New insights into TB drug selection and delivery

London; October 2018

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Challenges with managing TB

- TB remains the top ID killer- 3 people die every minute!

- 1. Progressive amplification of resistance leading to increased mortality, loss of new drugs & unsustainable costs

  - ~25% strains globally resistant to 1 major TB drug
  - 2013: 29% of MDR-TB globally = resistance to FQ, and/or SLID
    2015: 51%
  - ~ 5 to 10% of XDR-TB are surviving BDQ failures

24-month treatment outcomes – BDQ and LNZ treated XDR-TB

Olayanju & Dheda, Eur Resp J, 2018

Outcomes	Bdq [n= 68(%)]
Favourable (cured/completed treatment)	45 (66.2)
Unfavourable outcome	23 (33.8)
Deceased	10 (14.7)
Failed	4 (5.9)
LTFU	8 (11.8)
Defaulted	1 (1.5)

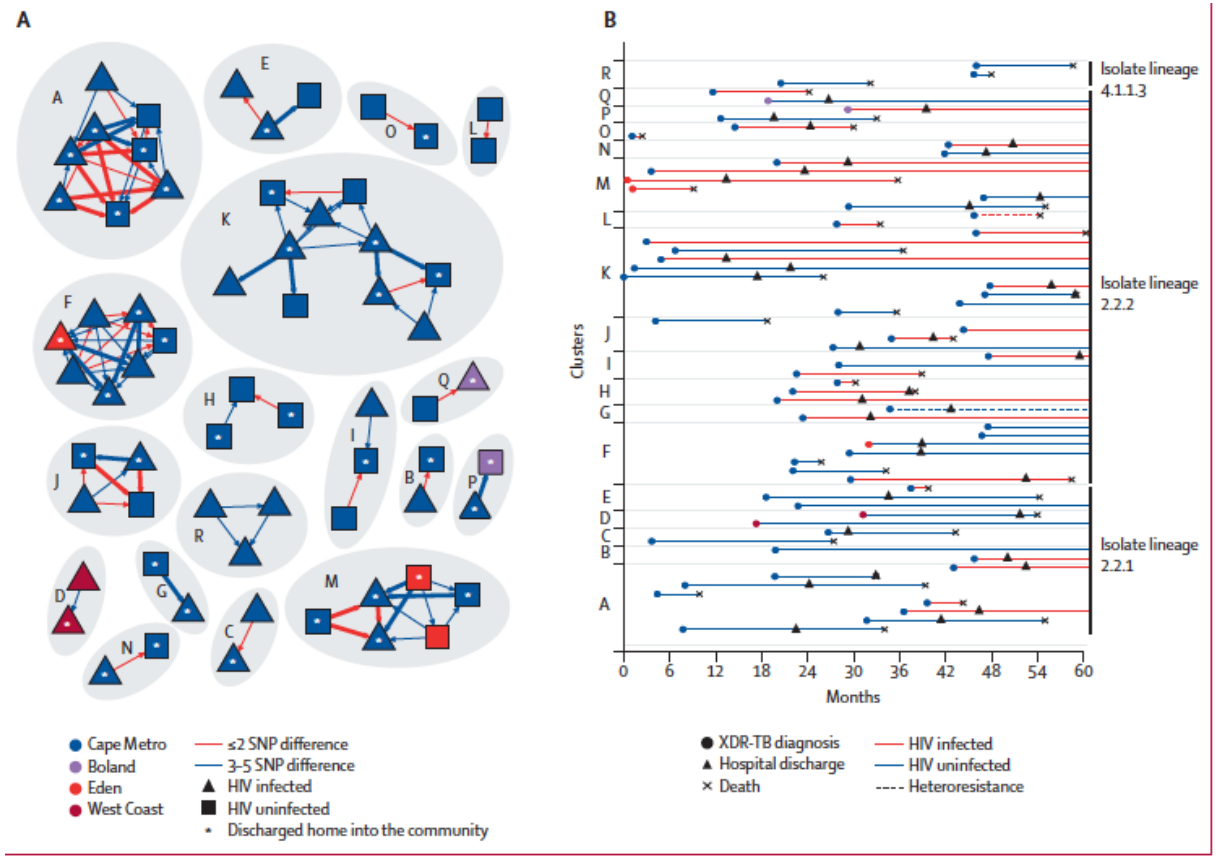
Several case reports of patients resistant to both BDQ and DLM

Bloemberg, NEJM, 2015

Kohl, AJRCCM, 2016

WGS on n= 153 XDR-TB isolates:

- 17/90 (19%) home-discharged treatment failures likely caused a secondary XDR-TB case (n=20)



Dheda K, Lancet Resp Med, 2017

Challenges facing TB

- 2. Dose-limiting toxicity of certain Group A drugs like linezolid thus driving resistance amplification.

Probability of PK efficacy target attainment 61.5% (95% CI, 40.6 to 79.8) at the critical concentration of 1 mg/L (AUC/MIC= 119).

Wasserman S, submitted, 2018

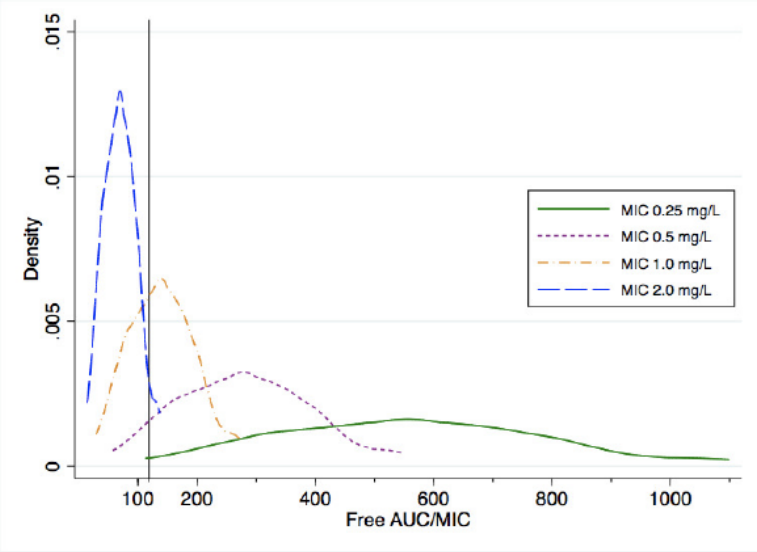
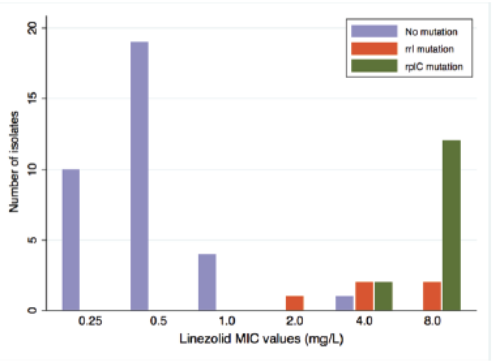


Figure 2. Probability density distributions for efficacy target attainment of linezolid for subjects on 600 mg daily.
The solid vertical line on the x-axis represents the experimentally-derived efficacy target fAUC/MIC0-24 of 119. Note the log-scale on the x-axis.

MIC distribution



Threatens the viability of a shorter (pan)-TB regimen, which relies on minimal resistance amplification over time.

12/40 (30%) culture +ve at 4 months LNZ resistance

THE LANCET

The global rise of extensively drug-resistant tuberculosis: is the time to bring back sanatoria now overdue?

Keertan Dheda, Giovanni B Migliori

Sondalo (1938)- 3500 beds

WHAT DRIVES RESISTANCE AMPLIFICATION?

~ 10% MDR-TB develop FQ resistance despite good adherence?

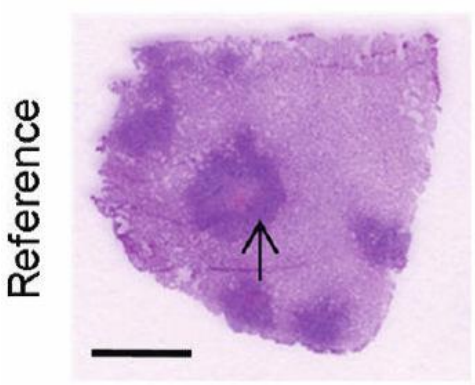
Cegielski JP, Clin Infect Dis, 2014 (PETTS);
Kemker RR, Emerg Infect Dis, 2015

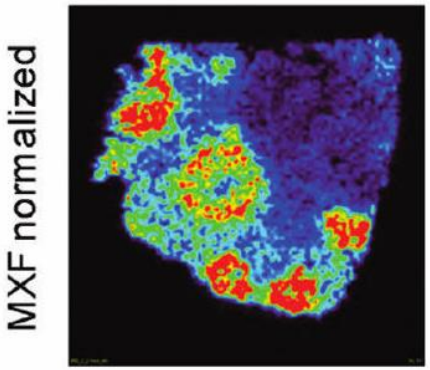
Genesis of acquired drug resistance= PK mismatch

(a sub-optimal number or level of a drug relative to MIC)

- **Bug-related factors** (poor diagnostic readouts; hetero-resistance due to multiple strains; MIC breakpoints; efflux pumps)
- **Host-related** biological and metabolic factors (pharmacogenomics; drug metabolism; population PK variability)

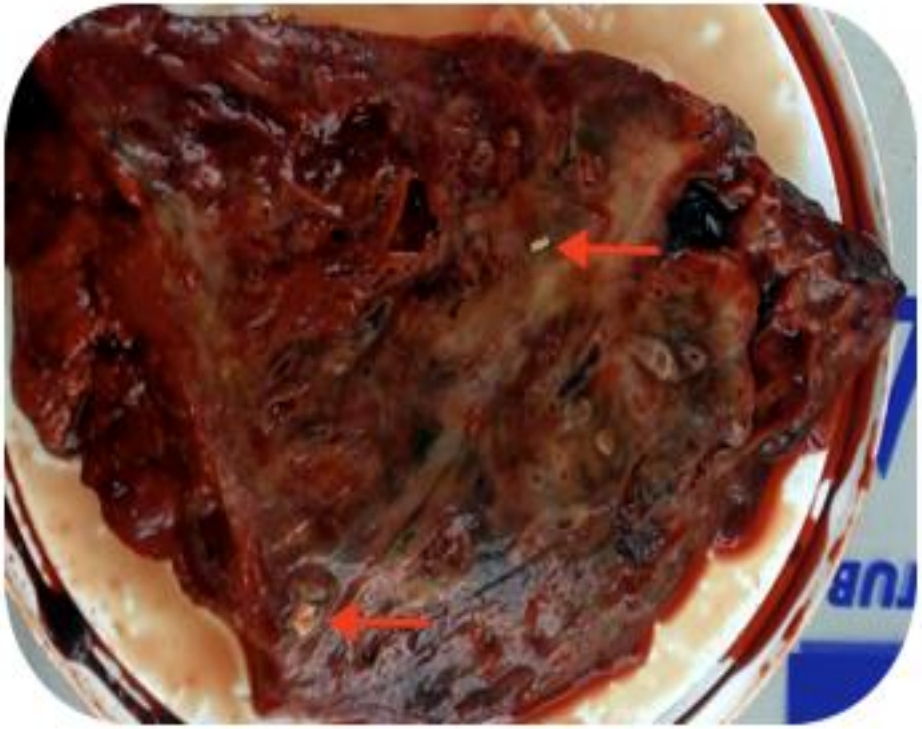
PK mismatch due to **drug gradients within TB lesions**





Relative mass spec on archived slide material

Prideaux B, Nat Med 2015



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N= 14

Dheda & Gumbo, AJRCCM, 2018

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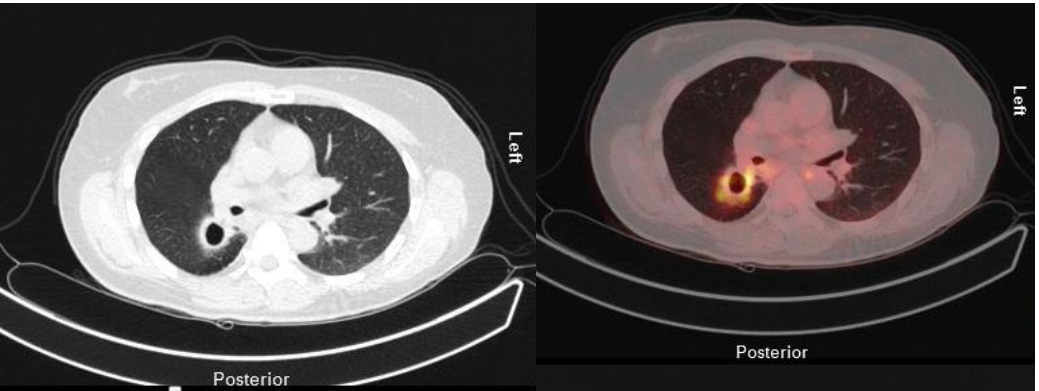
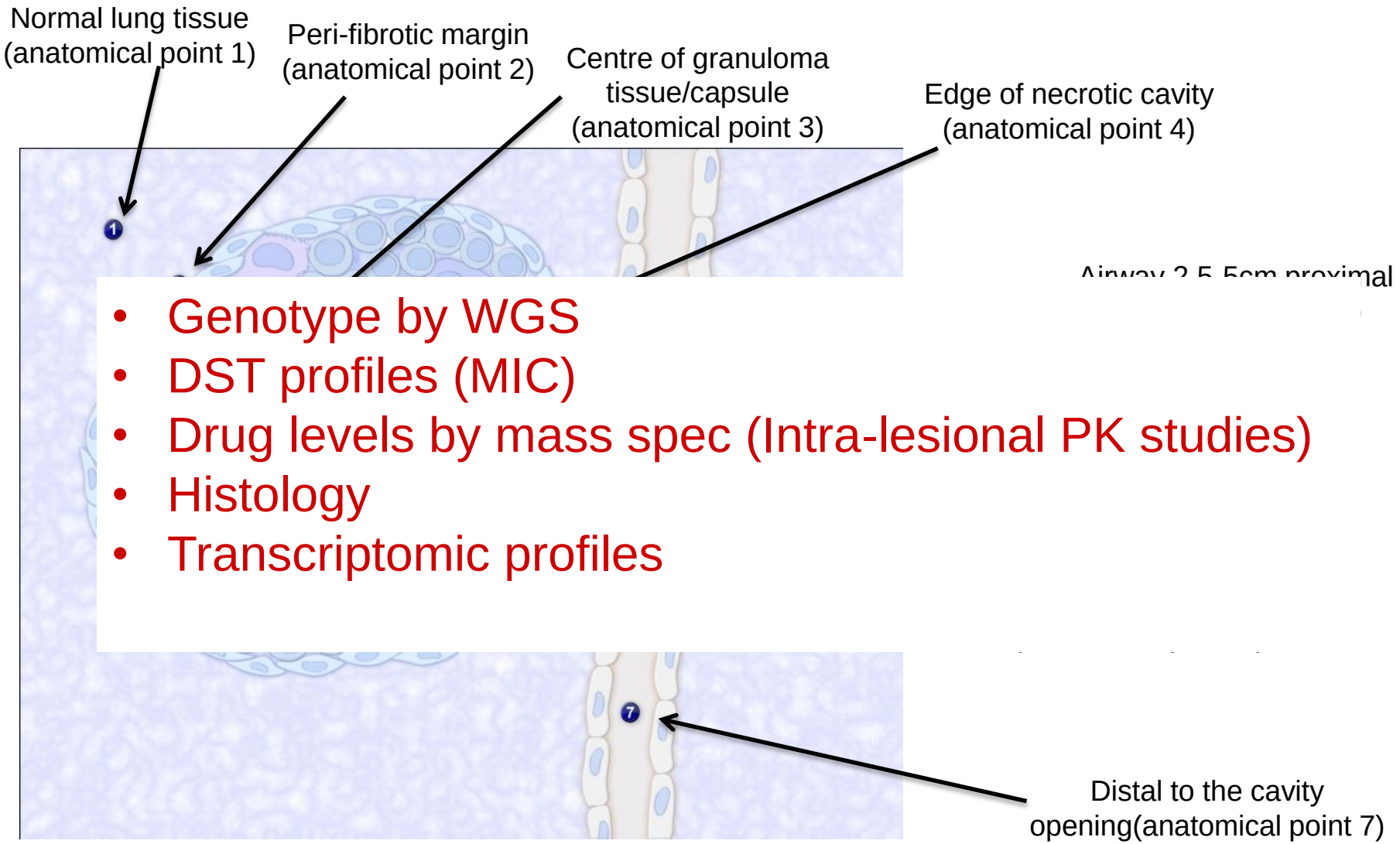




- Genotype by WGS
- DST profiles (MIC)
- Drug levels by mass spec (Intra-lesional PK studies)
- Histology
- Transcriptomic profiles

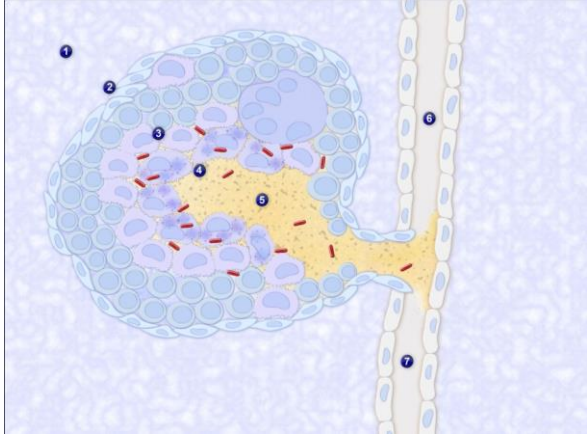
Figure 2. Lung compartments to be investigated

Hypothesis: Resistance is driven by sub-therapeutic drug concentrations in different anatomical micro-compartments in the human lung

+ sputum

Clonal heterogeneity

Patient 2 (PK002)	Sputum	Lung Cavity			
		Point 2	Point 3	Point 4	Point 5
Strain type	X1	X1	LCC Beijing	X1	X1



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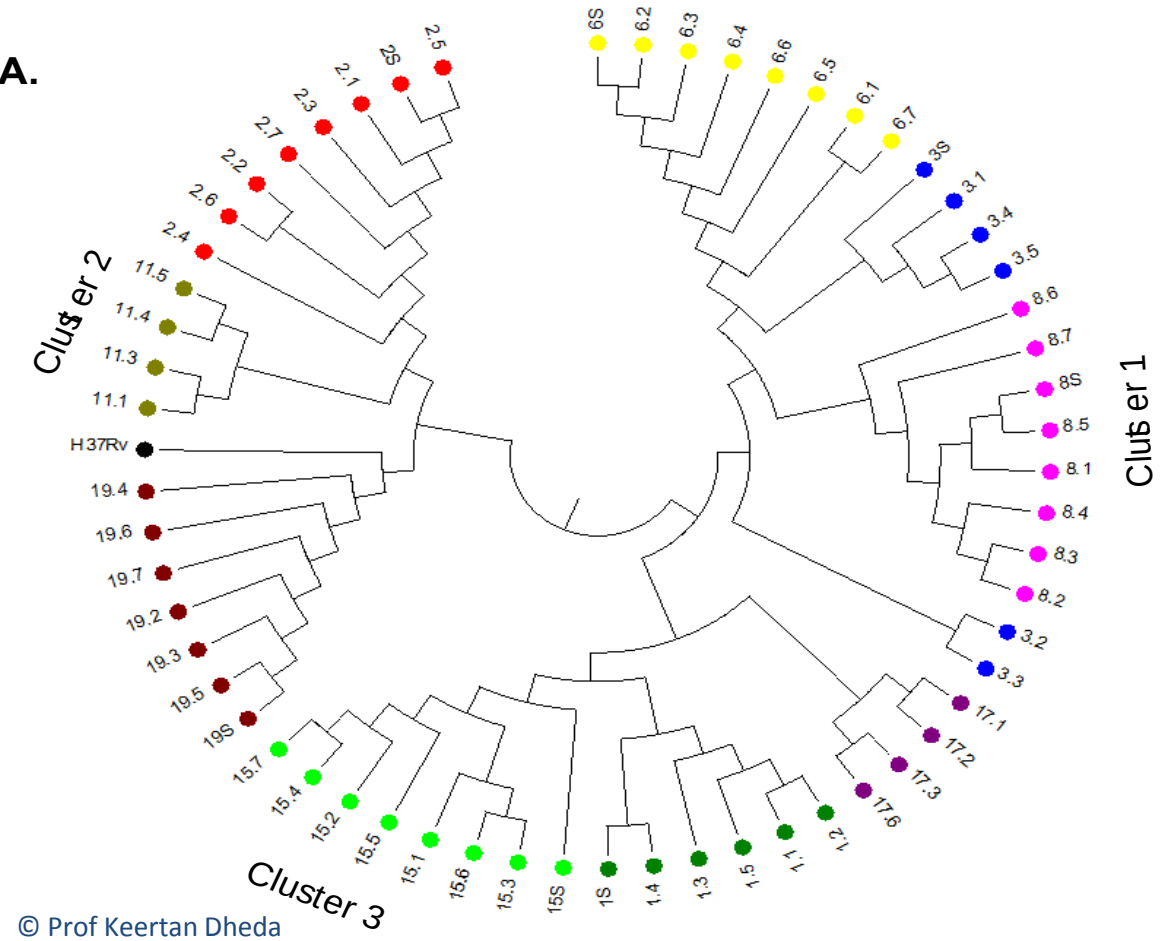

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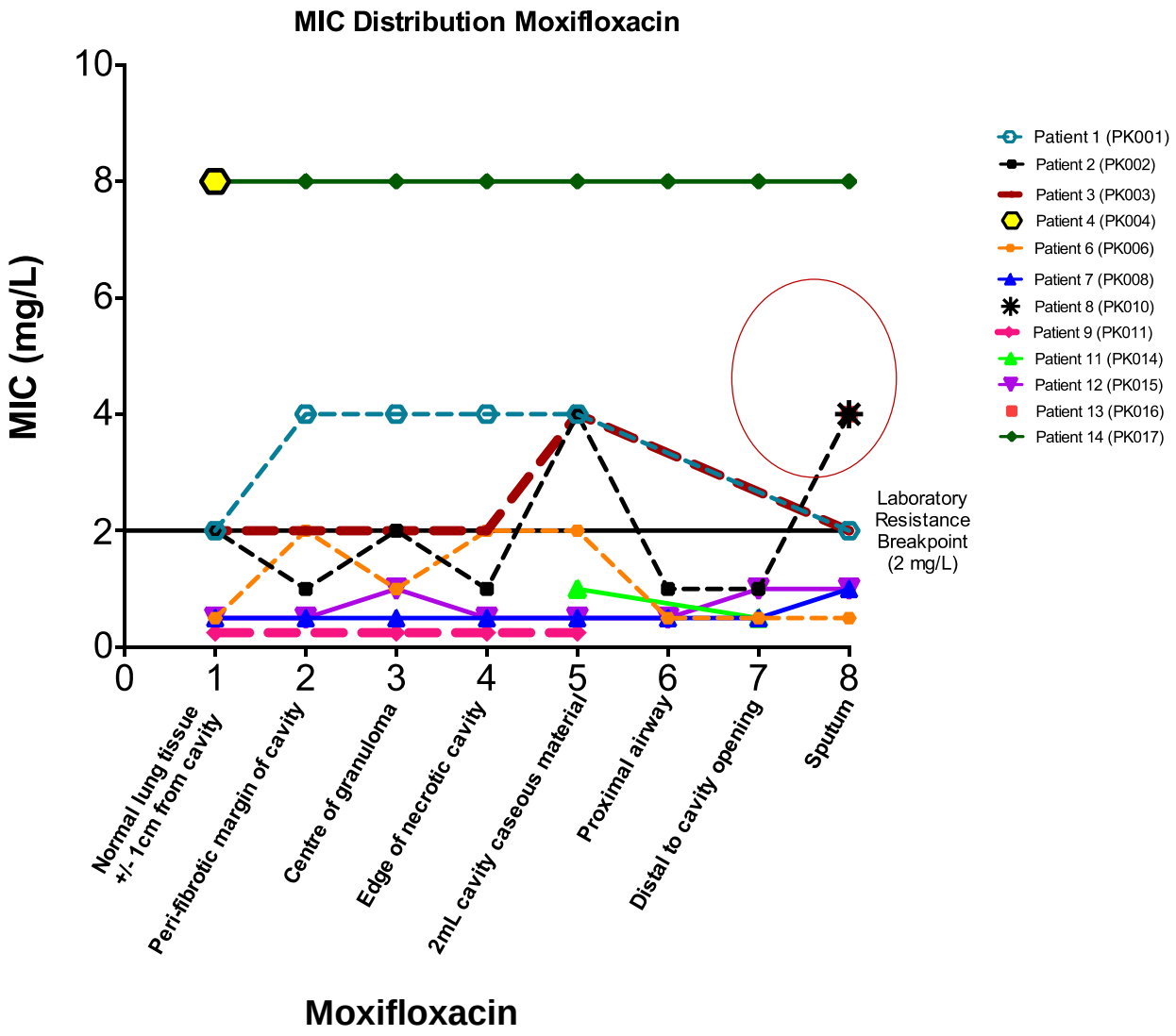
Vadwai V, PLoS One, 2011 (n= 5)

Different cavities of the same lung

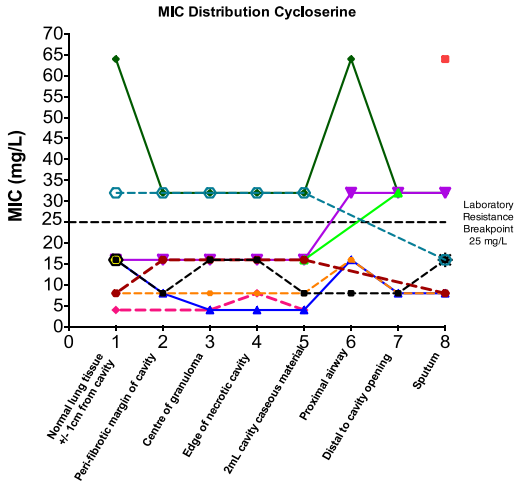
duPlessis DG, Tuberculosis, 2001 (n=2)
PM study of 15 patients

Liu Q, Scientific Rep, 2015 (n=1)
Hetero resistance by sputum deep sequencing but same strain

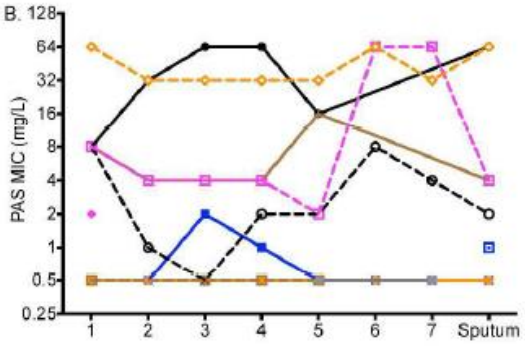
DST (MIC) Results n=14 (data for INH, RIF, EMB, RFB, STR, KAN, AMI, MXF, OFL, PAS, ETH, CYC analysed)



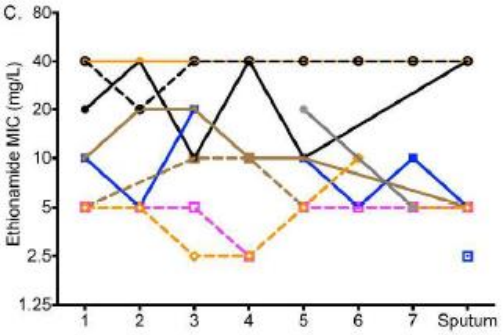
Cycloserine



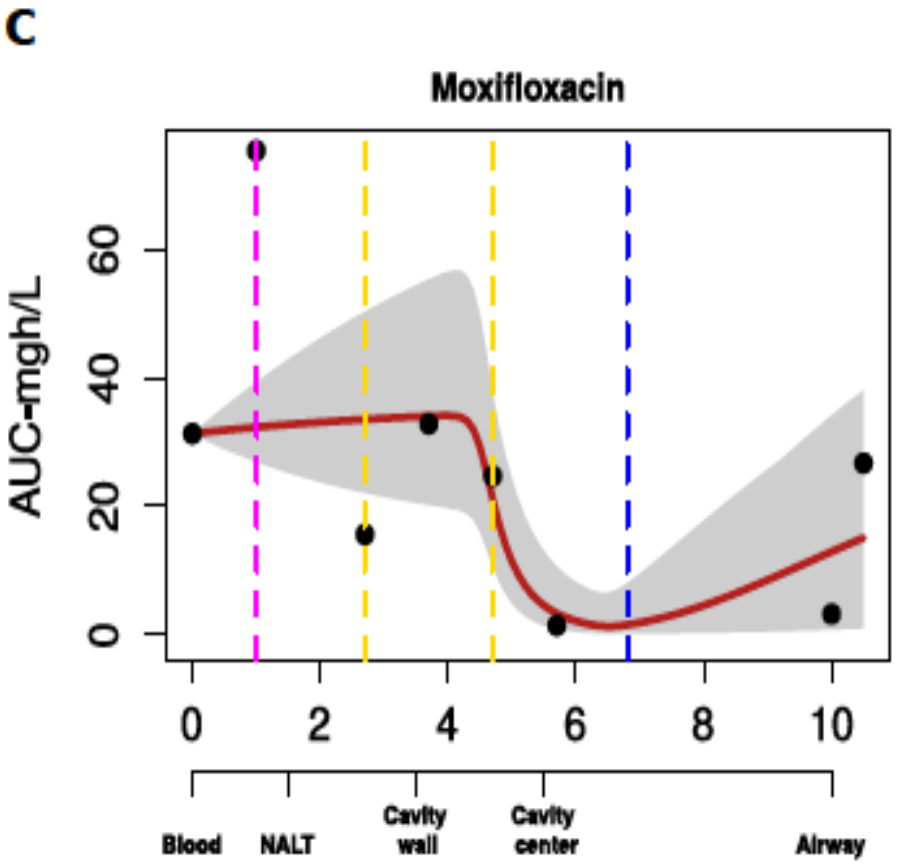
PAS

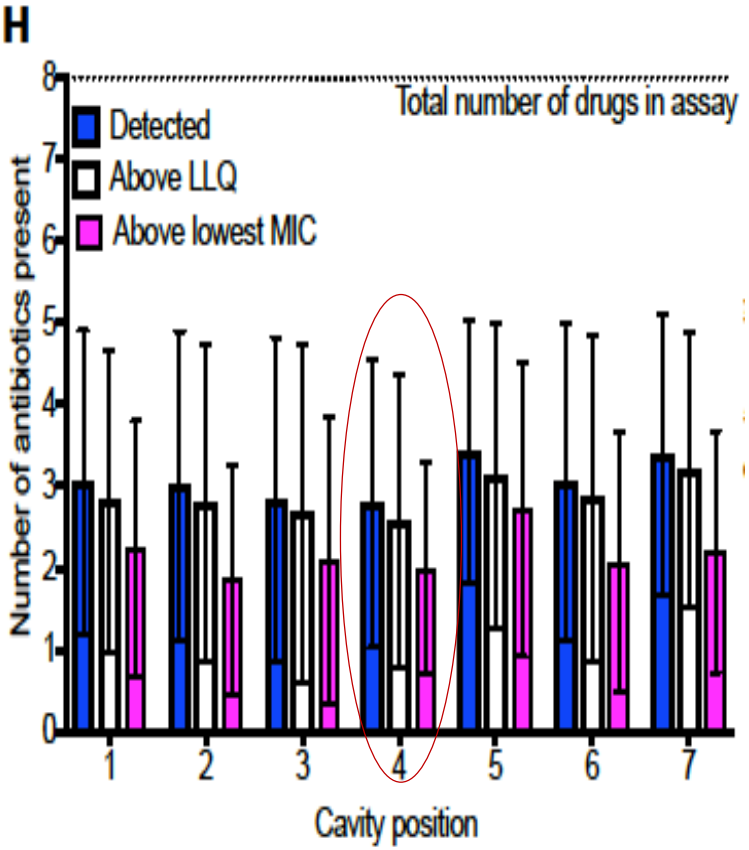


Ethionamide



➢ **Considerable variability by biopsy site**



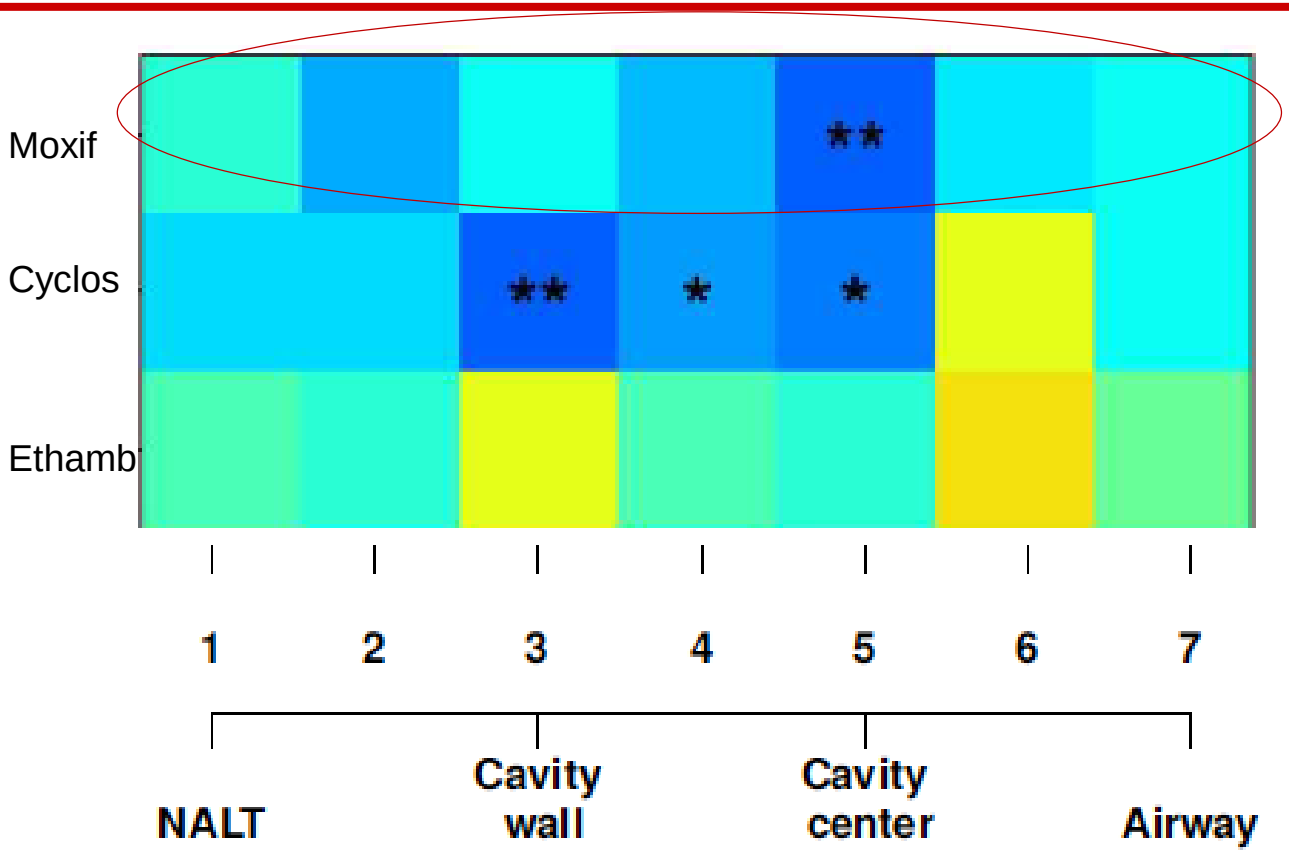


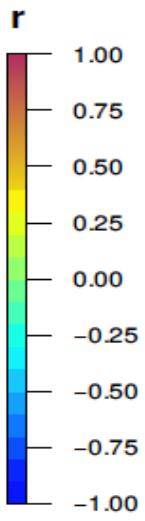
Reducing drug gradient across the cavity wall (and this correlated with increasing MIC)

The number of drugs detected at each position above lowest MIC for the drug

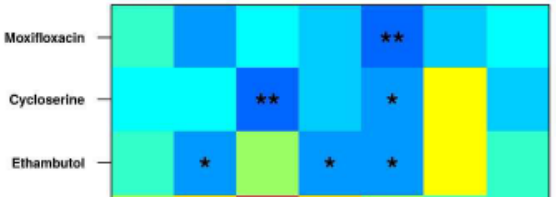
MIC versus 24 hour AUC (drug level correlation)

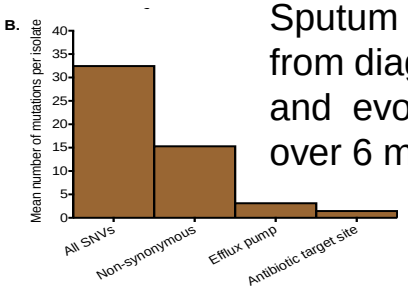
(minus 1= dark blue= perfect inverse correlation i.e low drug level and high MIC)





MIC vs. Gradient (blood to cavity position)





Sputum SNPs from diagnosis and evolving over 6 mnths

As AUC decreases MIC increases

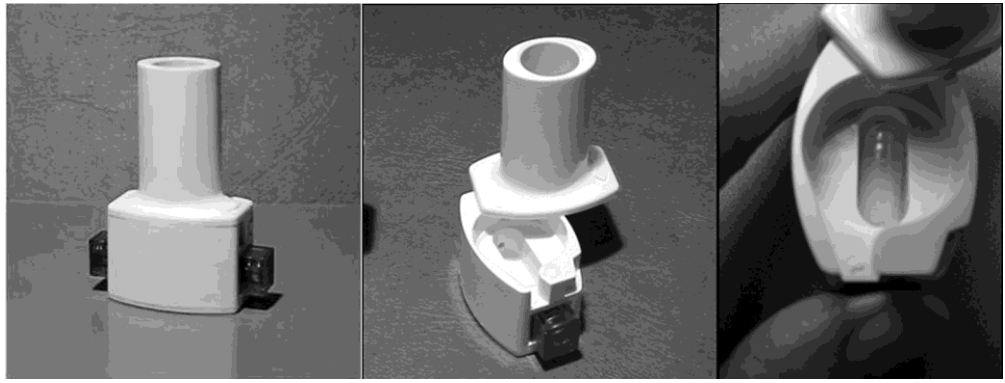
Implications

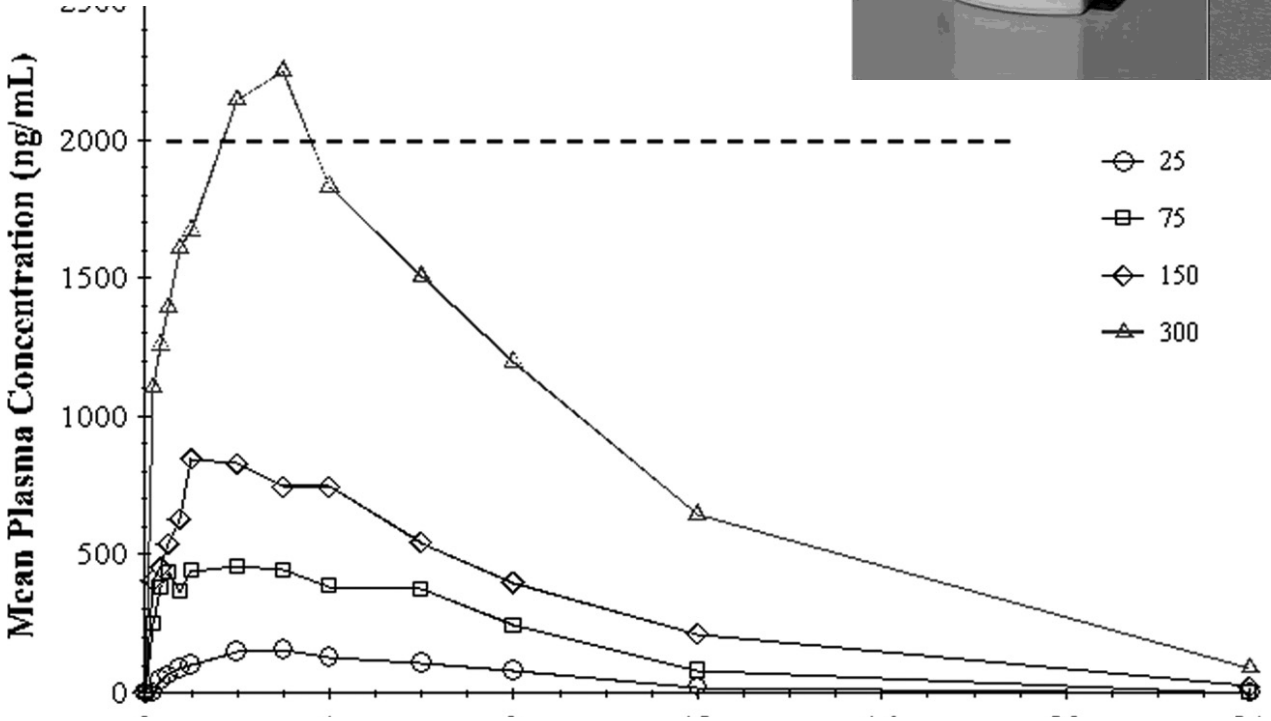
Alternative approaches may prevent PK mismatch and resistance amplification (in addition to programmatic strengthening):

- **Adjunct inhaled antibiotics**
- Efflux pump inhibitors
- TDM (FQ, LNZ, BDQ) for optimal dosing to achieve good intra-cavitory levels
- Selection of drugs for clinical trials with high intra-cavitory penetration (dynamic sink models for each drug linking serum levels and the hollow fibre system) - will be able to monitor like other biomarkers of treatment response

Phase 1 study of inhaled capreomycin- well tolerated

Dharmadhikari and Nardell, AAC, 2013





- Adjunctive inhaled therapy is feasible in MDR-TB

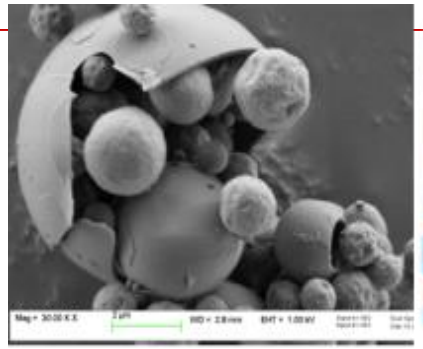
Implications

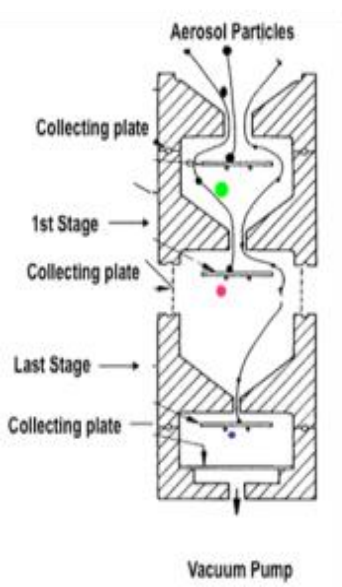
- Alternative approaches may prevent PK mismatch and resistance amplification (in addition to programmatic strengthening):

- **Adjunct inhaled antibiotics**
- Efflux pump inhibitors
- TDM (FQ, LNZ, BDQ) for optimal dosing to achieve good intra-cavitory levels
- Selection of drugs for clinical trials with high intra-cavitory penetration (dynamic sink models for each drug linking intracavitory levels with serum levels and the hollow fibre system) – Future we may be able to monitor levels like other biomarkers of treatment response

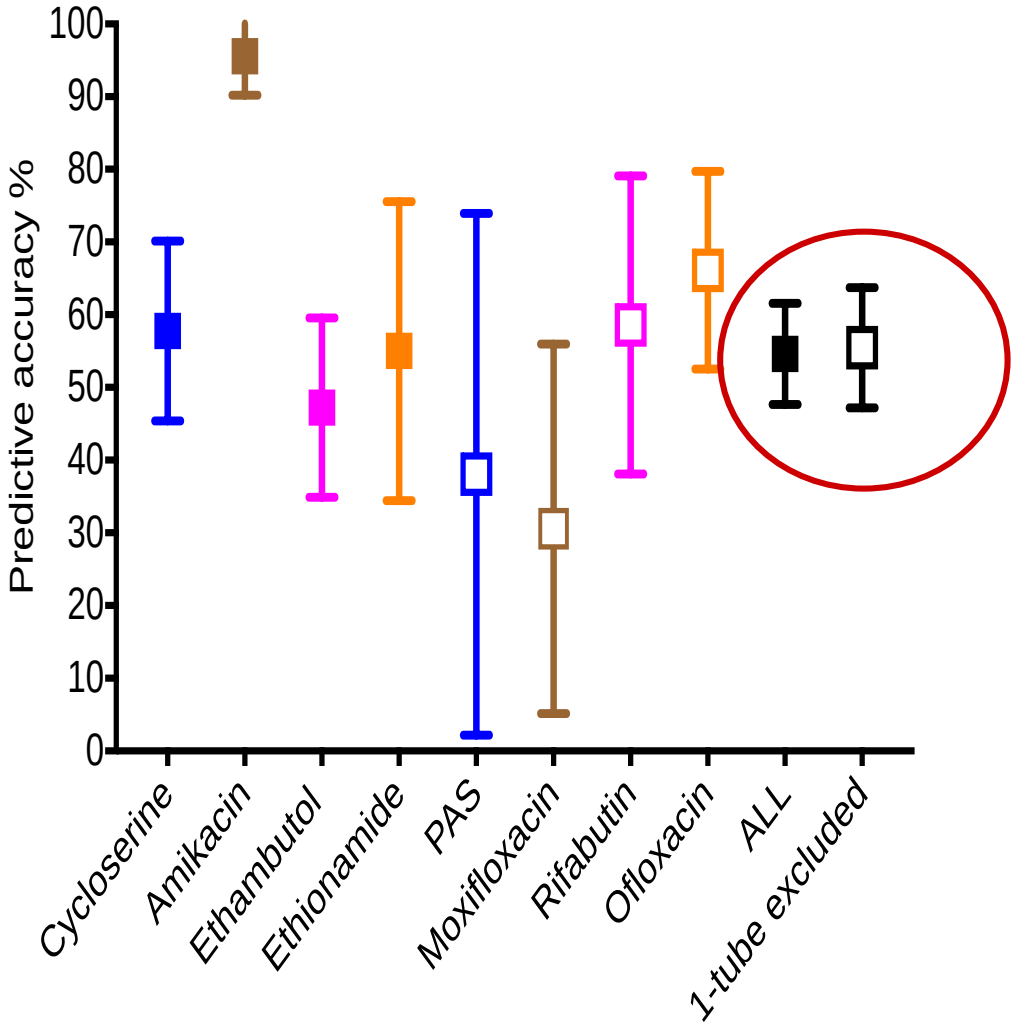
Ongoing work

- Inhaled formulations of ultrafine particles developed: CFZ, LNZ, AMIK, Others….
- Phase 1 safety studies of adjunct inhaled antibiotics, progressing to phase 2 lung explant and EBA studies



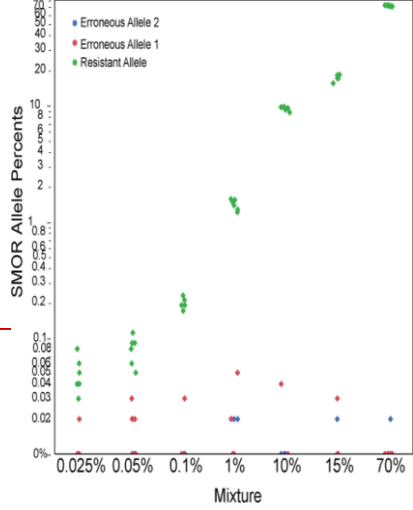


Lung Explant Study

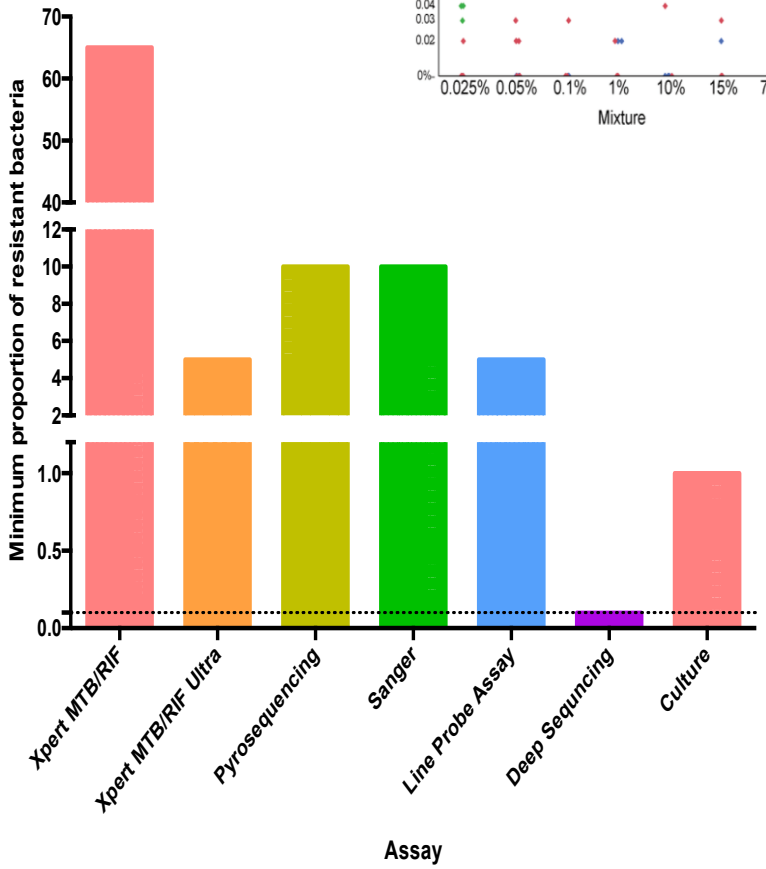


Accuracy of sputum MIC in predicting the MIC of isolates obtained from the tuberculosis cavity

Deep Sequencing using Sputum to Detect Low-level Resistance Populations and enabling Precision Medicine



- Targeted sequencing of resistance conferring genes
  - Multiplexed PCR followed by Illumina sequencing of amplicons (50k-200k)
- Detect resistance populations of 1:1000
  - Is this clinically relevant?
    - We currently treat based on ≥1% of bacterial population



Metcalfe, John Z., et al. Cryptic micro-heteroresistance explains *M. tb* phenotypic resistance, AJRCCM, 2017

Acknowledgements

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Prof Edward Wakeland, Prithvi Raj, Chaoying, Igor, Kasthuri, Ben)

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