Therapeutic Drug Levels for Tb: When and Why

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Protecting You and Your Environment

The Problem

- Slow response to tuberculosis (TB) treatment leads to prolonged infectiousness, may increase the likelihood of acquired drug resistance and extends treatment duration

- Our assumption is low drug levels is a contributor to slow response, at least in some patients

In VA, since 2007, initiative for patients slow to respond to TB therapy to have therapeutic drug level monitoring

Therapeutic drug monitoring among TB slow responders

Among patients treated for pulmonary TB in the state of Virginia-

Primary aim:

1. Determine the frequency of low levels (C_{2hr}) of first-line medications among slow responders to TB therapy

Secondary aims:

2. Determine risk factors for slow response

3. Determine risk factors for low isoniazid or rifampin among slow responders

4. Compare outcomes among slow responders with low and normal drug levels

Methods

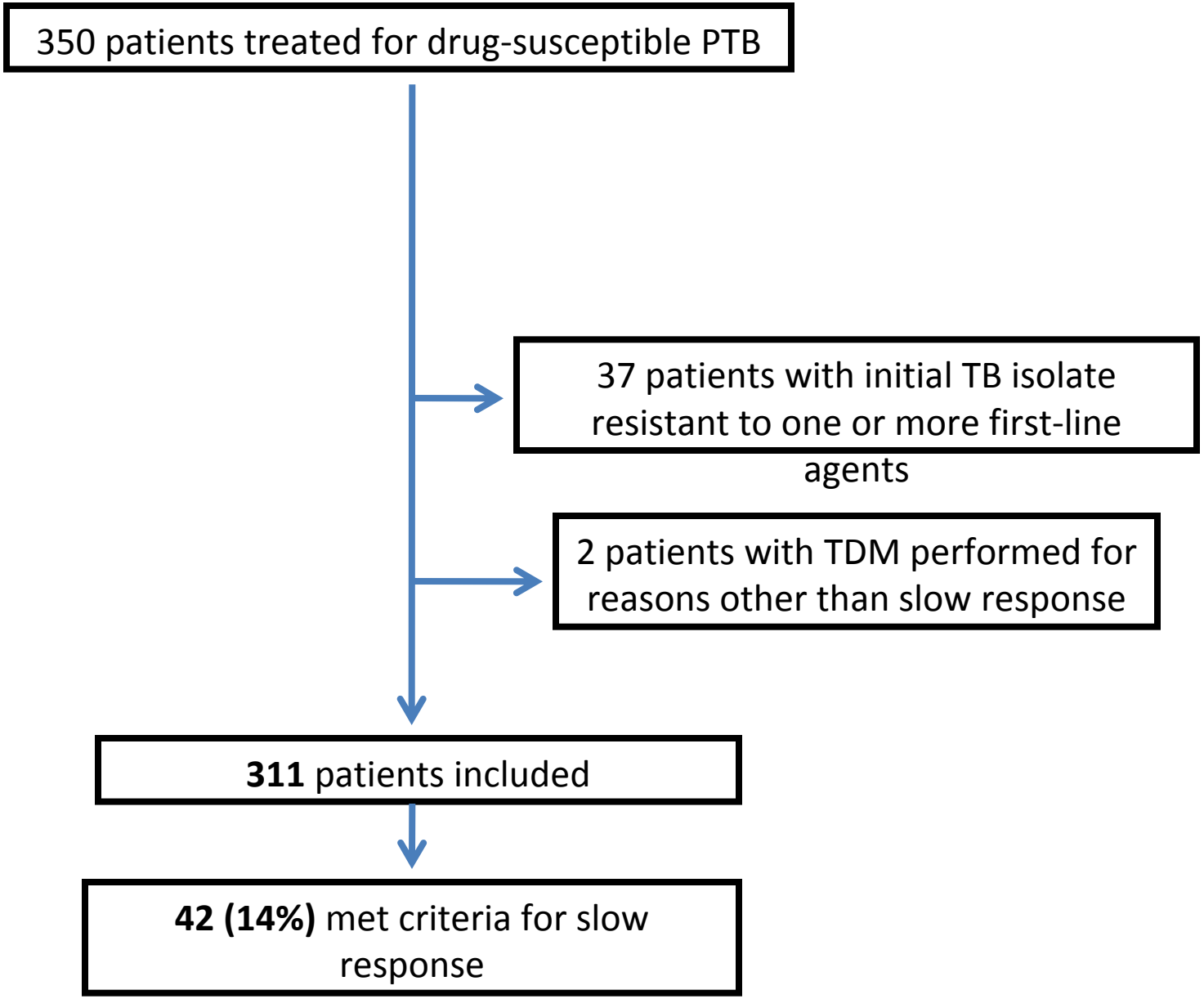
Design: retrospective cohort, all adults treated for pulmonary TB from 3/1/07-5/1/09

Eligibility: ≥18 years, culture-positive, started on first-line TB regimen; excluded if drug monitoring for other reasons, or if TB isolate resistant to one or more first-line drugs

Definitions:
Slow response- After 4 weeks of therapy: two or more of the following- 1.persistent TB symptoms, 2. positive sputum smear, 3. no improvement in chest x-ray

Drug levels: drawn at 2 hrs after observed morning dose of all medications, serum separated and sent on ice to referral laboratory in Florida for HPLC.

Outcomes: death from any cause, treatment duration, acquired drug resistance, medication toxicity following dose adjustment


350 patients treated for drug-susceptible PTB
37 patients with initial TB isolate resistant to one or more first-line agents
2 patients with TDM performed for reasons other than slow response
311 patients included
42 (14%) met criteria for slow response

Diabetes is a risk factor for slow response

	Total N= 311 (%)	Slow response N=42 (%)	Normal response N= 269 (%)	Risk Ratio [95% CI] p-value
Age 18-39 40-64 ≥65	151 (49) 90 (29) 70 (22)	16 (38) 13 (31) 13 (31)	135 (50) 77 (29) 57 (21)	referent 1.4 [0.65-3.1] p=0.38 1.9 [0.87-4.3] p=0.11
Female	107 (35)	13 (31)	94 (35)	0.84 [0.42-1.7] p=0.61
Race/Eth Asian Hispanic Black White	 102 (33) 82 (26) 86 (28) 41 (13)	 19 (45) 11 (26) 8 (19) 4 (10)	 83 (31) 71 (26) 78 (29) 37 (14)	 referent 0.67 [0.30-1.5] p=0.34 0.45 [0.19-1.1] p=0.07 0.47 [0.15-1.5] p=0.20
Foreign-born	228 (73)	33 (79)	195 (72)	1.4 [0.64-3.0] p=0.41
HIV Yes Unk.	 11 (3) 34 (11)	 0 5 (12)	 11 (4) 29 (11)	 p>0.99 1.1 [0.39-2.9] p=0.90
Alcohol abuse	35 (11)	4 (9)	31 (11)	0.81 [0.27-2.4] p=0.70
Diabetes	**41 (13)**	**17 (40)**	**24 (9)**	**6.9 [3.3-14.6] p<0.001***
Initial smear Positive Unavailable	 193 (62) 24 (8)	 30 (72) 3 (7)	 163 (61) 21 (8)	 1.7 [0.79-3.8] p=0.17 1.3 [0.34-5.4] p=0.67
Chest x-ray abnormal Cavitary	 173 (56) 122 (39)	 19 (45) 21 (50)	 154 (57) 101 (38)	 0.86 [0.18-4.1] p= 0.85 1.5 [0.31-6.8] p=0.64

Majority of slow responders had low C_{2hr} levels of INH and rifampin

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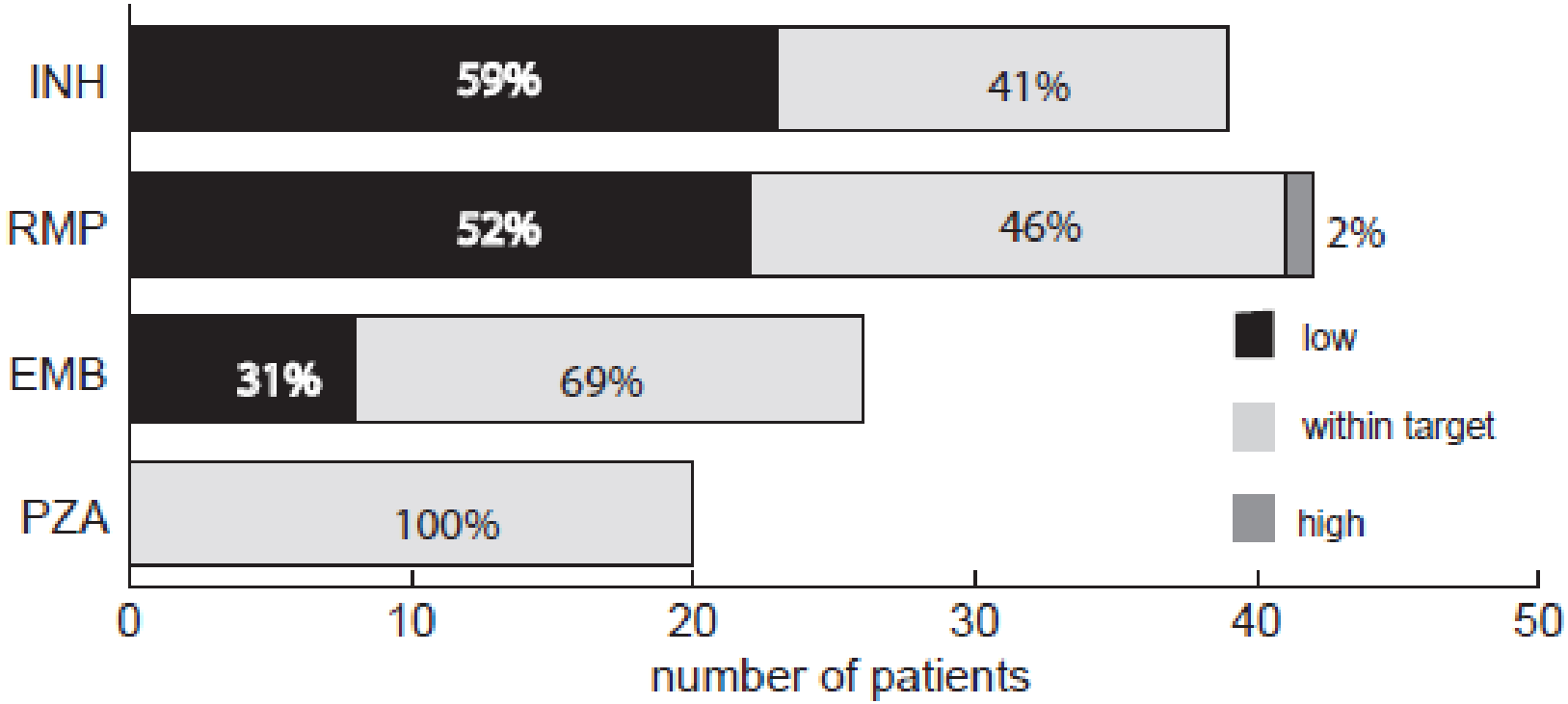


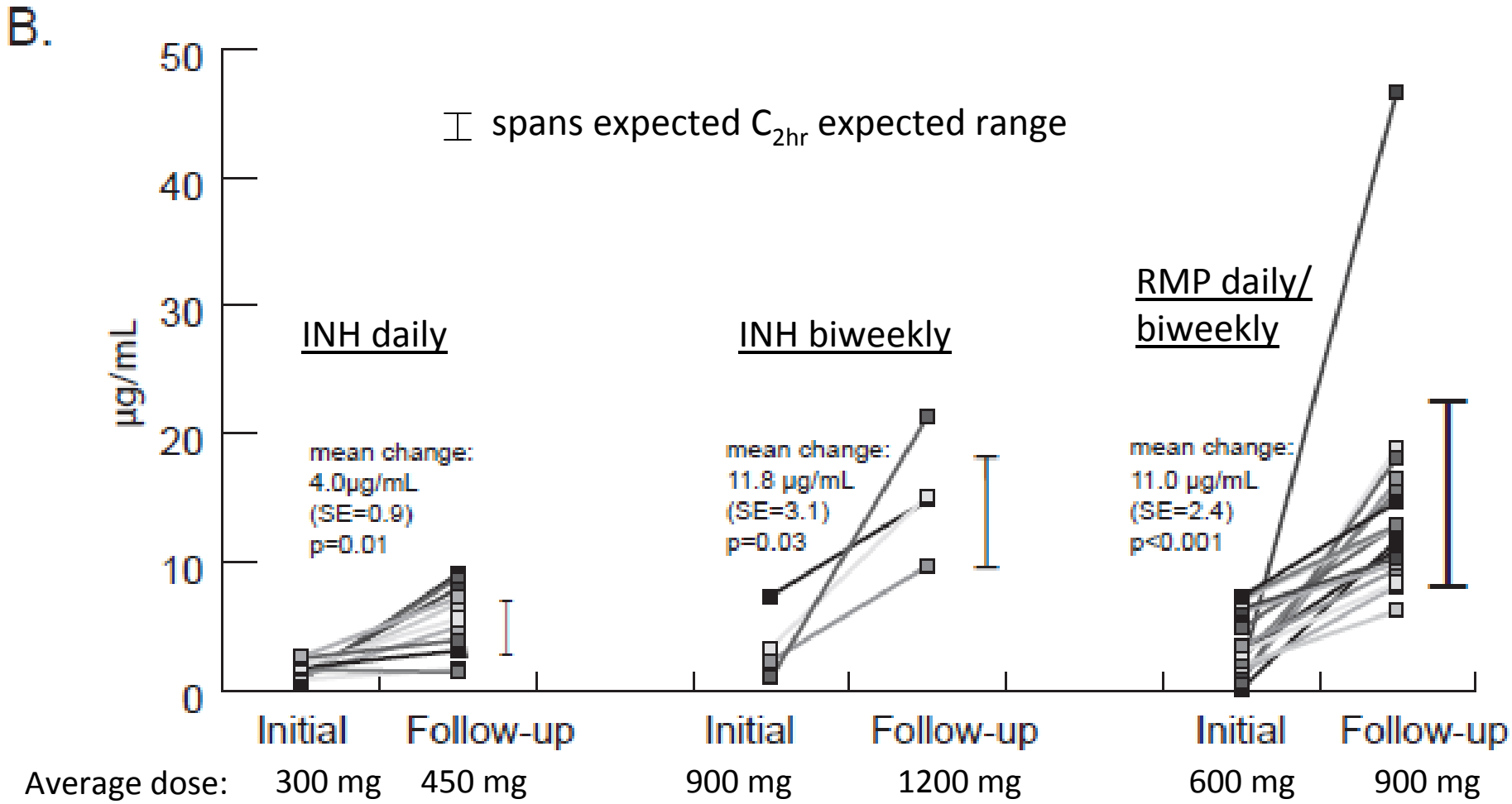
82% had low levels to one of INH or RMP

Heysell et al, *Emerg Infect Dis*, 2010

Diabetes was a significant risk factor for low rifampin levels

	Normal INH N=16 (%N)	Low INH N=23 (%N)	Risk Ratio [95% CI] p-value	Normal RMP N=20 (%N)	Low RMP N=22 (%N)	Risk Ratio [95% CI] p-value
Age 18-39	4 (25)	8 (35)	referent	5 (25)	10 (46)	referent
40-64	7 (44)	8 (35)	0.57 [0.12-2.8] p=0.49	8 (40)	7 (32)	0.44 [0.10-1.9] p=0.27
≥65	5 (31)	7 (30)	0.70 [0.13-3.7] p=0.67	7 (35)	5 (22)	0.36 [0.07-1.7] p=0.20
Female	5 (31)	8 (35)	1.2 [0.30-4.6] p=0.82	7 (35)	7 (32)	0.87 [0.24-3.1] p=0.81
Race/Eth						
White	1 (6)	3 (13)	1.9 [0.16-22.3] p=0.61	3 (15)	1(5)	0.37 [0.3-4.2] p=0.42
Asian	7 (44)	11 (48)	referent	10 (50)	9 (41)	referent
Hispanic	6 (38)	4 (17)	0.42 [0.09-2.1] p=0.43	3 (15)	8 (36)	3.0 [0.60-14.7] p=0.18
Black	2 (12)	5 (22)	1.6 [0.24-10.6] p=0.63	4(20)	4 (18)	1.1 [0.21-5.8] p=0.90
Foreign-born	13 (81)	17 (74)	0.65 [0.14-3.1] p=0.59	14 (70)	19 (86)	2.7 [0.58-12.8] p=0.21
Diabetes	6 (37)	10 (43)	1.3 [0.35-4.7] p=0.71	**4 (20)**	**13 (59)**	**5.8 [1.4-23.1] p=0.01***
EtOH use	1 (6)	1 (4)	0.69 [0.4-11.7] p=0.79	2 (10)	2 (9)	0.90 [0.12-7.1] p=0.92
Dose interval						
Daily	8 (50)	19 (83)	referent	11 (65)	16 (73)	referent
Biweekly	8 (50)	4 (17)	0.21 [0.05-0.9] p=0.04†	6 (35)	6 (27)	0.88 [0.23-3.3] p=0.85

INH and rifampin levels correct easily after first dose adjustment



No drug related toxicities associated with dose increase

Heysell et al, *Emerg Infect Dis*, 2010

Patients with low/corrected rifampin levels were deemed cured 7 wks earlier (than those with normal levels)

	Total, N= 42 (%)	Low RMP, N=22 (%)	Normal RMP, N=20 (%)
Death	3 (7)	1 (5)	2 (10)
Acquired resistance	0	0	0
Moved out of state	2 (5)	1 (5)	1
Remains on treatment	10 (24)	6 (27)	4 (20)
Treatment duration*, median weeks [IQR]	45 [40-51]	40 [38-48]	47 [44-55] Log-rank p=0.17

Conclusions

- The majority of patients that met this criteria for slow response had low C_{2hr} levels to isoniazid and rifampin, while many had low levels of ethambutol

- Diabetics were significantly more likely to meet criteria for slow response

- Among slow responders, diabetes was significantly associated with C_{2hr} levels of rifampin below the expected range

- In patients with follow-up levels after dose adjustment, the majority achieved levels within the expected range, though significantly more often for rifampin

- **Drug level monitoring could be considered at the start of treatment for high risk groups (eg. rifampin for diabetics)**

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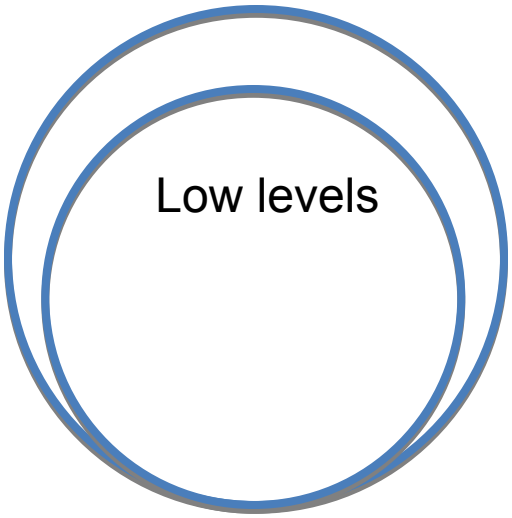
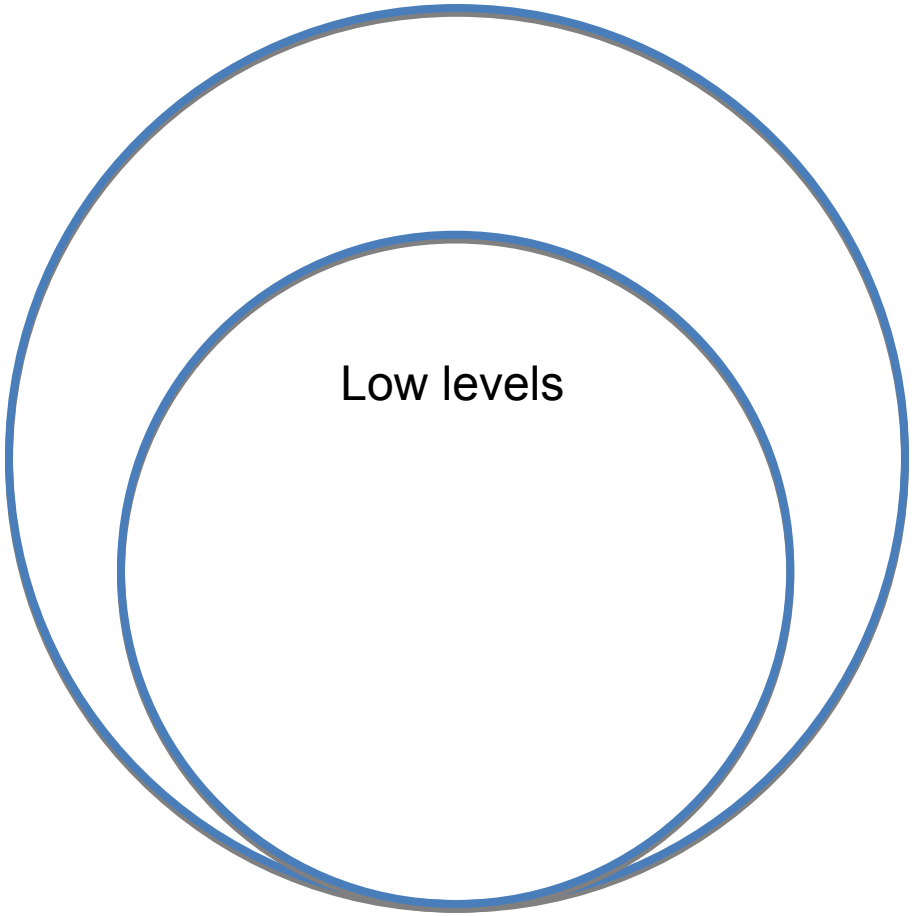
Slow responders



Normal responders



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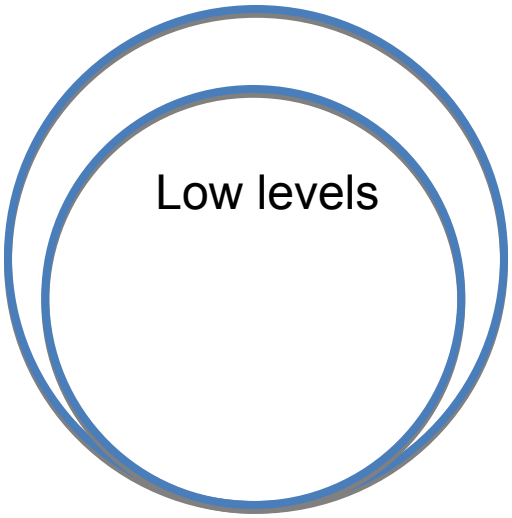
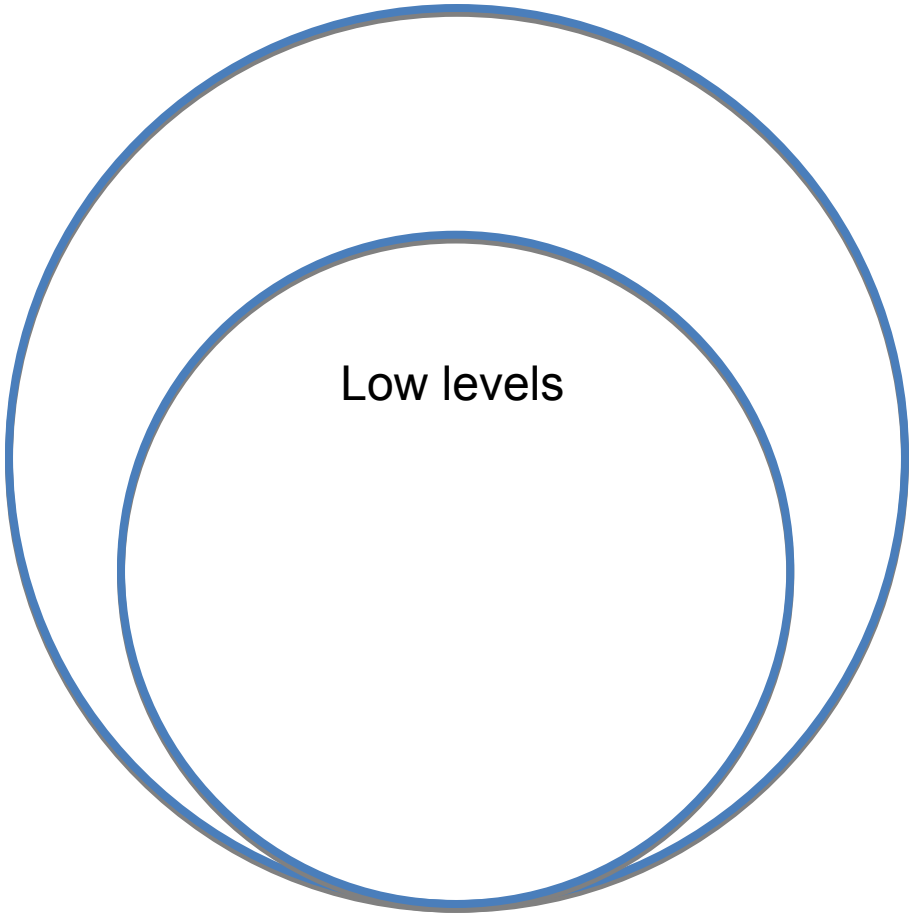
Slow responders



Diabetes
HIV
Extensive Tb disease
Tb strain
Low drug levels
…

Normal responders



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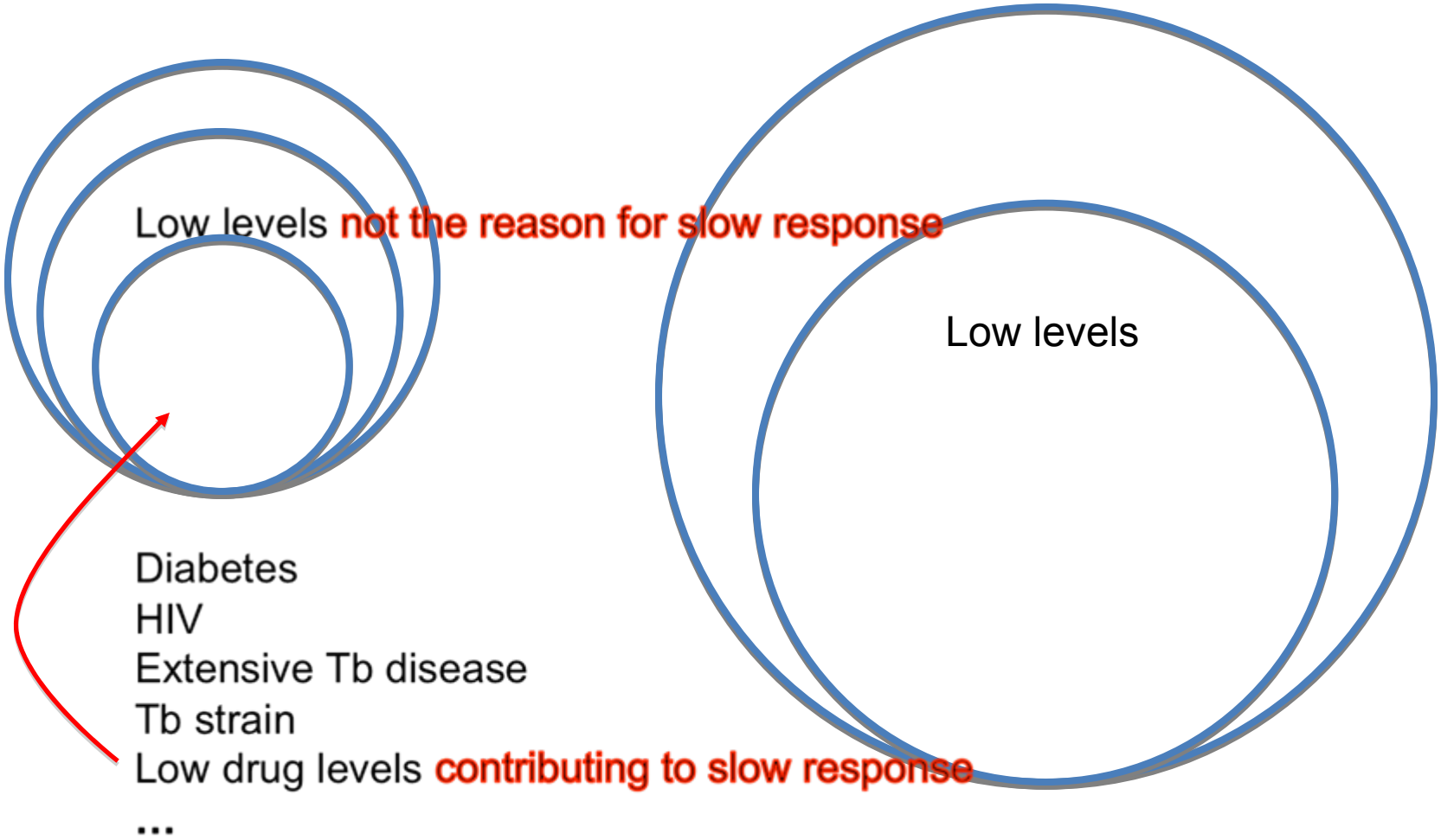
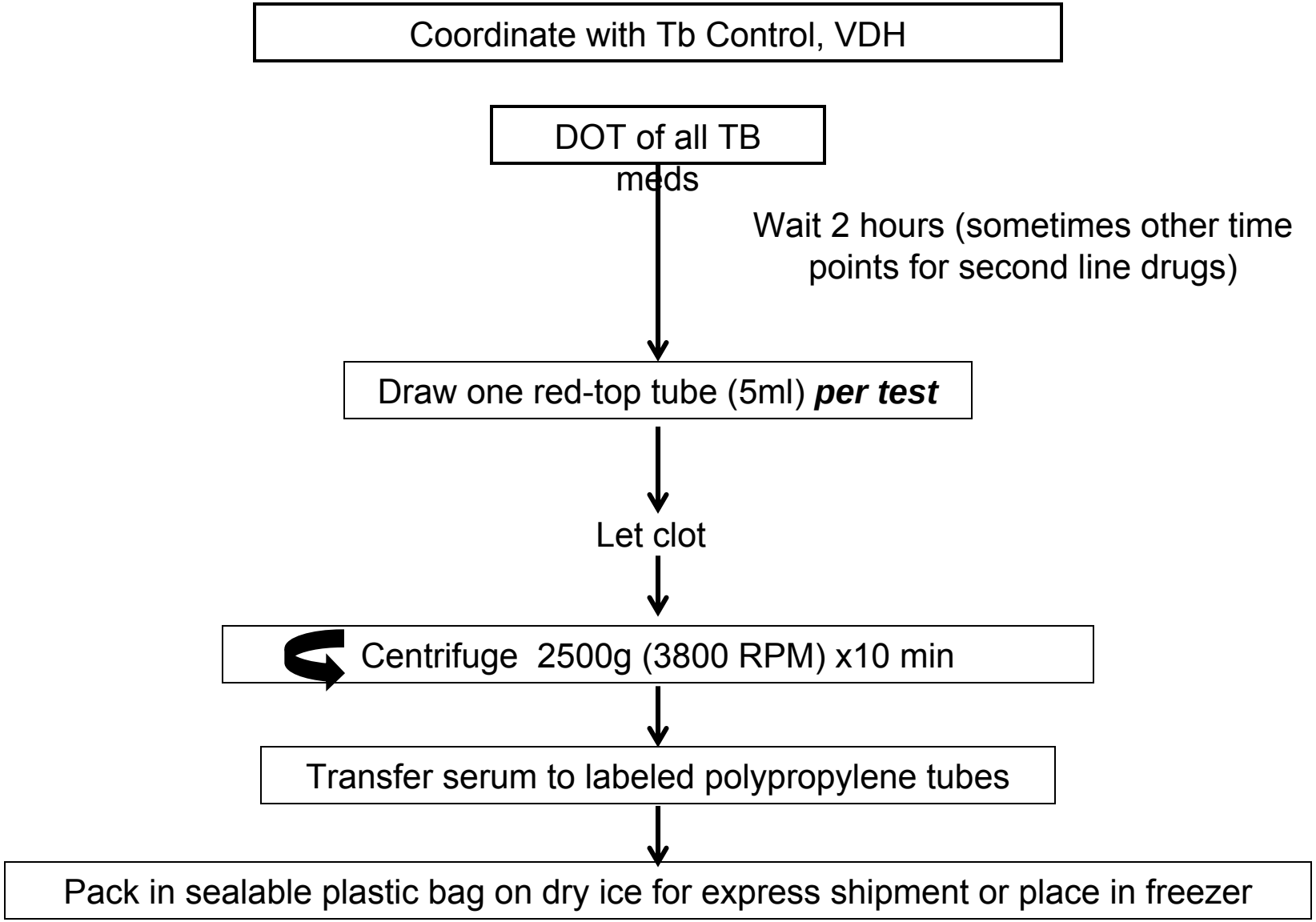
Slow responders

Normal responders



When to consider checking

Reason for TDM	Drugs to check
In any patient with slow response at 4-8 weeks of treatment suggested by: 1. Sputum smear (+) (pulmonary TB) AND/OR 2. No improvement in TB symptoms (e.g., no weight gain)	INH, RIF
New clinical deterioration and unclear if related to TB (e.g., new evaluation for TB relapse, drug-susceptibility testing)	All anti-tuberculosis medications
Persistent diarrhea (> 2 weeks), GI malabsorption	All anti-tuberculosis medications
Consider at the start of therapy	
Diabetes	INH, RIF
HIV ▪ Of even higher priority if on antiretrovirals	INH, RIF (or rifabutin)
Rifampin resistance (e.g., MDR) ▪ In INH mono-resistance consider checking rifampin level	All anti-tuberculosis medications (including second-line medications)

Medication (expected C_{max} range in µg/ml)	Dose adjustment
Isoniazid / daily (3-6) / biweekly (9-18)	↑ if daily <2 (300 mg dose increase to 450 mg) ↑ if biweekly <7 (900 mg dose increase to 1.2 g)
Rifampin (8-24)	↑ <6 (600 mg dose increase to 900 mg)
Pyrazinamide for 25 mg/kg dose (20-40) –	Why is PZA low? consider malabsorption/poor adherence
Ethambutol for 15 mg/kg dose (2-6)	Not routinely increased- consultation on case-by-case basis

Serum drug level monitoring methodology