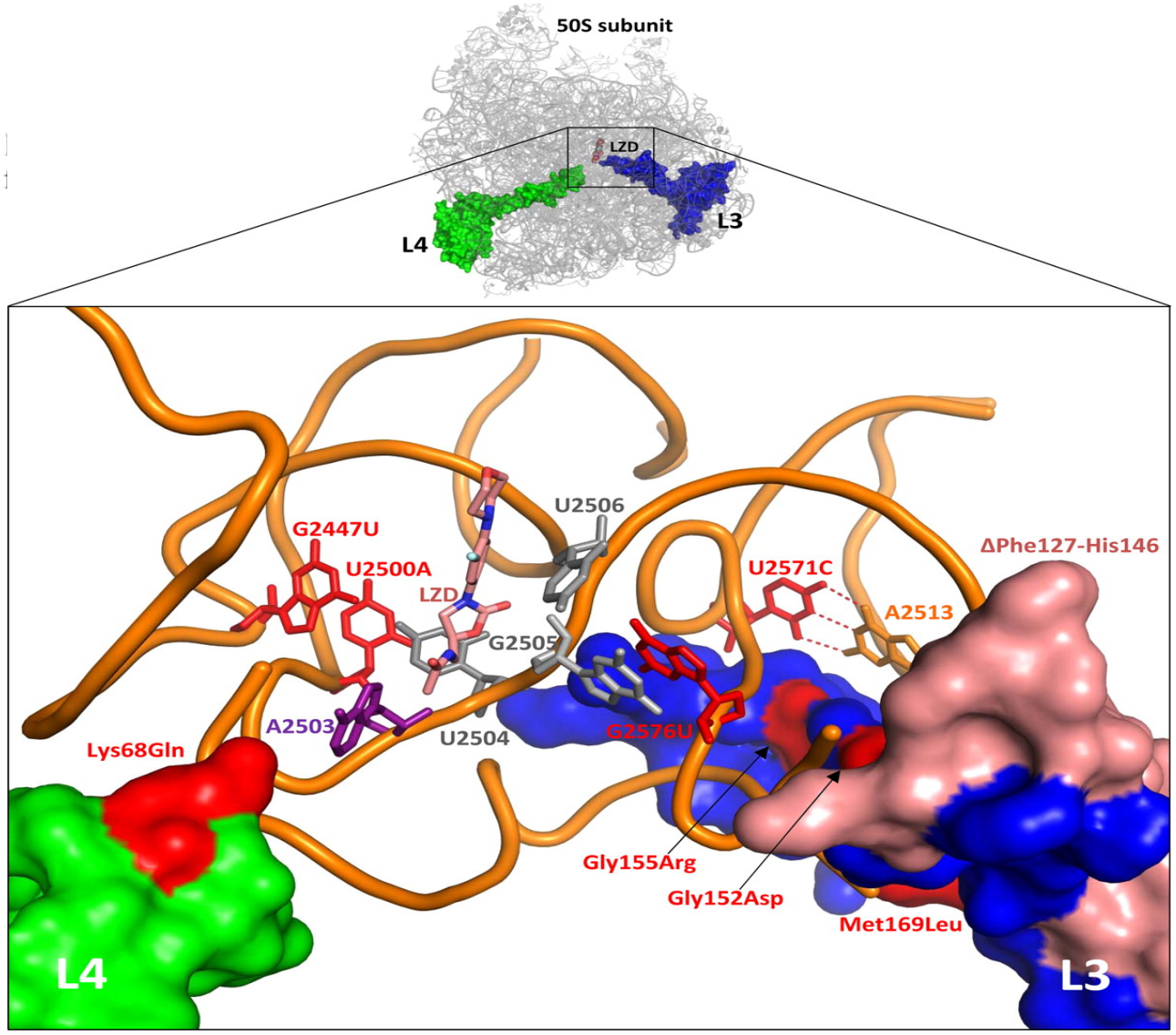
We don’t know

- How do you define LZD resistance and it is a problem?

We don’t really know

LZD is a potent anti-TB drug

- Unique mechanism of action
- Blocks translation of mRNA and protein synthesis
- No cross-resistance with other anti-TB drugs



Livermore JAC 2003
Locke JAC 2009

LZD is a potent anti-TB drug

- Excellent *in vitro* activity: DS- and DR-TB
- MICs ≤ 1 mg/L in clinical strains
- Recommended susceptibility breakpoint 1 mg/L

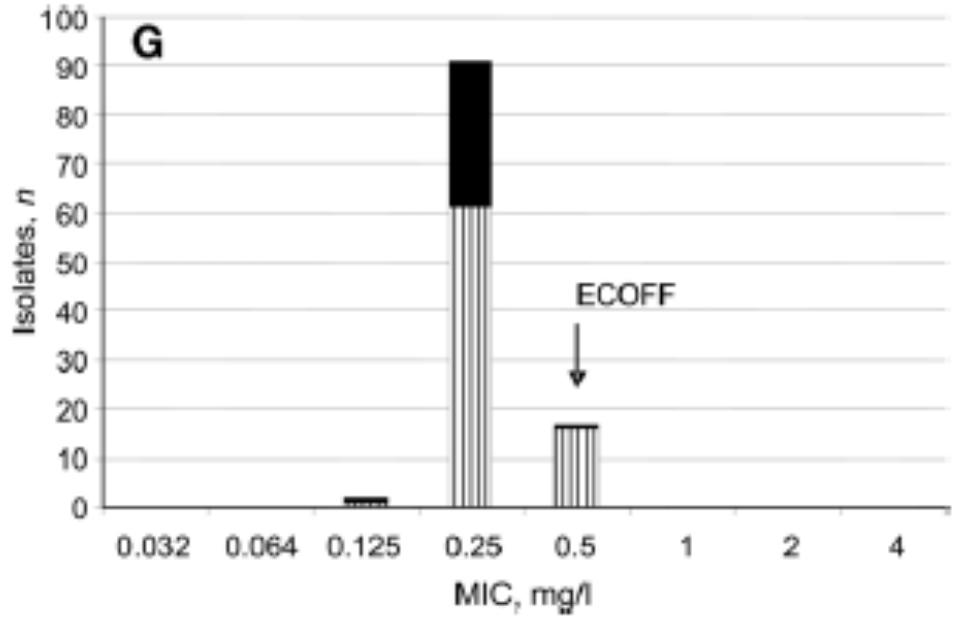


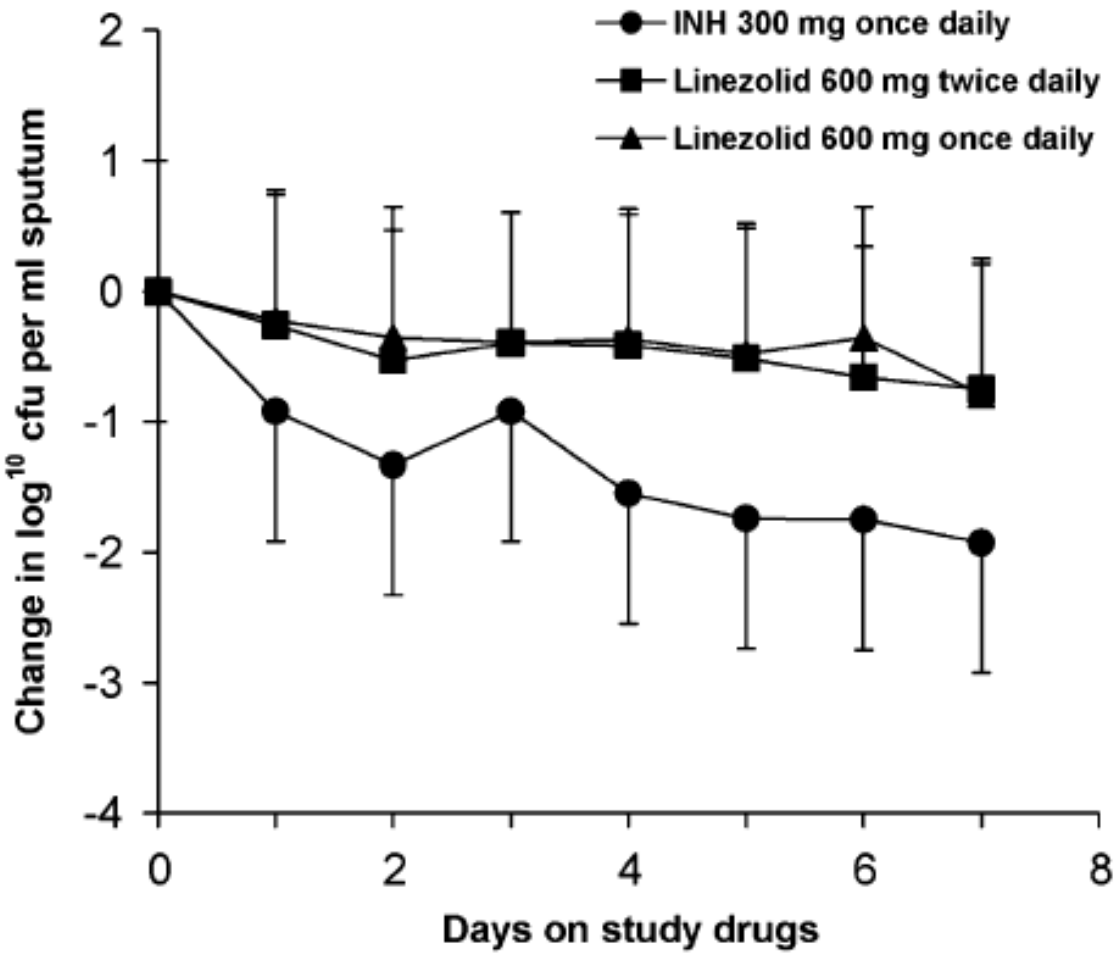
TABLE 1. In vitro activities of linezolid against 117 clinical isolates of *M. tuberculosis*[a]

M. tuberculosis isolates (no. of isolates)	MIC (μg/ml)			
	Range	50%	90%	Geometric mean
Susceptible to first-line drugs (73)	0.25–1	0.5	0.5	0.524
Resistant to first-line drugs (44)	≤0.125–1	0.5	1	0.477
Resistant to one first-line drug (25)	≤0.125–1	0.5	1	0.529
Resistant to multiple first-line drugs (19)	0.25–1	0.5	0.5	0.417
All (117)	≤0.125–1	0.5	1	0.506

Alcala AAC 2003
Schon IJTLD 2011

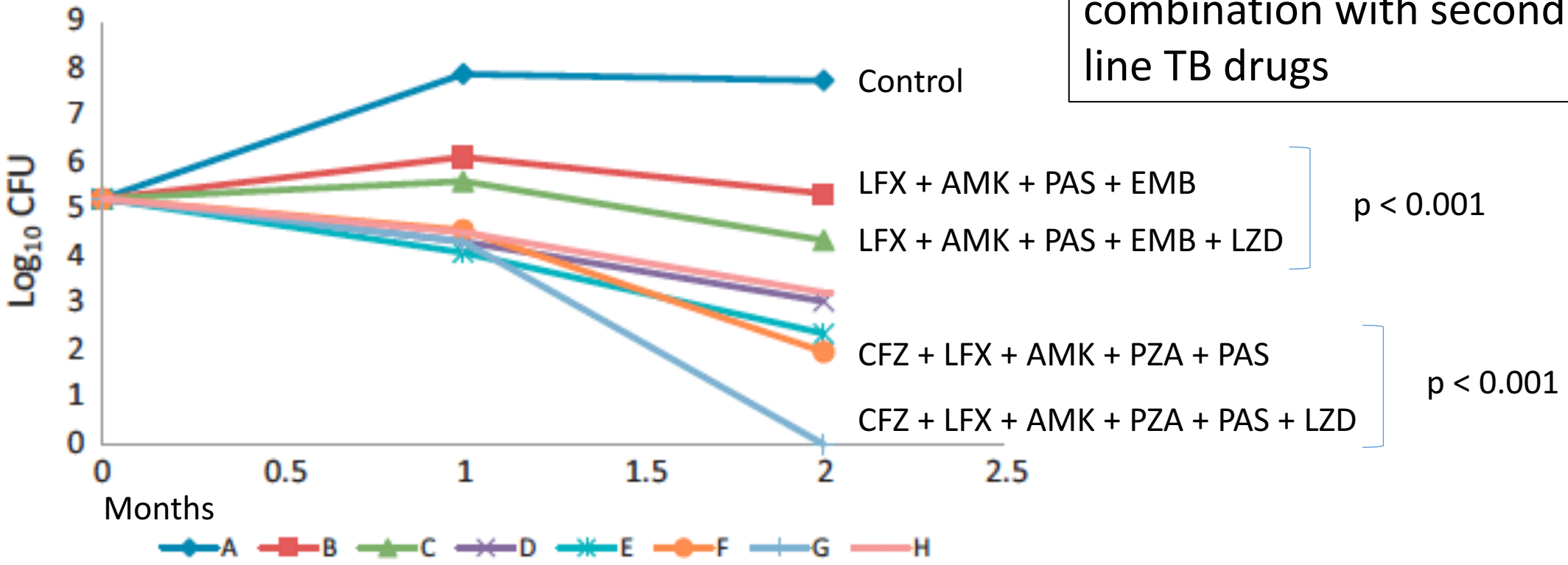
Modest EBA in humans

- Mostly in exponential growth phase
- Less than INH (Δ in CFU)
  - But mean EBA not different at 600 BD
- No difference between LZD doses (not powered)
- No correlation with PK in this study
- Poor extended EBA activity suggesting limited sterilising ability



Dietze AJRCCM 2008

Sterilizing ability in mouse model; bactericidal against non-replicating MTB strains



Lung sterilization in combination with second line TB drugs

Zhao IJAA 2014

Potent activity when added to new drugs in mice

- Superior sterilising activity to first line drugs when combined with BDQ/PMD (and increases activity of BDQ+PMD)
- Also reduces relapse when added to BDQ/PMD/PZA for **1 or 2 months**

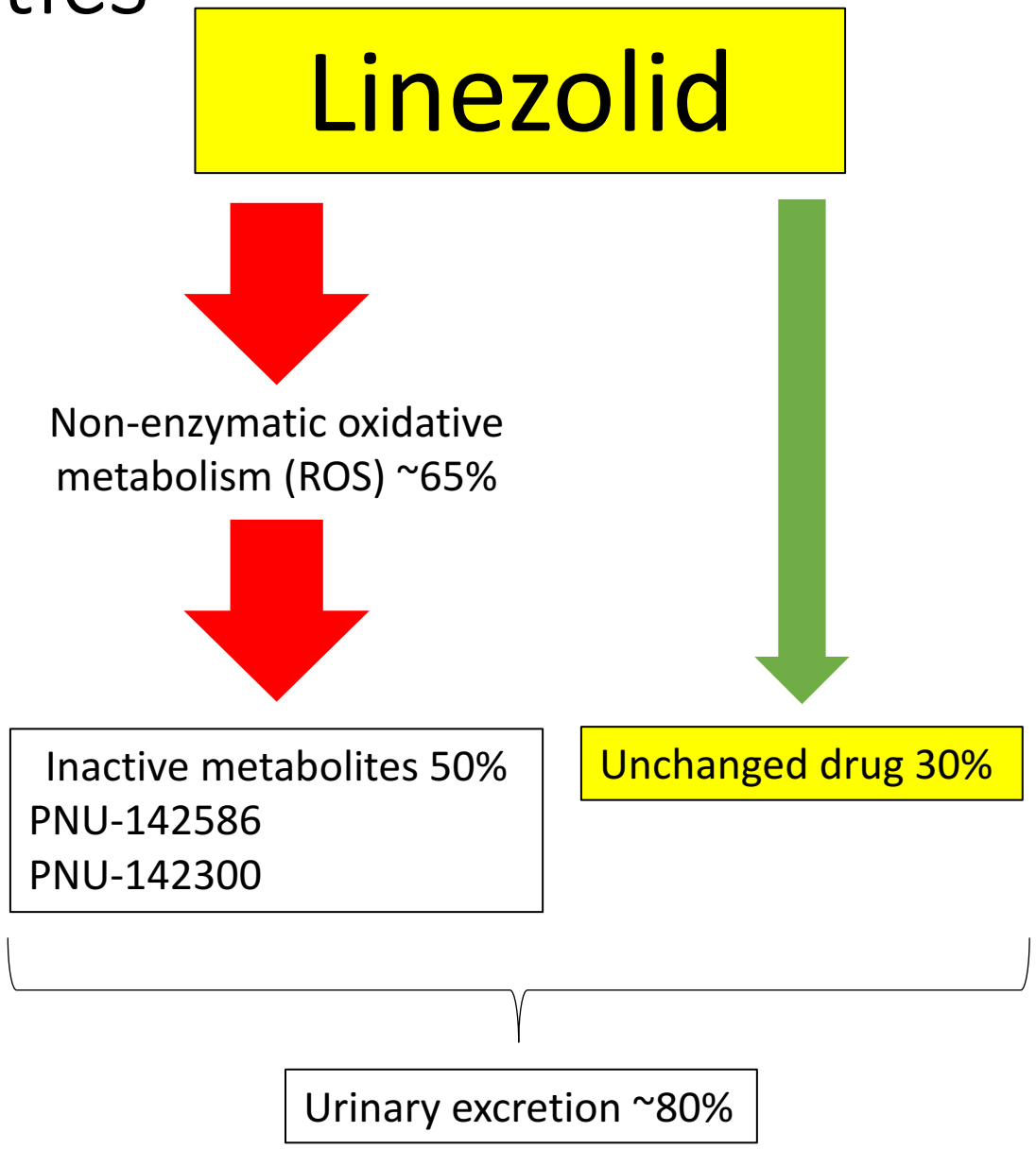
Tasneen AAC 2016

	Mean (±SD) $\log_{10}$ CFU count at[a]:					Proportion (%) relapsing after treatment for:		
Drug regimen	D13	D0	M1	M2	M3	2 mo	3 mo	4 mo
Untreated	2.69 ± 0.13	6.17 ± 0.27	6.47 ± 0.06					
2RIF+INH+PZA/RIF+INH			3.47 ± 0.37	1.59 ± 0.25	0.50 ± 0.51		13/15 (87)	1/20 (5)
BDQ			3.24 ± 0.25					
PMD			4.57 ± 0.22					
LZD			4.97 ± 0.26					
SZD			3.85 ± 0.37					
BDQ+PMD			4.21 ± 0.40	1.62 ± 0.19	0.52 ± 0.36	15/15 (100)	10/15 (60)	2/20 (10)
BDQ+LZD			2.82 ± 0.15	1.91 ± 0.66				
BDQ+SZD			2.88 ± 0.07	0.65 ± 0.50				
PMD+LZD			3.23 ± 0.41	1.48 ± 0.12				
PMD+SZD			1.65 ± 0.33	0.23 ± 0.40				
BDQ+PMD+LZD			3.28 ± 0.65	0.34 ± 0.41	0.00 ± 0.00	12/15 (80)	0/14 (0)	0/20 (0)
BDQ+PMD+SZD			0.94 ± 0.14	0.00 ± 0.00		14/20 (70)	1/14 (7)	

Favourable PK characteristics and few DDIs

- Metabolised (mainly) by non-enzymatic pathways
- Good tissue (incl lung and CSF) penetration

- Caution with:
  - SSRIs
  - PGP inhibitors (macrolides)
  - CYP inducers (rif)
  - CYP inhibitors (PIs)
  - AZT



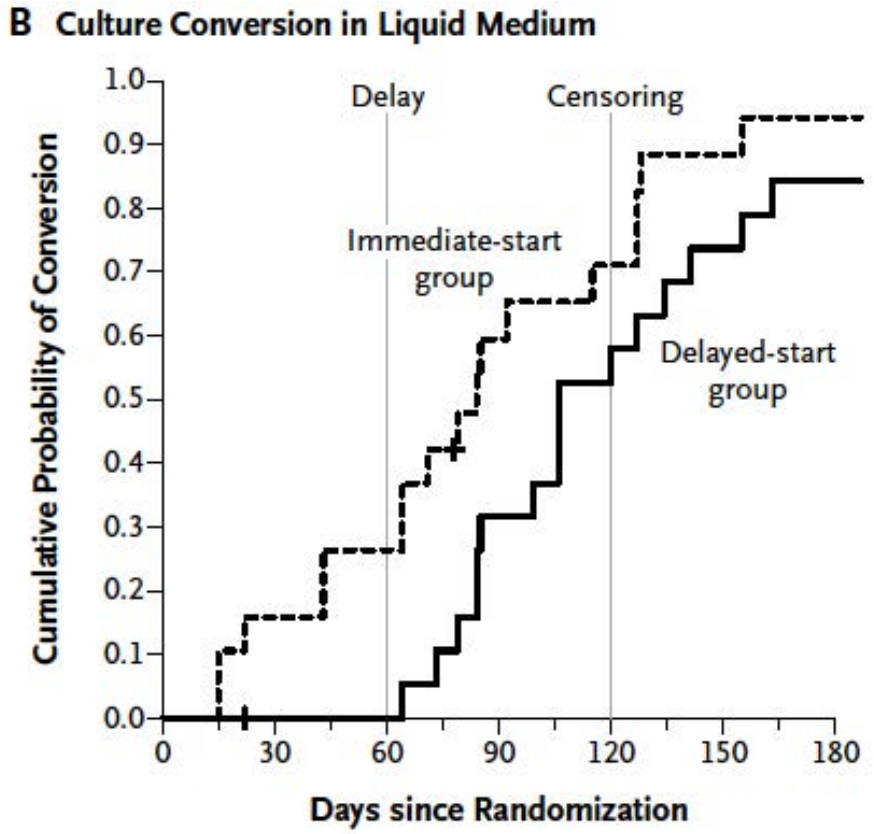
Dryden JAC 2011

Impressive clinical efficacy

ORIGINAL ARTICLE

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

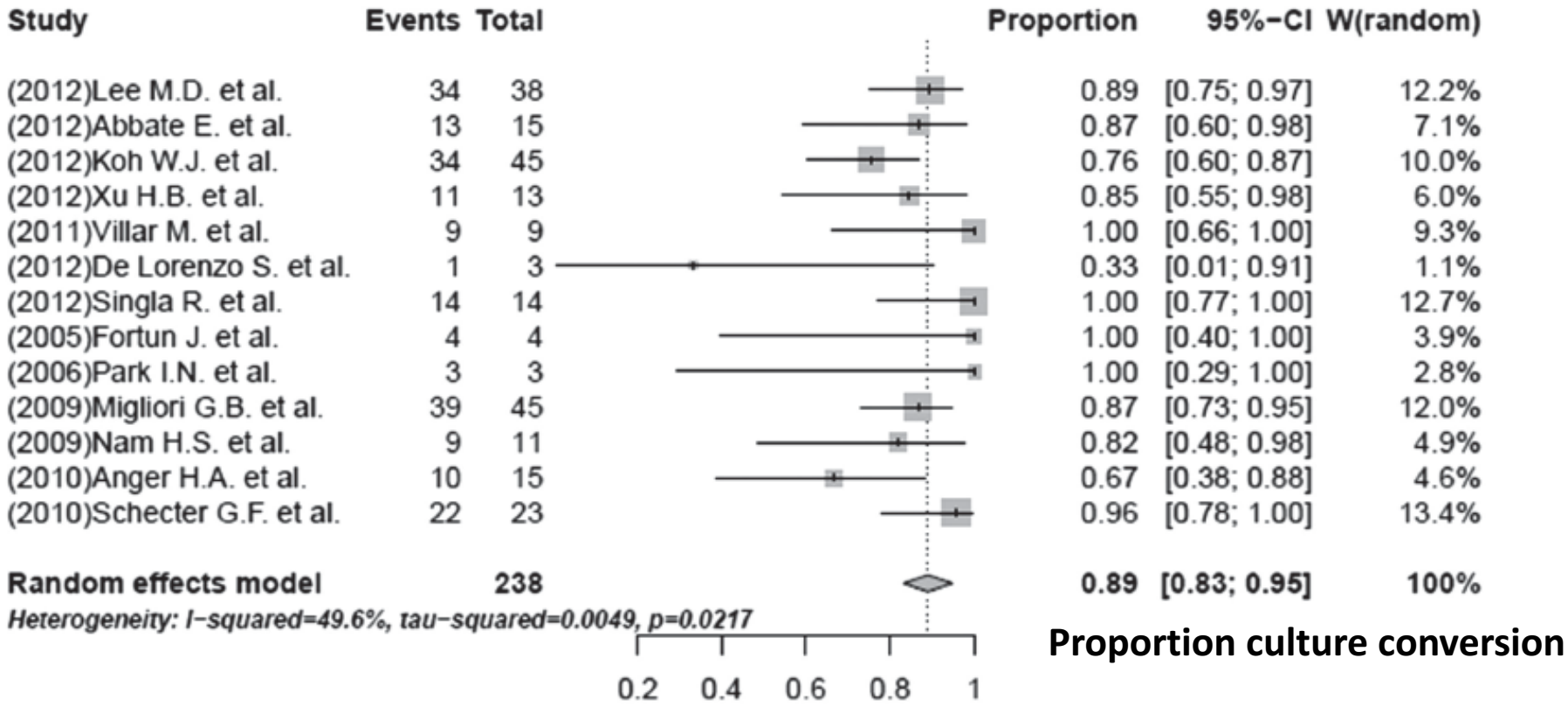
- 39 HIV-negative patients
- LZD added to failing regimen: immediate vs delayed
  - 79 vs 35% culture conversion at 4 months
  - 87% culture negative after 6 months
  - 71% cured at 1 year after completion



Lee NEJM 2012
Lee NEJM 2015

Impressive clinical efficacy

- Systematic review: 239 patients; 46% XDR; only 8.2% HIV-infected
- Favourable outcome 83% (cure/completed)



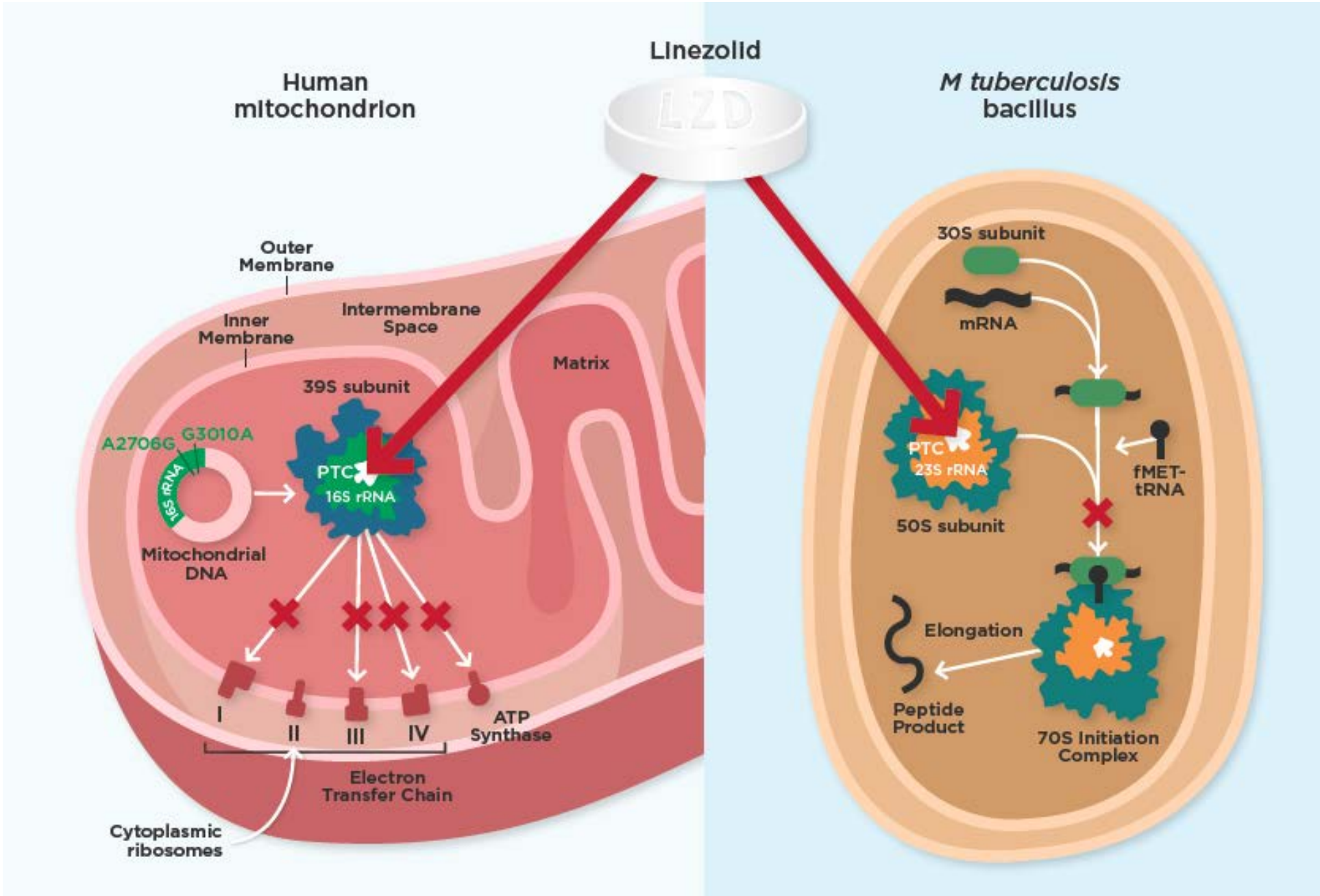
Zhang J Thorac Dis 2015

WHO treatment guidelines for drug-resistant tuberculosis

2016 update

Table 6. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

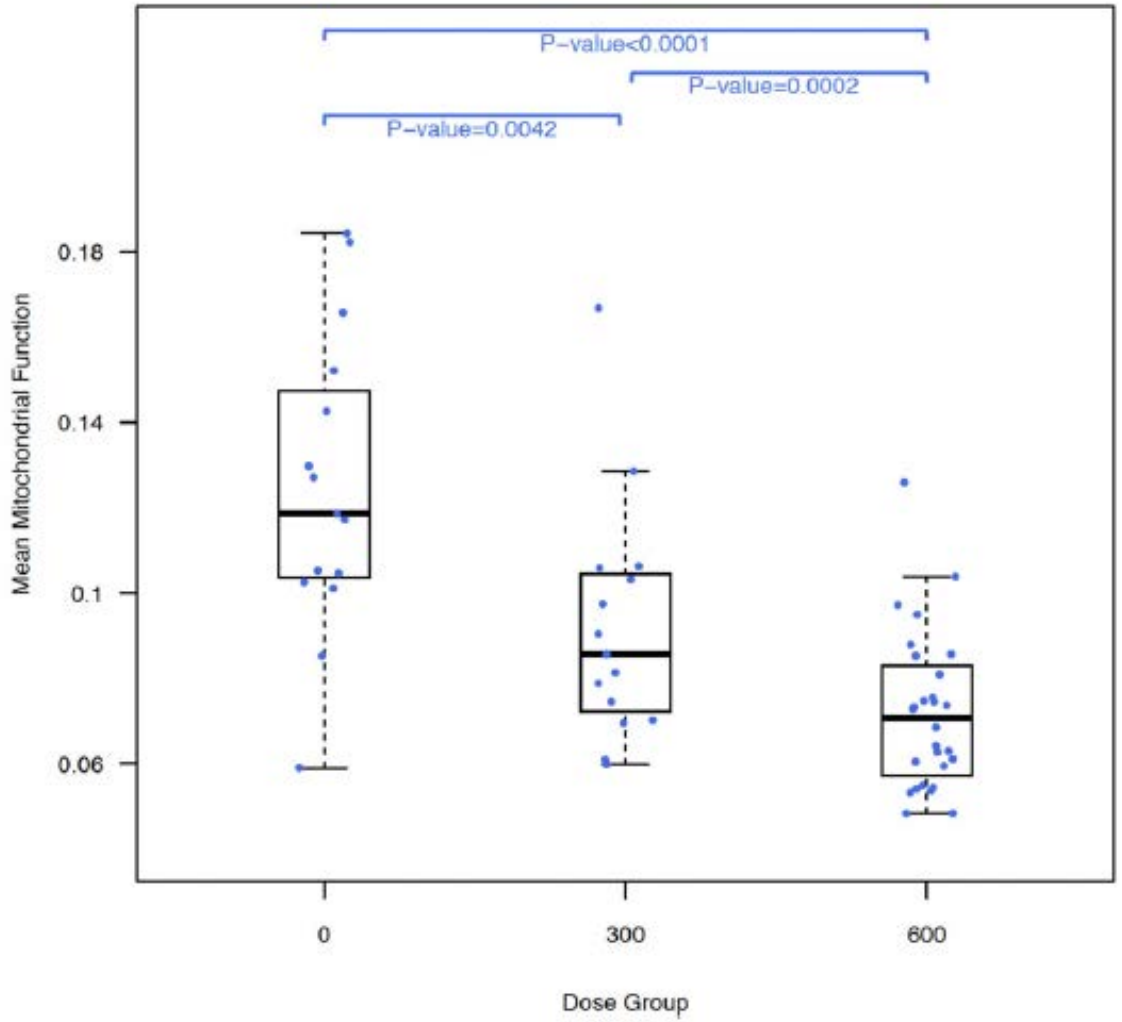


Wasserman Exp Rev Anti-infective Ther 2016

Mitochondrial toxicity dose related and associated with clinical AEs

Mitochondrial function correlates with risk of AEs in patients

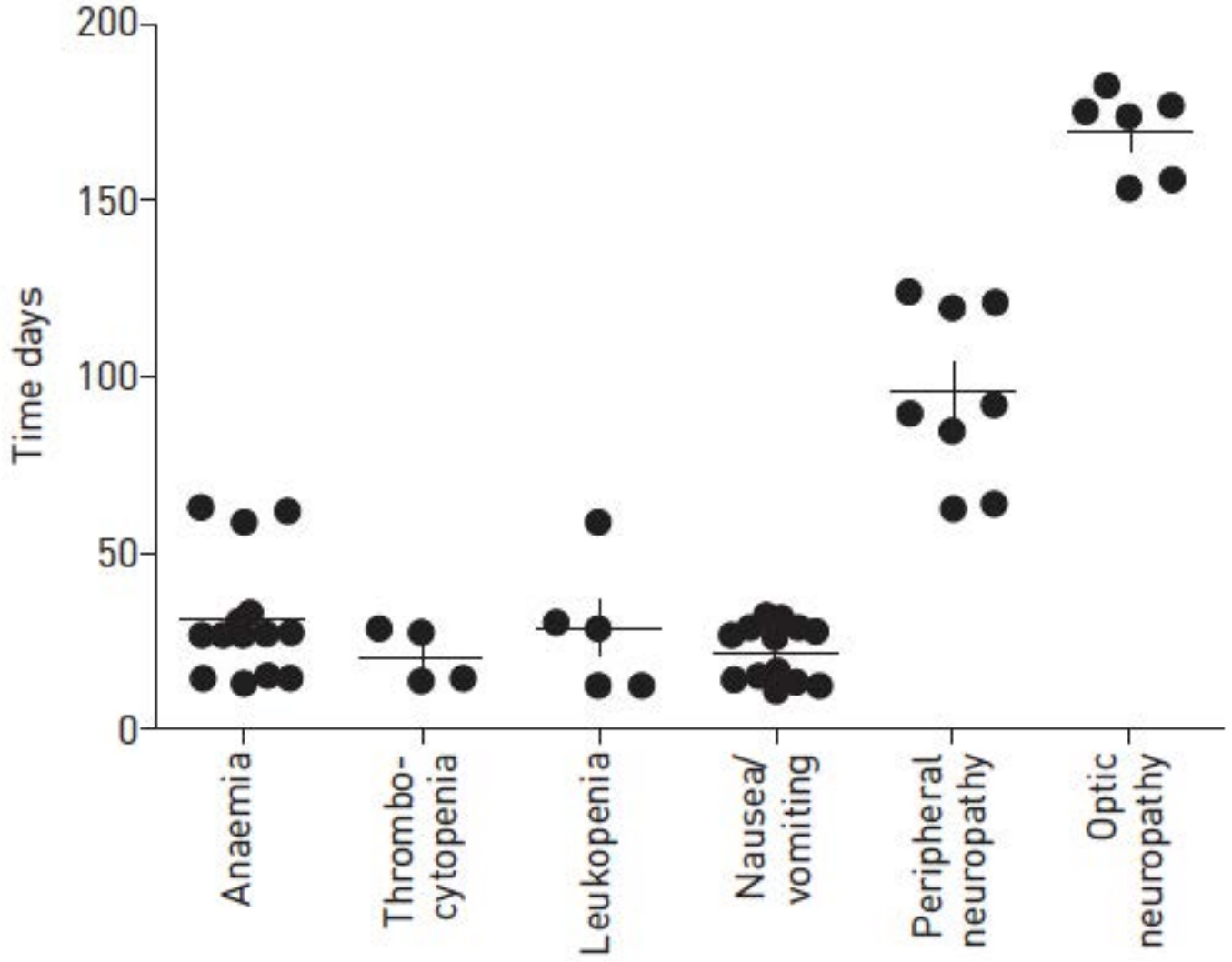
Baseline time for analysis:	Hazard ratio (95% CI)	Z-statistic	P-value
Time varying mitochondrial function and risk of AE			
Time from second randomization	0.49 (0.30, 0.93)†	−2.17	0.030
Time from linezolid initiation	0.53 (0.25, 0.93)†	−2.21	0.027



Song eBioMedicine 2015

Clinical toxicity dose and duration-related

- Chinese RCT
- 65 HIV-neg, XDR-TB
- 1200 mg/day for 4 – 6 weeks then 600/300 mg/day
- 82% AEs



Tang ERJ 2015

LZD toxicity is frequent and treatment-limiting

Variables	Total	LNZ ≤600 mg/day	LNZ >600 mg/day	P value
The number of the patients included in the systematic review, n (%)	367 (100.0)	151 (41.1)	216 (58.9)	–
Total adverse events presumably due to linezolid, n (%)	147/269 (54.6)	49/82 (59.8)	98/187 (52.4)	0.265
Major adverse events, n (%)	108/367 (29.4)	39/151 (25.8)	69/216 (31.9)	0.206
Total adverse events in nervous system, n (%)	108/367 (29.4)	65/151 (43.0)	43/216 (19.9)	0.000
Total adverse events in hematogenic system, n (%)	109/367 (29.7)	27/151 (17.9)	82/216 (38.0)	0.000
Anemia, n (%)	74/270 (27.4)	8/59 (13.6)	66/211 (31.3)	0.007
Leucopoenia, n (%)	19/262 (7.3)	8/81 (9.9)	11/181 (4.4)	0.273
Neutropenia, n (%)	3/262 (1.1)	0/81 (0.0)	3/181 (1.7)	0.244
Thrombocytopenia, n (%)	20/262 (7.6)	3/81 (3.7)	17/181 (9.4)	0.109
Pancytopenia, n (%)	4/262 (1.5)	0/81 (0.0)	4/181 (2.2)	0.178
Optic neuritis, n (%)	23/246 (8.0)	13/115 (8.6)	10/131 (7.6)	0.669
Peripheral neuropathy, n (%)	79/256 (30.9)	51/137 (37.2)	28/119 (23.5)	0.018
Gastro-intestinal disorders, n (%)	28/208 (13.5)	1/30 (3.3)	27/178 (15.2)	0.079

Zhang J Thorac Dis 2015

WHO treatment guidelines for drug-resistant tuberculosis

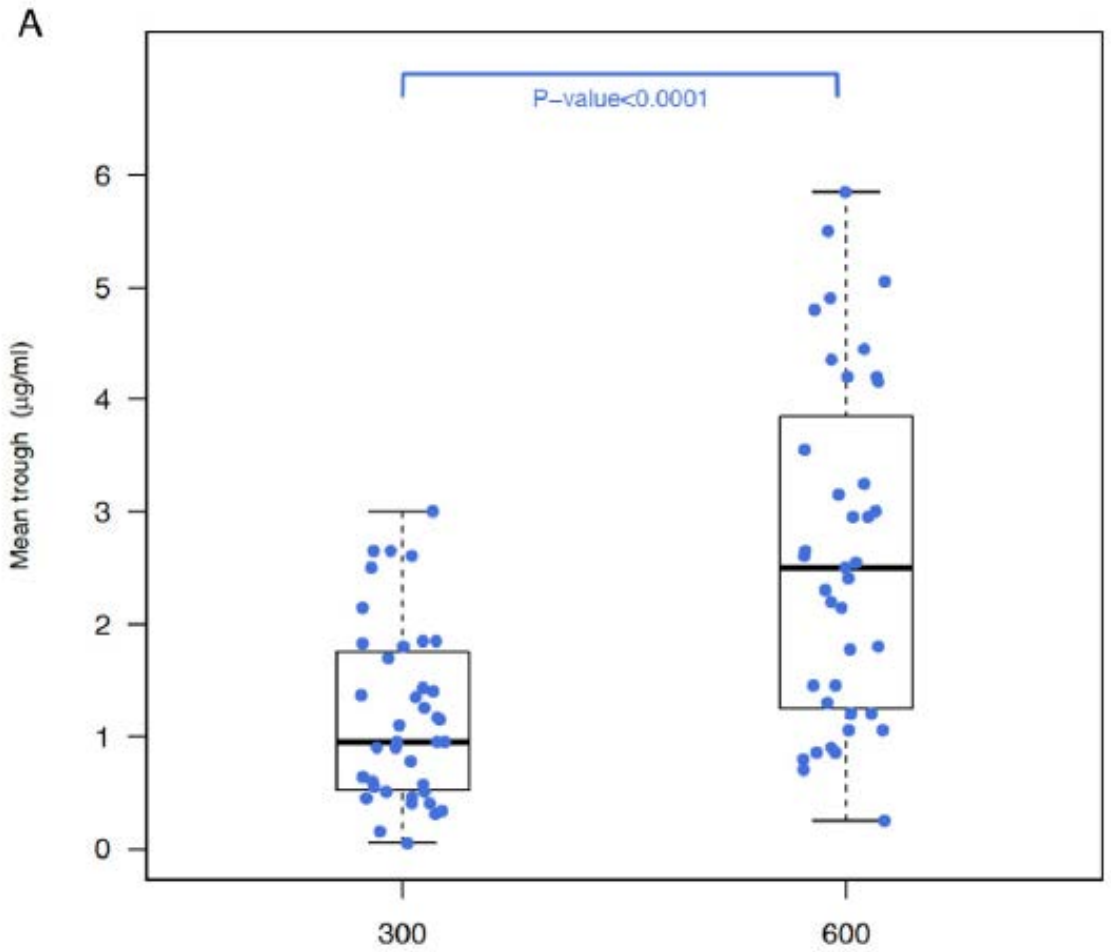
2016 update

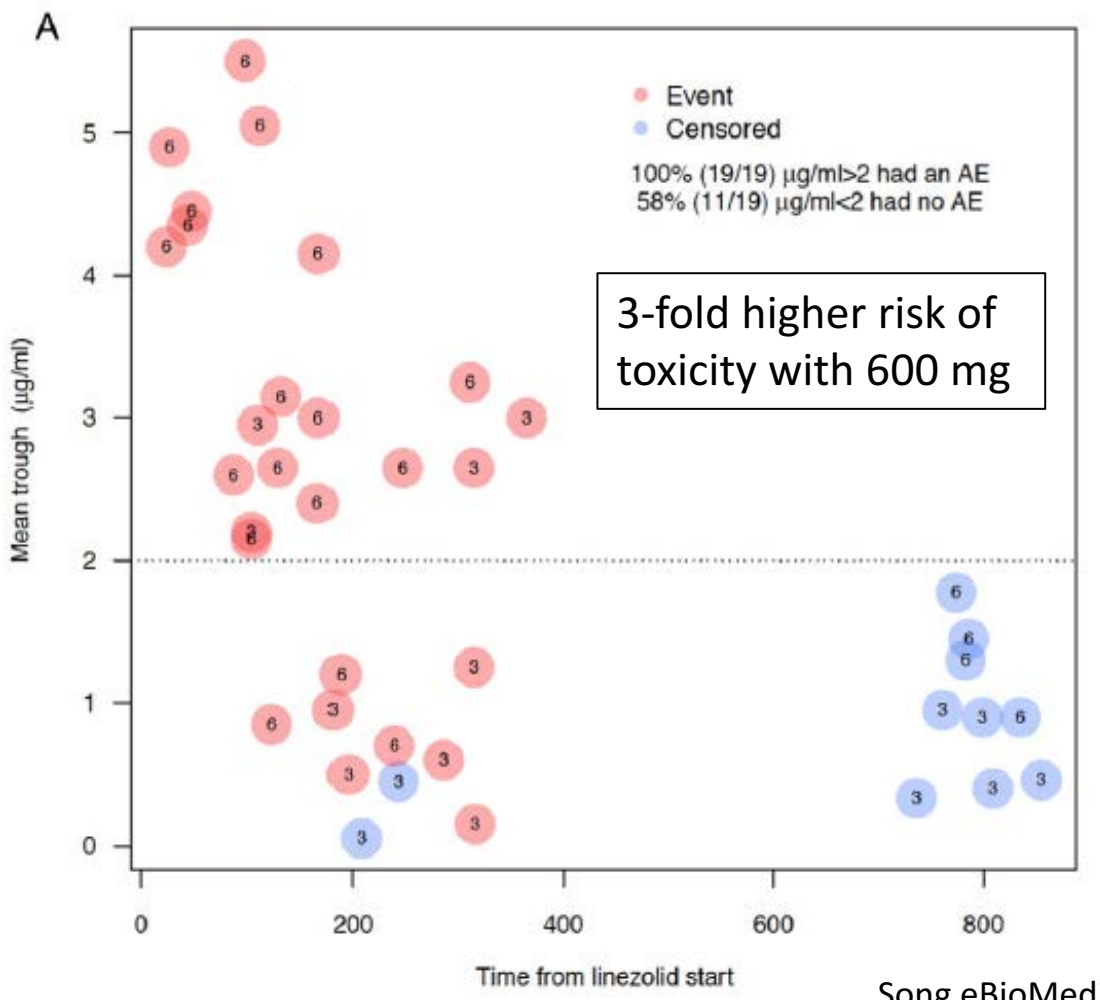
emergency. Given the potentially serious adverse effects of linezolid – particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy - the decision to use linezolid must balance its risks and benefits and the availability of other TB medicines. Due to the potential for severe adverse events, linezolid use needs to be accompanied by close monitoring for adverse events. Where this is not possible, linezolid

What is the lowest effective dose of LZD (that limits resistance)?

What are the optimal PK/PD parameters for toxicity and efficacy?

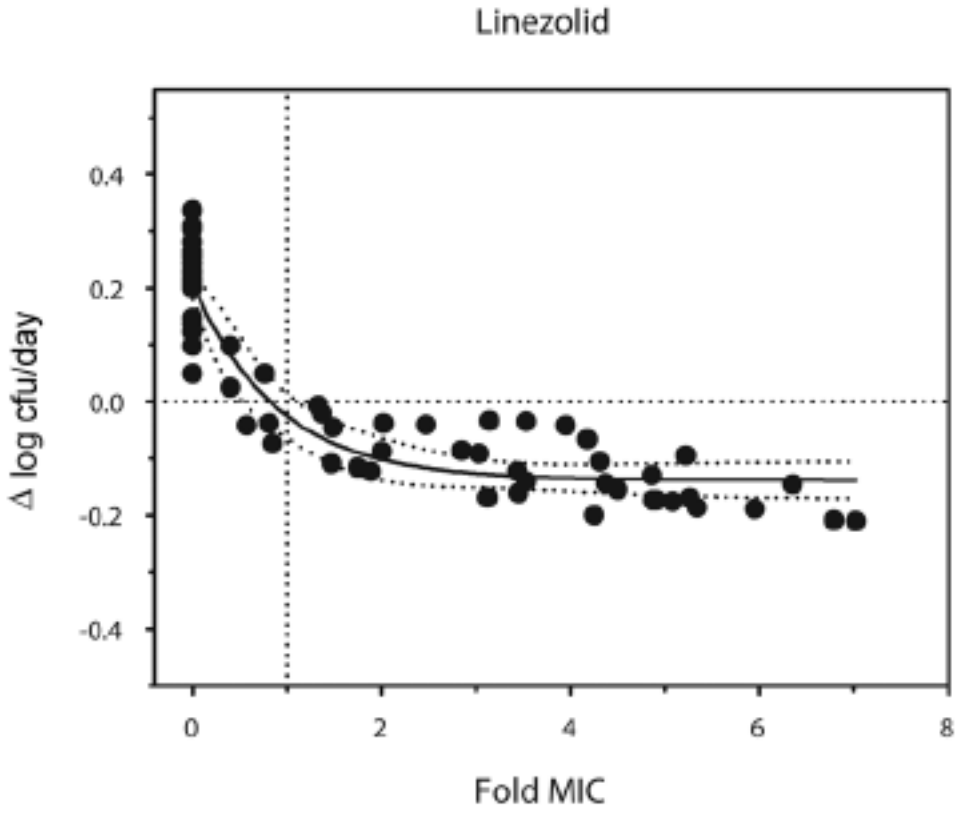
Relationship between dose, trough concentrations, and clinical toxicity





Song eBioMedicine 2015

LZD appears to have a narrow therapeutic index



- Maximal EBA at concentrations 2x MIC (2 mg/L)
  - 300 mg daily: achieved only 50% of dosing interval
  - 600 mg daily: ~60% predicted
  - 600 mg BD: ~100% predicted
- But trough concentrations > 2 mg/L predict toxicity

Wallis JID 2010

LzTB

Optimising linezolid use for drug-resistant tuberculosis: the effects of exposure on toxicity, treatment response, and linezolid resistance

1. Develop a population PK model of linezolid

2. Determine the effects of linezolid dose and exposure on toxicity, treatment response, and resistance to develop PK/PD targets

3. Define the relationships between linezolid PK parameters, functional mitochondrial activity, and clinical toxicity, and explore the association of SNPs in mtDNA with the risk of linezolid toxicity in this population

EDCTP

LzTB

Optimising linezolid use for drug-resistant tuberculosis: the effects of exposure on toxicity, treatment response, and linezolid resistance

STUDY OVERVIEW

Prospective observational study

200 adults with DR-TB

Known HIV status

Starting LZD

3 study sites in SA

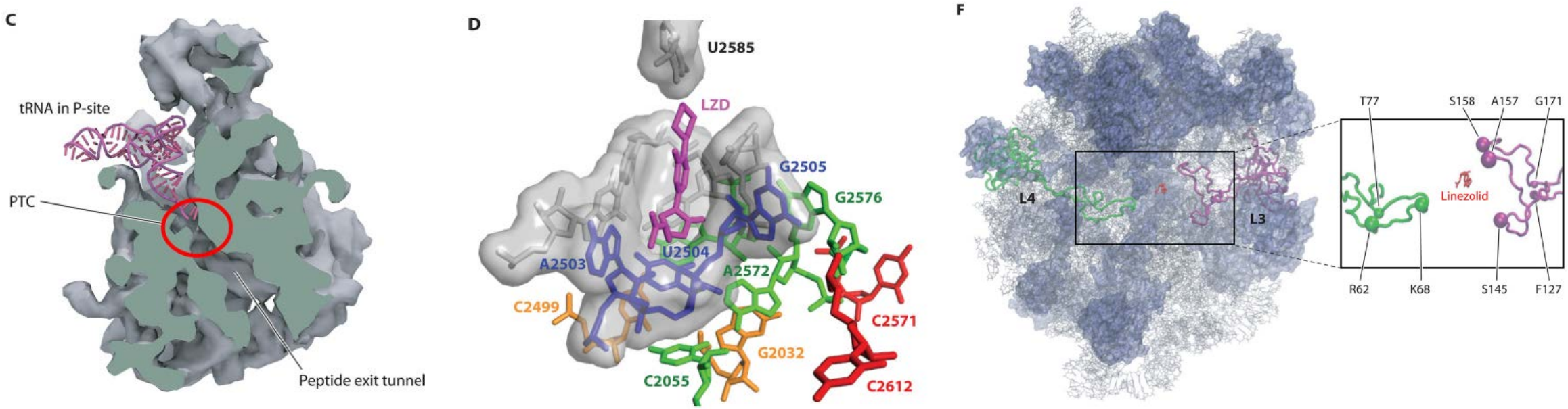
Follow-up for 2 years: 15 visits

159 enrolled (33 in PE)

EDCTP

LZD resistance

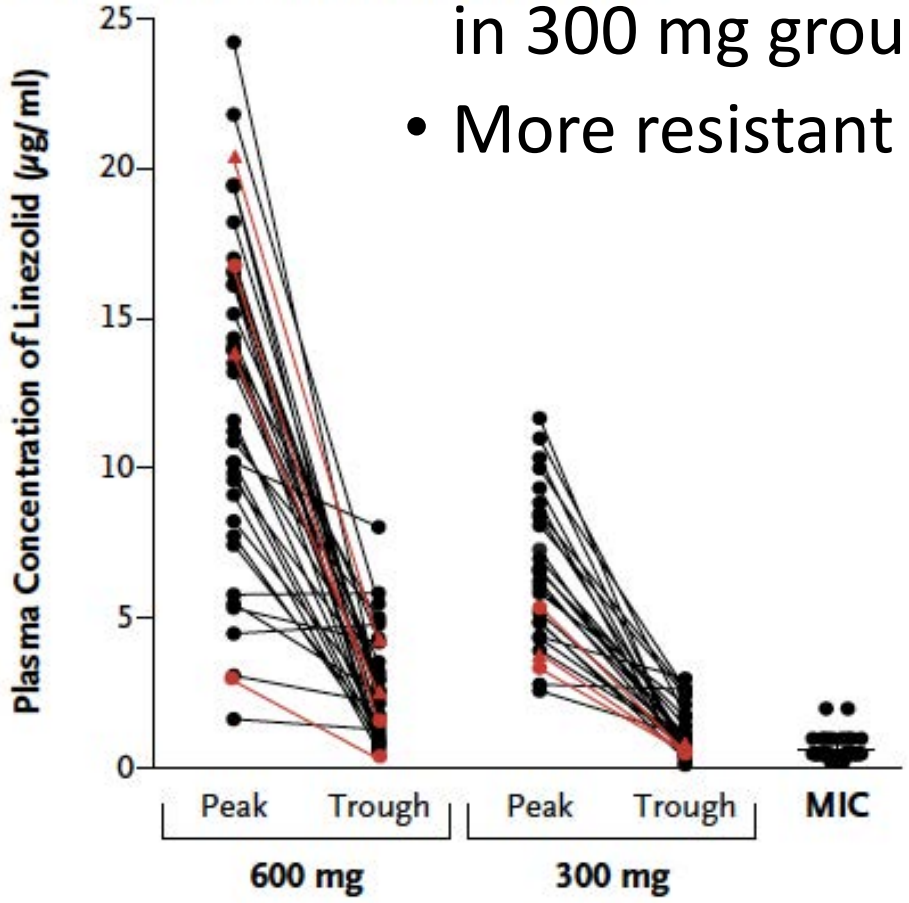
- High barrier: spontaneous mutation frequency 2 x 10^{-8} - 5 x 10^{-9}
- Associated with mutations in LZD binding site and L3

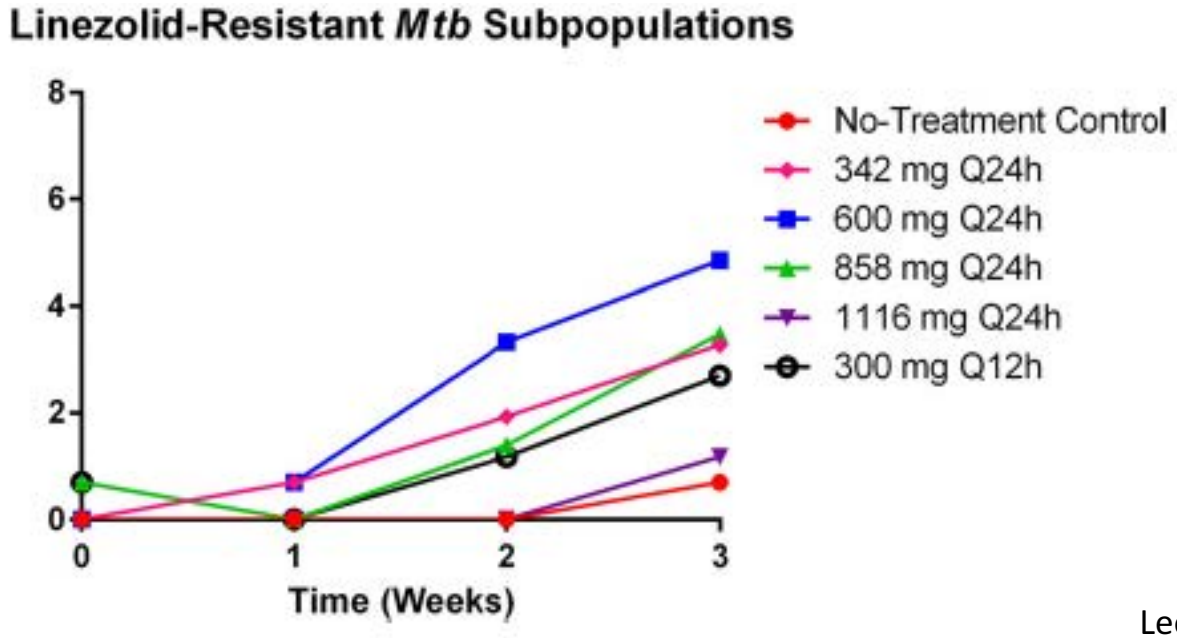


Long AAC 2012

Risk may be related to lowering dose for toxicity

- 11% developed resistance in Korean RCT; 75% of these in 300 mg group; most Cmin below MIC
- More resistant populations in lower doses in HFIM





Lee NEJM 2012
Brown mBio 2015

Resistance is being reported

Study	Author, year	Description	Gene(s) sequenced	Mutations	MIC range (µg/mL)
1	Richter, 2007[21]	4/210 **clinical** isolates were resistant	23S rRNA (*rrl*), L4 (*rplD*), L22, 23S rRNA methyltransferase (*erm*-37)	None found	4 – 8
2	Hillemann, 2008 [18]	10 resistant isolates selected *in vitro*	23S rRNA (*rrl*)	G2061T	32
				G2576T	16
3	Beckert, 2012[23]	**Clinical** and *in vitro* resistant isolates	L3 (*rplC)*	T460C	4 – 16
4	Lee, 2012[4]	4/38 isolates from a **clinical** trial were resistant	23S rRNA (*rrl*)	G2447T	16
				G2576T	4
			L3 (*rplC)*	T460C	2 – 4
5	Zhang, 2014[24]	17/ 158 **clinical** isolates were resistant	23S rRNA (*rrl*)	G2061T	32
			L3 (*rplC)*	T460C	16 - 32
6	McNeil, 2017[22]	28 resistant strains selected *in vitro*	23S rRNA (*rrl*)	G2576T G2061T A2451T G2576T	Not reported
			L3 (*rplC)*	T460C	
7	Zimenkov, 2017[30]	10/27 **clinical** isolates resistant to linezolid	23S rRNA (*rrl*)	G2576T G2056A	Not reported
			L3 (*rplC)*	T460C	
			L4 (*rplD*)	None found	
8	Pang, 2017[31]	5/90 **clinical** isolates resistant to linezolid	23S rRNA (*rrl*)	None found	4 – 16
			L3 (*rplC)*	T460C	
			L4 (*rplD*)	None found	

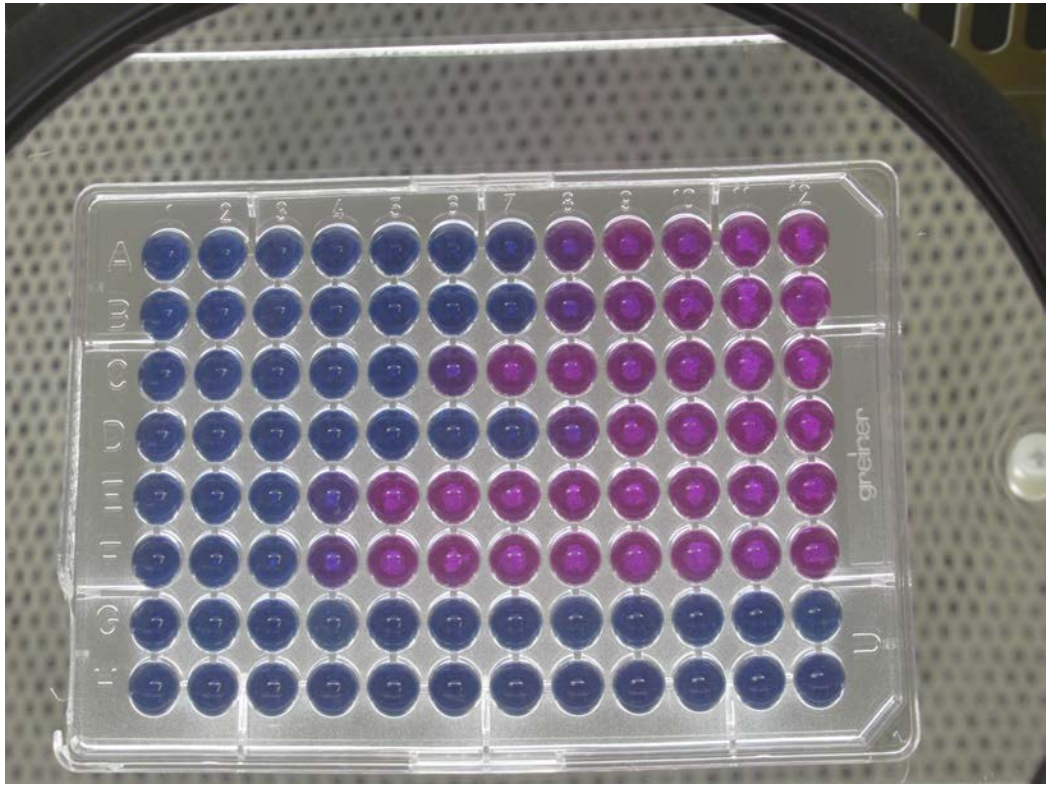
LZD resistance study

- Are there other unidentified mutations or other resistance mechanisms?
- What are the predictors (risks) of resistance?
- What is the epidemiology and transmission dynamics of LZD resistance?

STUDY OVERVIEW
Retrospective study, 6 study sites in SA (including PE) Inclusion: • Treatment failure on LZD-containing regimen • LZD MIC ≥ 1 mg/L

Methods

- Microdilution method for MIC testing
- WGS for new mutations
- Case-control study for risk factors
- Determine transmission dynamics using molecular and social network approaches



Some early data from JP

43 possible cases identified so far (up to 80 more still to review)

14 with MIC/sequencing results

- 8/14 (57%) with phenotypic/genotypic resistance
- 2 cases with MIC ≥ 2 and no LZD exposure: transmitted?

PID	MIC	Mutation	
		rplC	*rrl*
1002	1	No	ND
1004	0.5	No	ND
1006	No growth	No	ND
1007	**2**	No	ND
1008	**4**	**T460C**	ND
1009	No growth	No	ND
1010	**2**	No	ND
1011	**4**	No	**G2814T**
1012	0.5	No	ND
1013	**4**	**T460C**	ND
1014	**8**	No	**G2814T**
1015	**4 to 8**	**T460C**	ND
1016	No growth	No	**G2399A**
1017	1	No	ND

LZD in clinical practice

- When do you use it?
  - Being evaluated in in novel regimens
  - Because of potency and low risk of resistance, should include in:
    - All XDR and pre-XDR
    - MDR with treatment failure
    - Empiric while awaiting DST results (if dual INH mutations or single drug substitution)

- What is the best dose?
  - BD dosing not ideal for toxicity
  - Initial high dose ‘induction’ for ~2 months followed by ’maintenance’ using reduced/intermittent dosing?

- How do you define LZD resistance?
  - More work needs to be done