Pharmacokinetics of TB drugs at the site of disease in children with pulmonary TB

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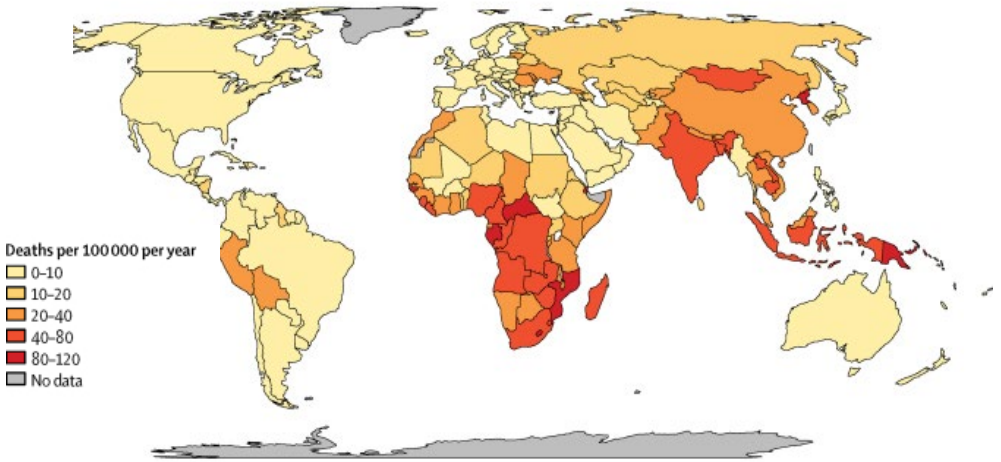
IMPAACT Annual Meeting 2021

The burden of paediatric TB

- 12% of global case burden
- 16% of mortality
- Excellent treatment outcomes
- ≈1.2m annual incident cases[1]
- Half remain untreated



Mortality rate paediatric TB (<5 years) in 2015 [1]

1. Global WHO TB Report, 2020,
2. Dodd Lancet Global Health 2017

Need for better TB treatment

Shorter duration, safe, tolerable

Optimization of dosing and regimens

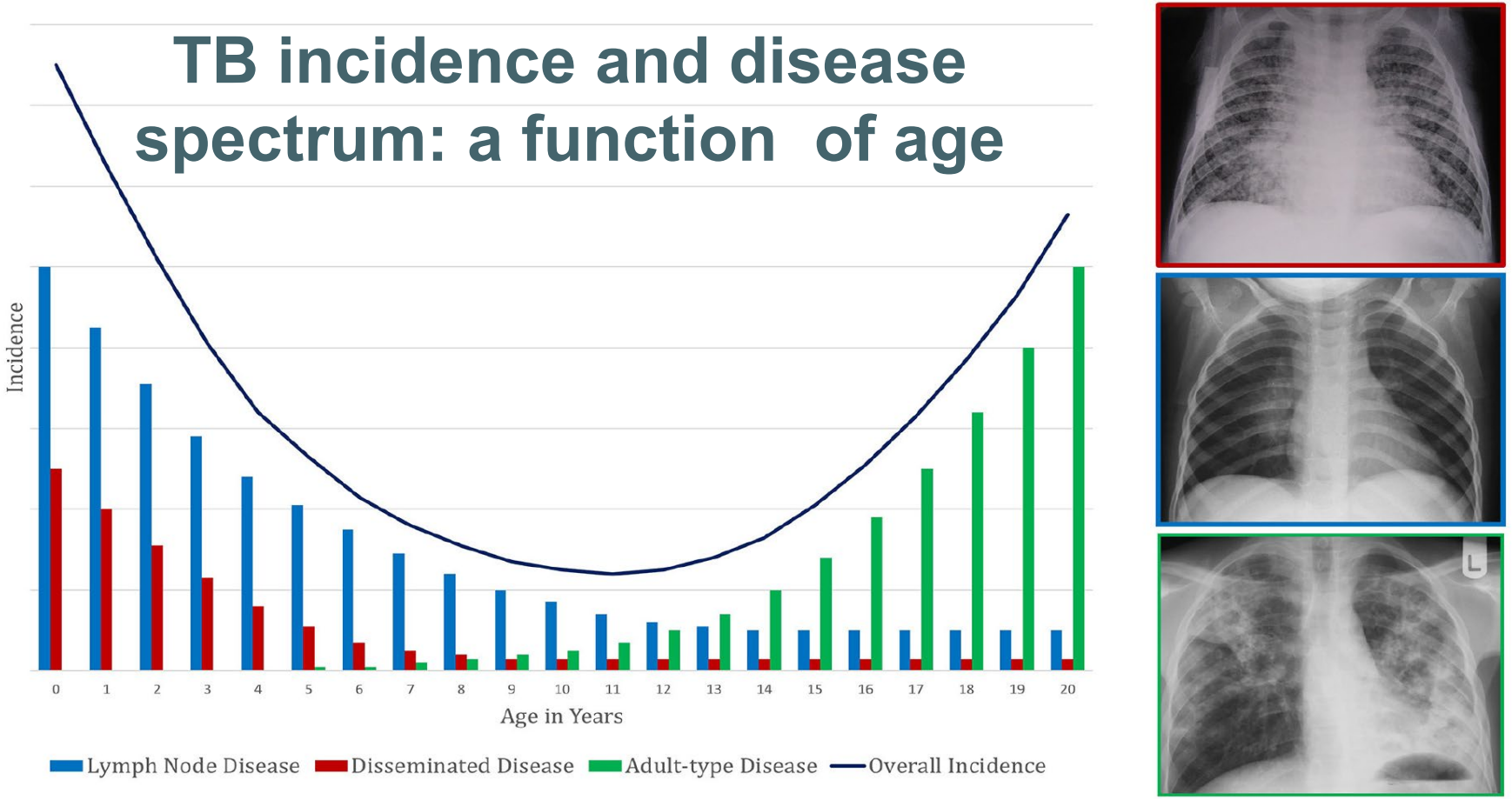
Adults->Suboptimal concentration (lung)→ Treatment failure

Sanctuaries- site of disease (TBM)

Specificities of certain populations: children

Paed TB treatment→ extrapolated from adult efficacy data

Limited consideration to spectrum of disease or PK variability



Front Immunol. 2018; 9: 2946

FIGURE 1 | Conceptual framework to demonstrate the pattern of change in tuberculosis incidence with age. This represents a composite of risk of infection and risk of subsequent disease progression. The presentation of disease is demonstrated by a representative X-ray in a box colored according to the disease phenotype legend.

PK: children are not small adults

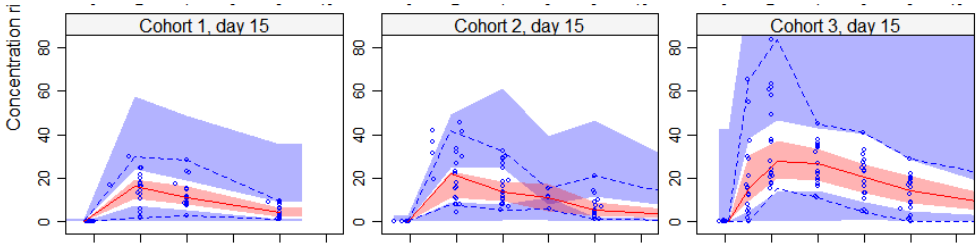
- PK variability
  - Relatively faster drug metabolism
  - Maturation of organs and absorption
- Lower plasma concentrations for same mg/kg
- Paediatric doses derived from extrapolating adult data-> underdosing
- Even with new WHO doses-> low plasma exposure

Rifampicin and children

- Higher RIF doses accelerate treatment response → enable shortening of TB therapy in adults [1,2,3]
- Low exposure to RIF→ possibly associated with worse treatment outcomes in children[4]

The OPTIRIF Study[5]

Rifampin doses needed for children to obtain exposures similar to adults on 35 mg/kg ($AUC_{0\text{-}24h}$ 235 mg/L*h) ?

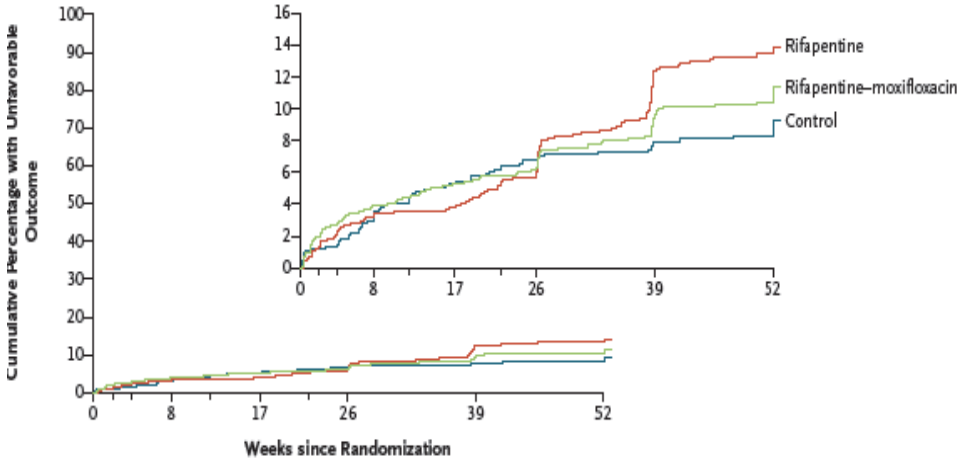


Doses of 60-75 mg/kg are needed for children to reach comparable exposures to adults getting a 35 mg/kg dose

1.Svensson et al. CID 2018; 2. Boeree et al. AJRCCM 2015; 3. Jayaram et al. AAC 200; 4. Swaminathan et al CID,
5. The OptiRIF study: pharmacokinetics and safety of high-dose rifampicin in children (PI Anneke Hesseling)

Shortening TB treatment

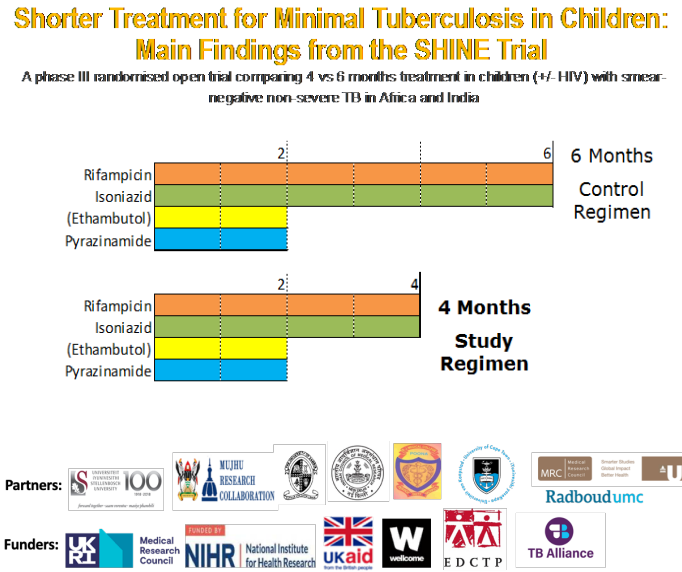
Study 31



4m rifapentine, isoniazid, pyrazinamide and moxifloxacin is NON INFERIOR to standard 6m treatment

Dorman NEJM 2021

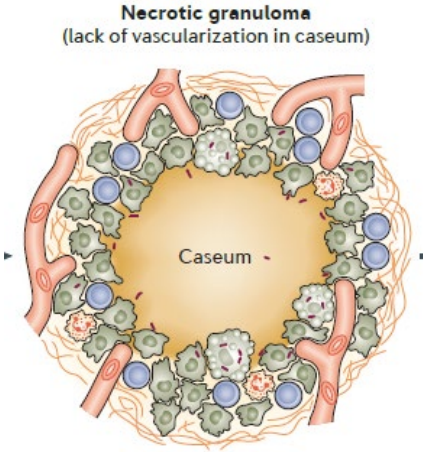
SHINE Trial



Turkova, under review

Site of Disease (SOD)

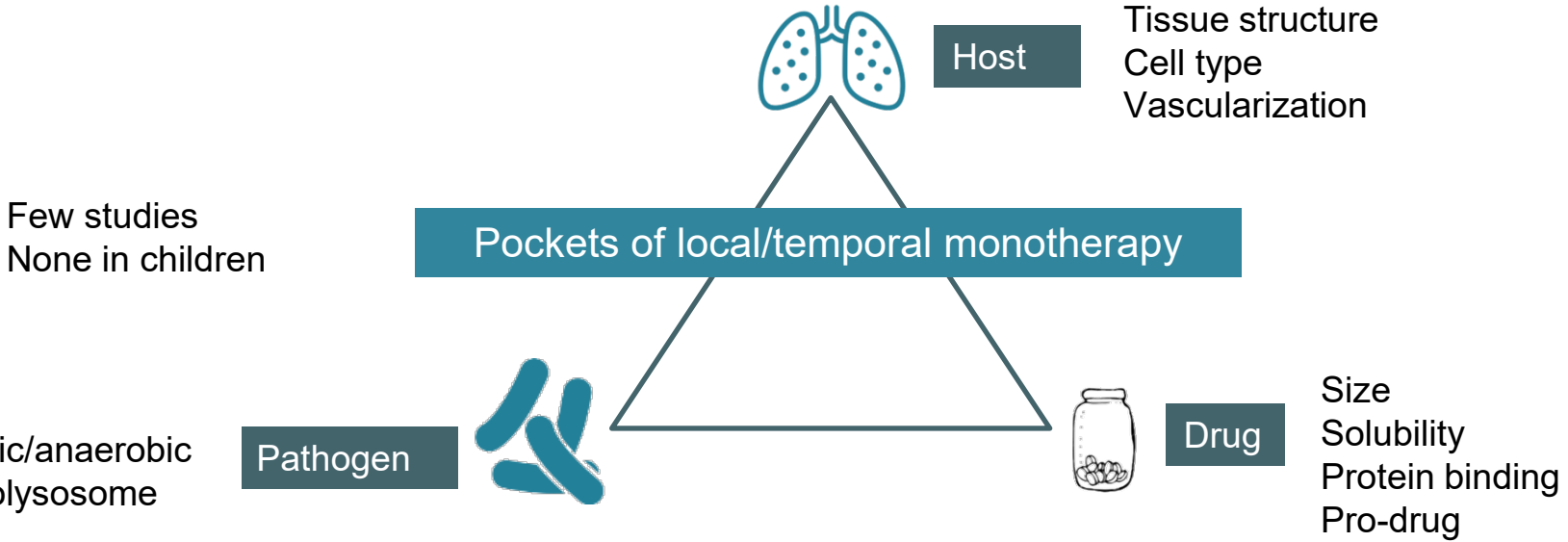
- Complex pathway of anti-TB drugs from blood → *M.tb* cells
- Most TB drugs were introduced without considering properties influencing drug distribution
- Plasma concentrations **not predictive** of SOD concentrations



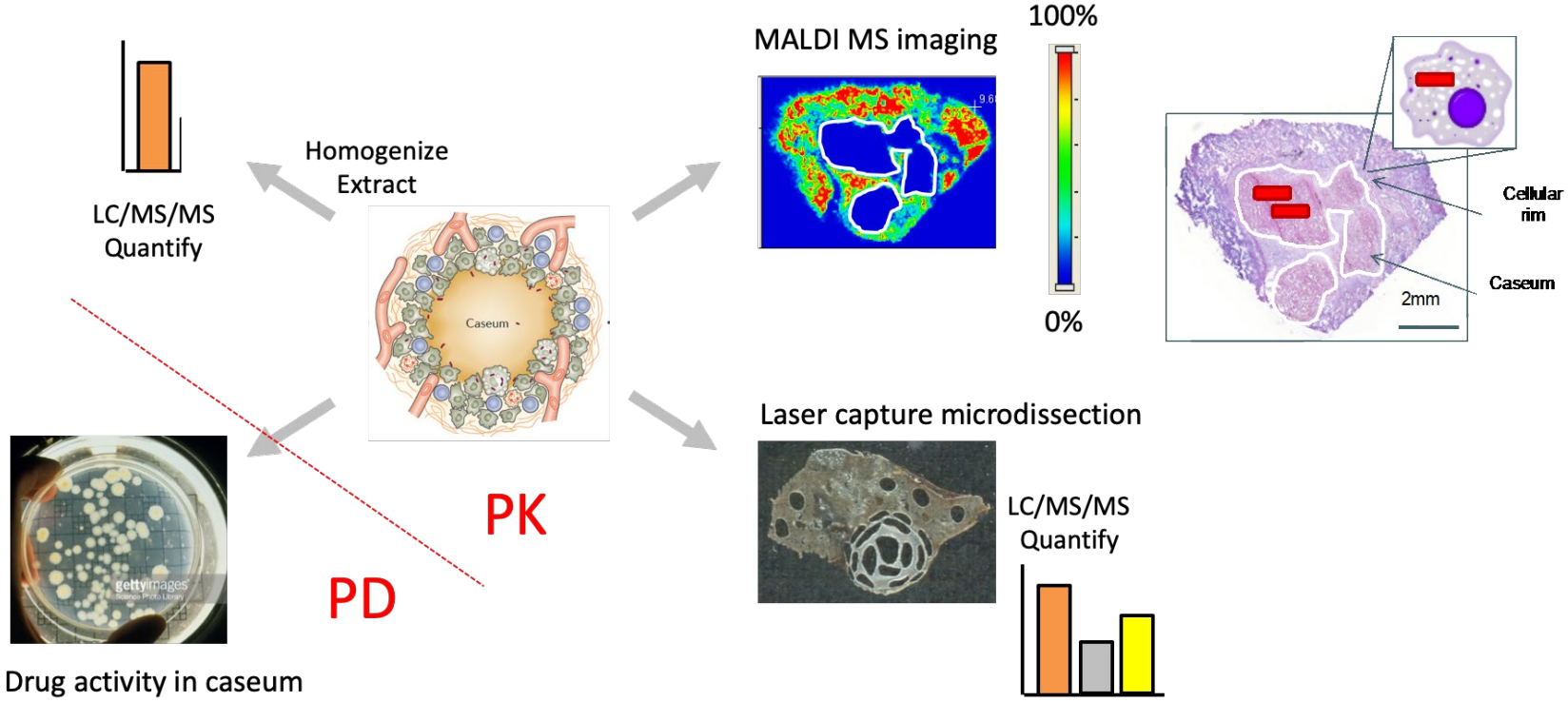
Dartois. Nature Review: Microbiology (2014)

Site of Disease (SOD)

Understanding factors that drive drug distribution at SOD could enable more effective use, design new regimens



SOD PK-PD methods



Courtesy of V Dartois, Center for Discovery and Innovation, Hackensak, NJ

Suboptimal concentrations:

Acquisition of Resistance

Drug-Penetration Gradients Associated with Acquired Drug Resistance in Patients with Tuberculosis

Keertan Dheda[1,2*], Laura Lenders[1], Gesham Magombedze[3], Shashikant Srivastava[3], Prithvi Raj[4], Erland Arning[5], Paula Ashcraft[5], Teodoro Bottiglieri[5], Helen Wainwright[6], Timothy Pennel[7], Anthony Linegar[7], Loven Moodley[7], Anil Pooran[1], Jotam G. Pasipanodya[3], Frederick A. Sirgel[8], Paul D. van Helden[8], Edward Wakeland[4], Robin M. Warren[8], and Tawanda Gumbo[1,3*]

American Journal of Respiratory and Critical Care Medicine Volume 198 Number 9 | November 1 2018

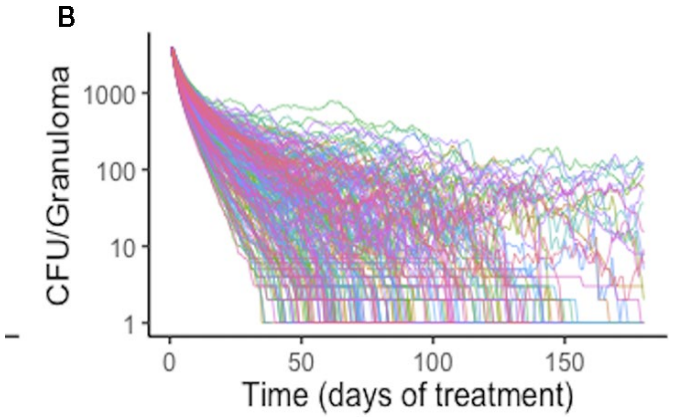
Genomic analyses of *Mycobacterium tuberculosis* from human lung resections reveal a high frequency of polyclonal infections

Miguel Moreno-Molina[1], Natalia Shubladze[2], Iza Khurtsilava[2], Zaza Avaliani[2], Nino Bablishvili[2], Manuela Torres-Puente[1], Luis Villamayor[3], Andrei Gabrielian[4], Alex Rosenthal[4], Cristina Vilaplana[5,6,7], Sebastien Gagneux[8,9], Russell R. Kempker[10], Sergo Vashakidze[2] & Iñaki Comas[1,11]

NATURE COMMUNICATIONS | (2021)12:2716 | https://doi.org/10.1038/s41467-021-22705-z | www.nature.com/naturecommunications

Suboptimal concentrations:

Ability to Sterilize



Both Pharmacokinetic Variability and Granuloma Heterogeneity Impact the Ability of the First-Line Antibiotics to Sterilize Tuberculosis Granulomas

Joseph M. Cicchese[1], Véronique Dartois[2,3], Denise E. Kirschner[4] and Jennifer J. Linderman[1]*

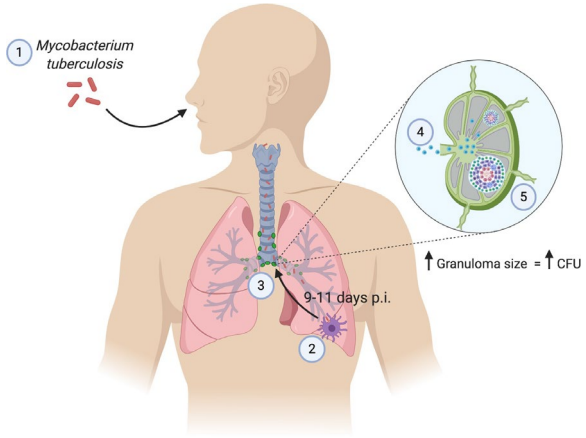
frontiers in Pharmacology

March 2020 | Volume 11 | Article 338

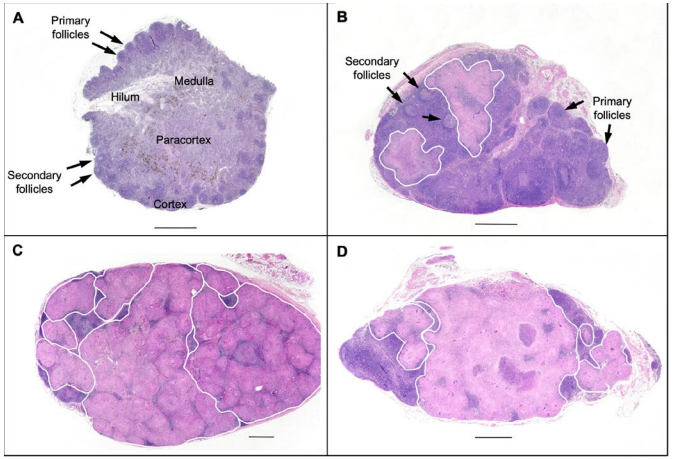
Rif most impacted natural variability in plasma PK

Wide spread of treatment outcomes (38-180days to sterilization)

Lymh node: neglected battlefield



12.



- Sites for antigen presentation and immune activation→ contain *M.tb*
- M.tb disrupts and replaces normal architecture LN
- Sites for mycobacterial persistence

Sharie Keanne C. GanchuaID. PLoS Pathog. 2020

Site of disease PK in children with complicated intrathoracic tuberculosis

SOD Study

IMPAACT Annual **Meeting** 2021

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Objective

Proof of concept study:

Characterize antituberculosis drug concentration in children with complicated severe intra-thoracic TB at the site of disease and to compare to those in plasma

Design

Tygerberg Hospital, Cape Town. Nov 2018-March 2019

Single site. Large collaboration

H (10-15 mg/kg),
R(10-20 mg/kg)
Z (30-40 mg/kg)
E(15-25 mg/kg)

INCLUSION CRITERIA

- **Intrathoracic complicated TB disease**
- RIF containing TB treatment regimen 14 days
- Admitted and scheduled to undergo EITHER

BRONCHOSCOPY

SURGICAL DECOMPRESSION

PROCEDURES

BAL,
LN TISSUE
RANDOMIZED
2,4,6H

TB drug DOSING (HRZE-)

PLASMA PK SAMPLING (0, +2, +4, +6h)
+
SOD PK SAMPLE (1 TIME-POINT)

LN TISSUE
ALL AT 2H

ANALYTICAL

LC/MS-MS: plasma and BAL
Tissue homogenizing PLUS LC-MS/MS for LN TISSUE (1)
laser capture microdissection (LCM) coupled to LC/MS-MS for LN TISSUE (2)

MODELLING

Plasma and SOD PK modelling
Penetration coefficient: RATIO drug concentration SOD /PLASMA

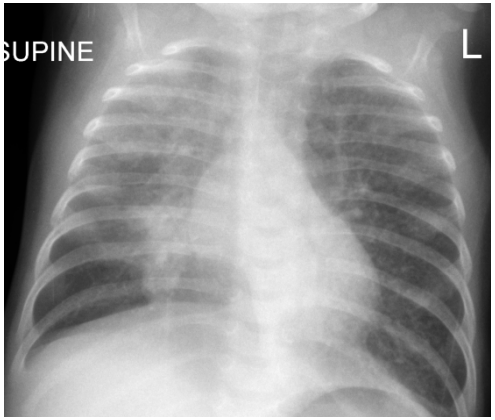
Baseline characteristics

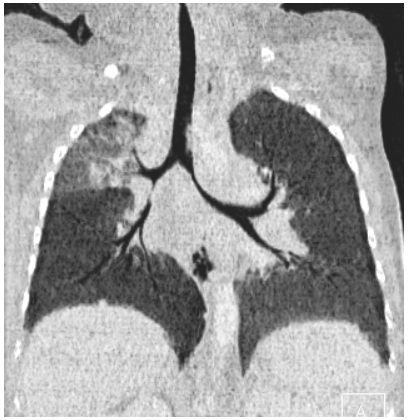
	BRONCHOSCOPY	SURGICAL DECOMPRESSION
	Group 1 (N=8)	**Group 2 (N=7)**
Sex (males/females)	3/5	4/3
Age (months)	**17.6 (6.3-41.0)**	**6.9 (3.4-17.2)**
Weight (Kg)	**9.9 (8.2-12.4)**	**7.1 (4.1-8.3)**
HIV positive	1	0
PTB	6	6
PTB+EPTB	2	1
Previous bronchoscopy	4 (50.0)	7 (100.0)
Days on TB treatment	**64 (60-73)**	**34 (28-74)**
Dose (mg/kg) PK day		
Rifampicin	12.8 (12.1-16.0)	12.3 (11.1-15.0)
Isoniazid	12.8 (11.4-14.8)	12.2 (11.1-12.7)
Pyrazinamide	28.5 (23.8-30.9)	30.5 (25.3-34.2)
Ethambutol	20.2 (18.6-22.8)	20.8 (20.2-24.1)
Corticosteroids	6 (75.0)	7 (100.0)

*2 patients recruited twice

Chest Radiology

	Group 1	Group 2
Consolidation	7 (87.5)	4 (57.1)
Collapse	3 (37.5)	1 (14.3)
Cavity	1 (12.5)	0 (0.0)
Paratracheal LN	3 (37.5)	4 (57.1)
Hilar LN	6 (75.0)	5 (71.4)
Subcarinal LN	7 (87.5)	6 (85.7)
Airway Compresion	6 (75.0)	6 (85.7)





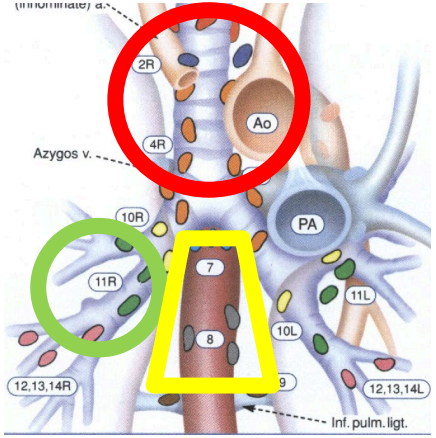
Bilat mediastilal necrotic hiliar LN and compression of LMB and BI (90%) and collapse consolidation of RU/RML with multiple scattered nodeules- (endobronchial spread)

Sample characteristics

BRONCHOSCOPY

BAL (8/8)
- 50% urea <BLQ
- All culture negative

LN (3/8) endobronchial biopsy



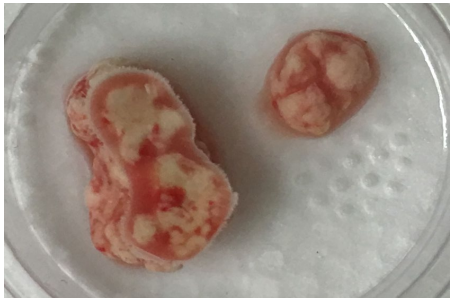
Paratracheal (2-upper; 4-lower paratracheal)
Hiliar (10, 11)
Subcarinal (7, 9)

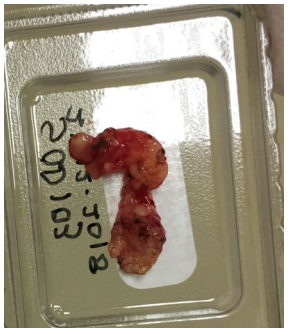
SURGICAL DECOMPRESSION

LN (7/7)
- necrotizing granulomatous inflammation
- little residual normal LN tissue

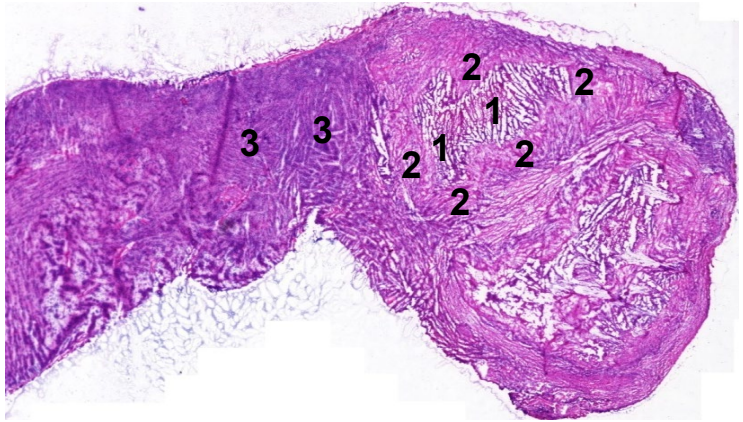
4/7 ZN +++

4/7 culture positive

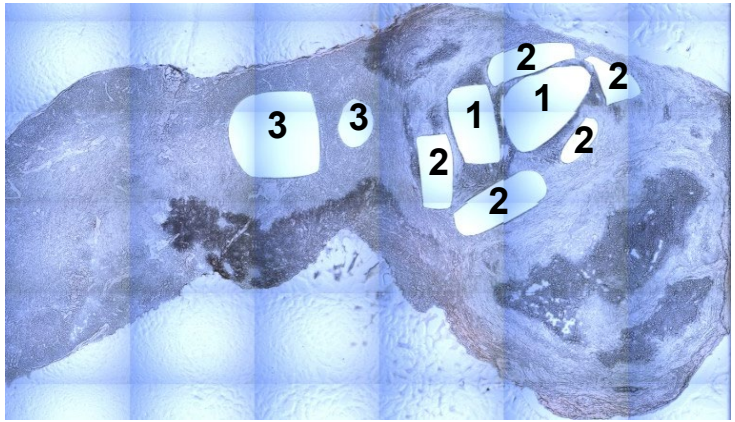




Laser capture microdissection (LCM)



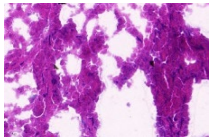
Hematoxylin and eosin stained lymph node containing two lesions



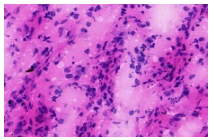
Corresponding serial sections taken for LCM-Regions 1-3 represent the areas dissected for drug quantitation by LC-MS/MS.

Histology of the different areas dissected

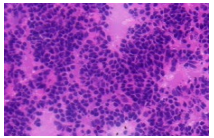
Caseum

1 

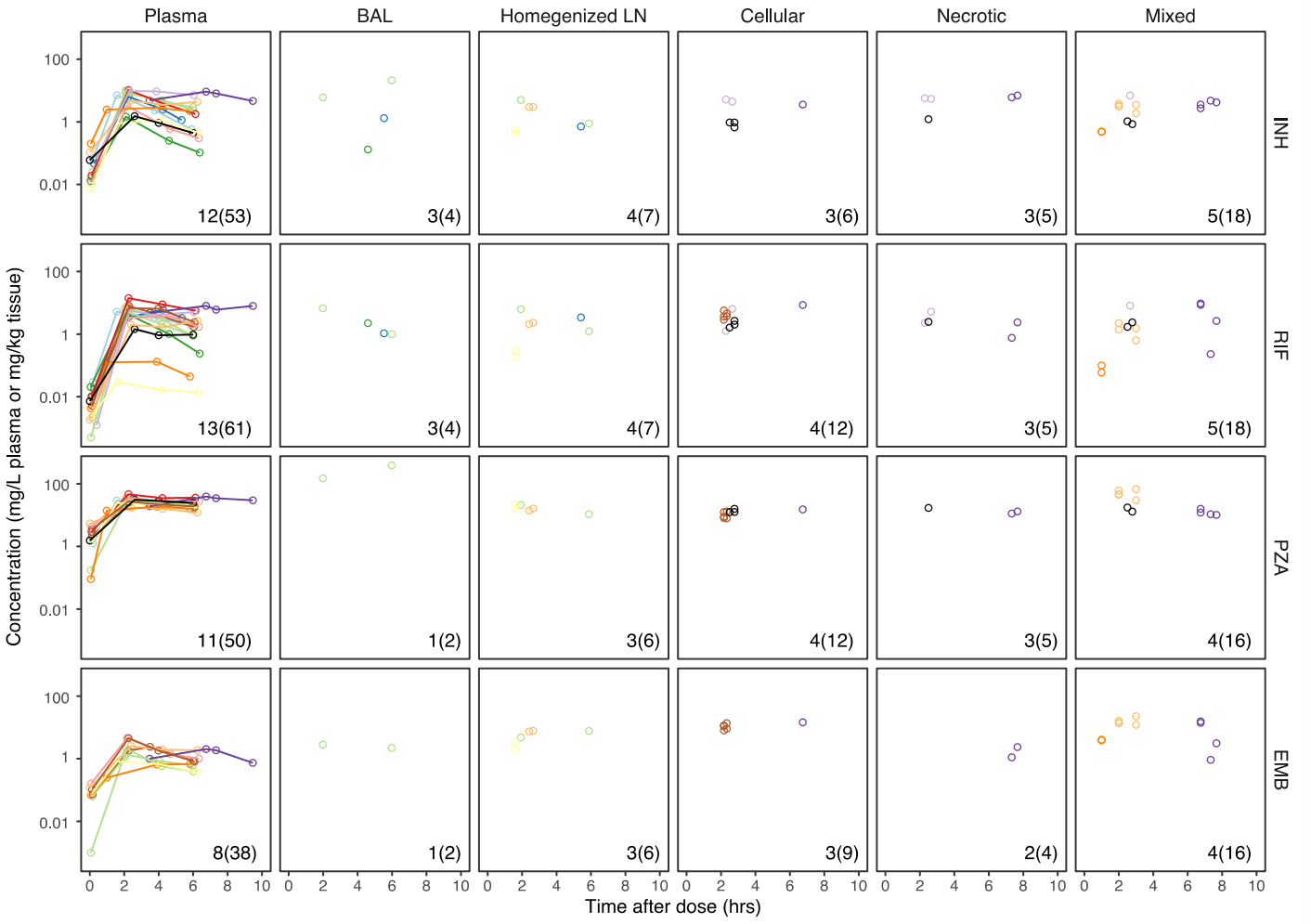
Cellular layer

2 

Lymphocyte rich region

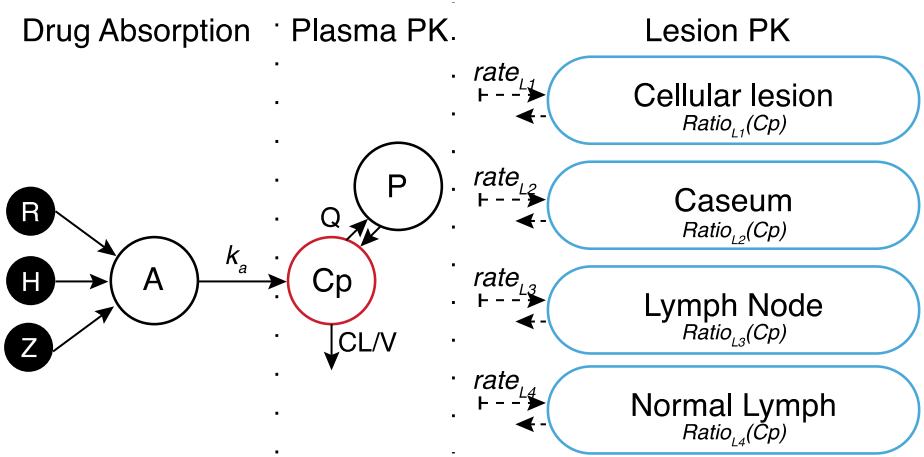
3 

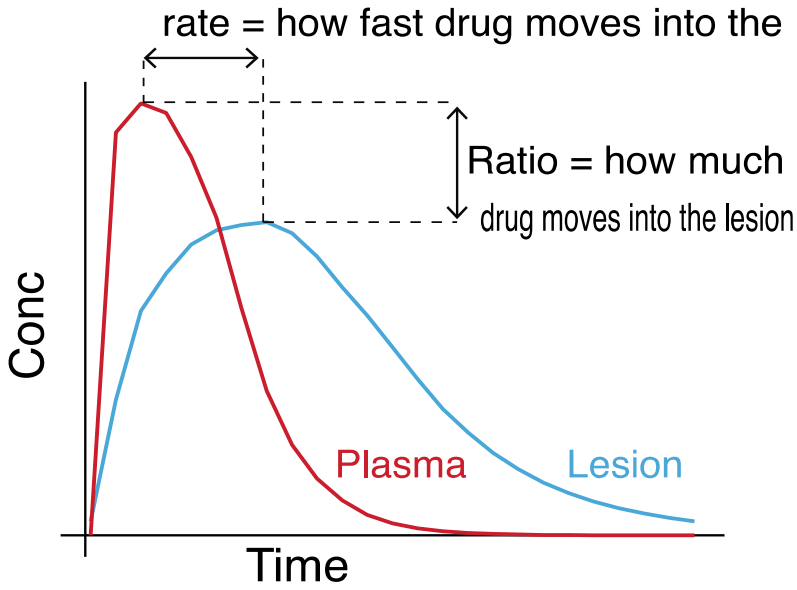
Raw PK data


Plasma
BAL
Homegenized LN
Cellular
Necrotic
Mixed
INH
RIF
PZA
EMB
12(53)
3(4)
4(7)
3(6)
3(5)
5(18)
13(61)
3(4)
4(7)
4(12)
3(5)
5(18)
11(50)
1(2)
3(6)
4(12)
3(5)
4(16)
8(38)
1(2)
3(6)
3(9)
2(4)
4(16)
100
1
0.01
0
2
4
6
8
10
Concentration (mg/L plasma or mg/kg tissue)
Time after dose (hrs)

Model structure

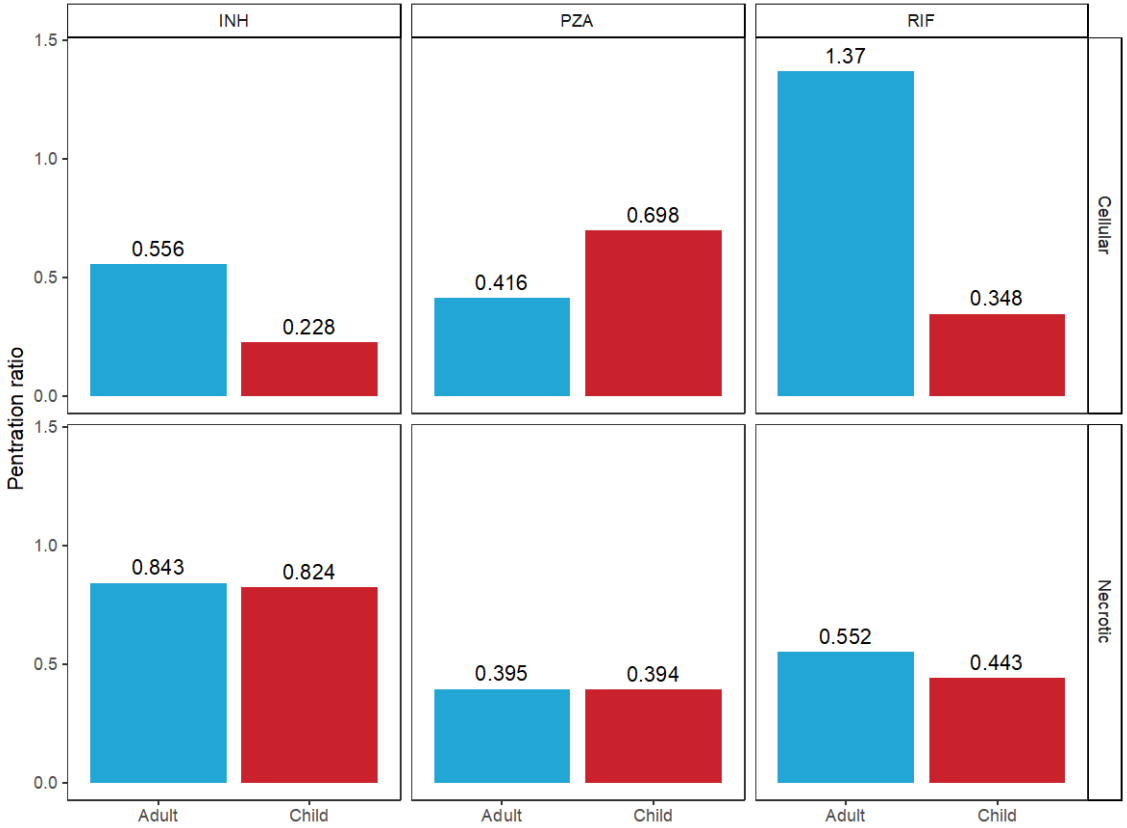
SOD Mechanistic population PK model (nonlinear mixed effect methodology)





Strydom et al., 2019

Penetration coeficients (ratio)



EMB
Cellular: 6.1
Necrotic: 1.1

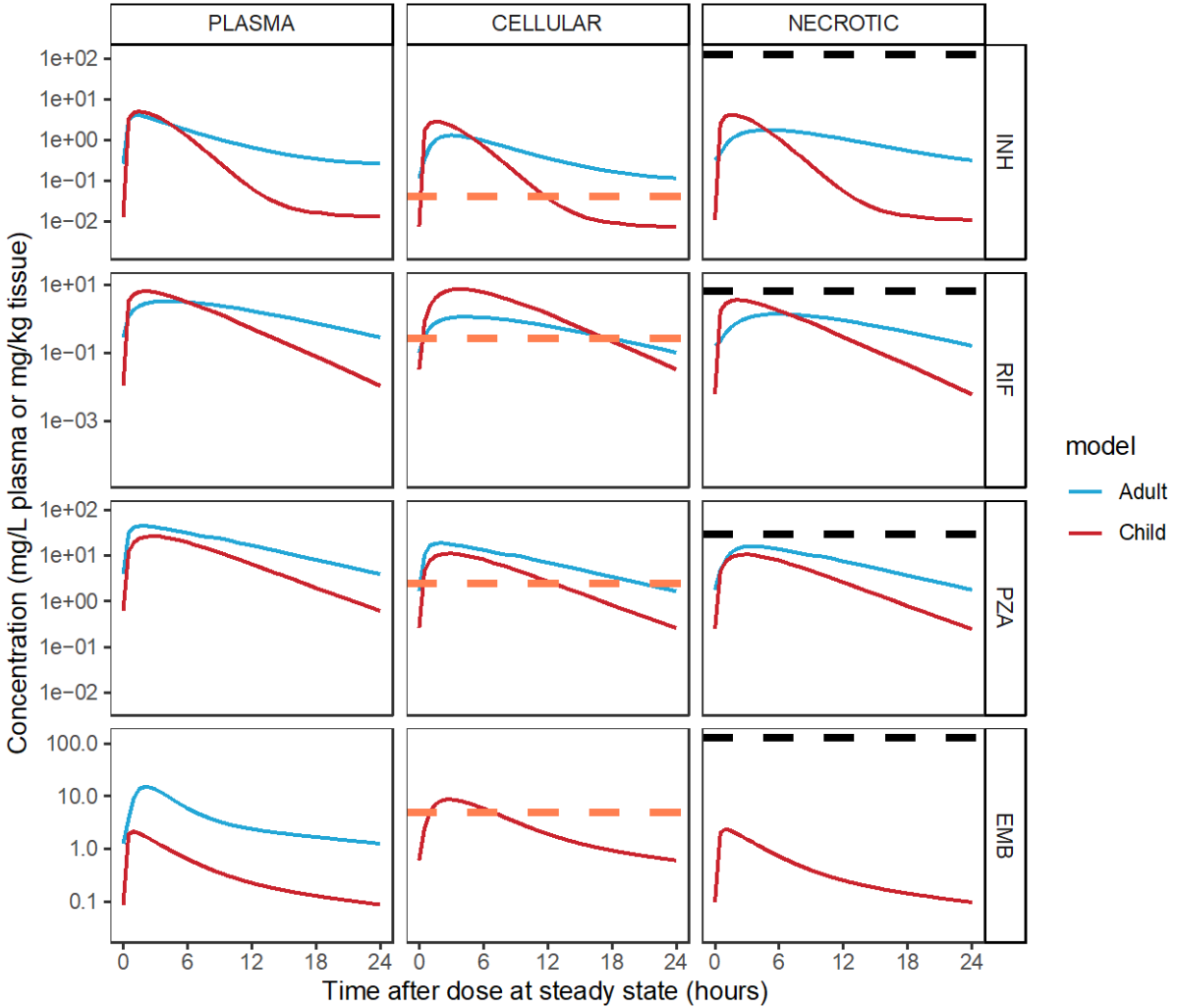
Model
Child
Adult

Adult data: Strydom et al., 2019

Simulation

	MIC [21–24]	Macrophage IC_{50} [25]	Caseum MBC[26]
Isoniazid	0·025 - 0·2	0·04	>128
Rifampicin	0·06 - 0.5	0·26	6·5
Pyrazinamide	25 - 100	>2·46	30
Ethambutol	0·5 - 5	>4·09	>128

Despite similar penetration coefficients compared to adults, overall low plasma exposures led to low site of disease exposures for all drugs except for isoniazid.



Conclusion and implications

Conclusions

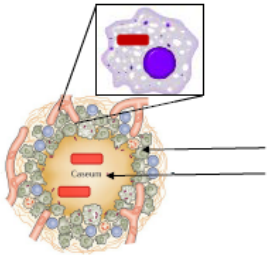
- Proof of concept study→ first data on paediatric SOD PK in PTB
- Feasible, but high technical expertise required
- Penetration coefficient better than in adults (good lesión penetration)
- Suboptimal plasma PK exposures leading to low SOD concentrations
- Possibility of achieving target concentration at SOD with ↑dosage?

Limitations

- Highly selected group of patients-severe PTB disease
- Impact of con-med and iv fluids (drug-drug interactions?)
- BAL- dilution factor
- Sparse sampling and SOD time-points

Next steps

- Optimization of doses/regimens should rely on SOD PK/PD and plasma based indices
- Methods: Less invasive methods? BAL, sputum?
- Correlate lesion PK, lesion PD and efficacy
- Immunology and microbiology
- Modeling- nesting within studies (disease spectrum, 2nd line drugs)



1. How much drug reaches each compartment?

PK

2. How much drug does it take to kill the resident bugs?

PD

3. How does that translate into lesion sterilization in an in vivo model?

PK-PD

↓ log CFU?
Sterilization?

Courtesy of V Dartois

Acknowledgments

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Natasha Strydom

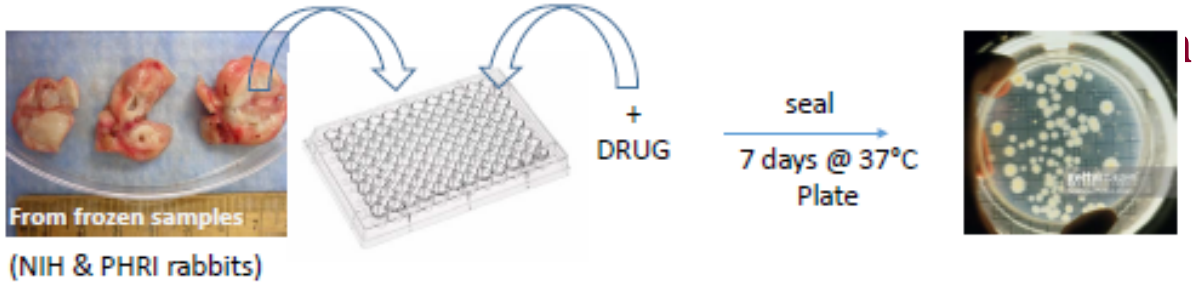
Elin M. Svensson

Thank you!

Elisa.lopez@isglobal.org

EXTRA SLIDES

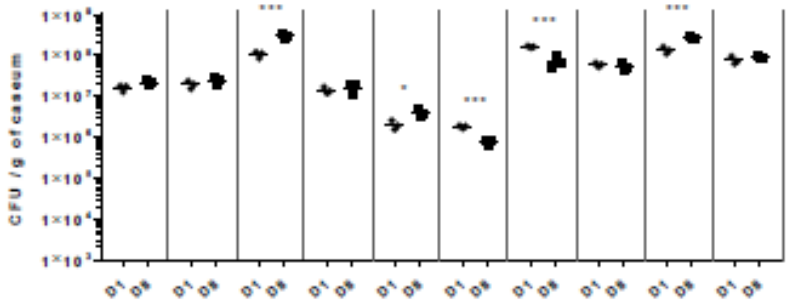
PK/PD



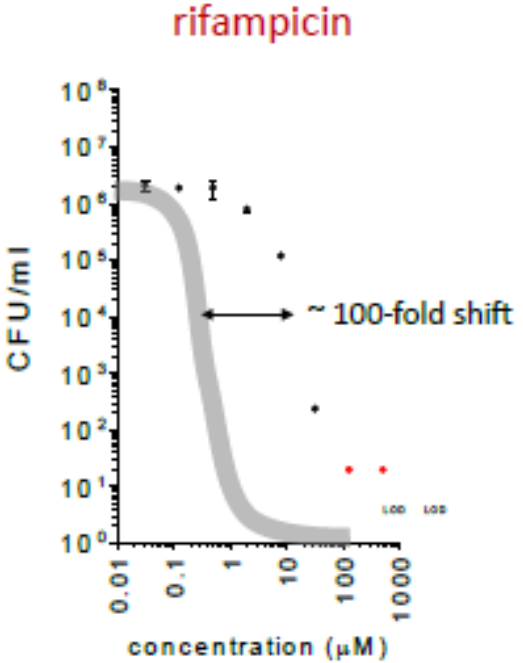
(NIH & PHRI rabbits)

NO DRUG control

Growth kinetics in 10 caseum batches from D0 to D7



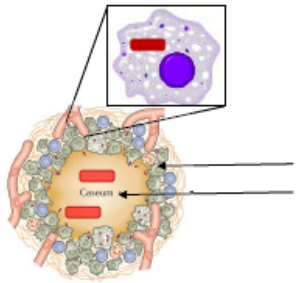
Caseum *M.tb* is highly drug tolerant to most drgs- only RFM sterilizing



Sarathy et al (2018) AAC.

Testing

- Optimization of doses and regimes should rely on SOD PK/PD plus plasma based indices.
  - Measure the concentrations of all TB drugs in cellular and necrotic lesion compartments
  - Measure the activity of all TB drugs against Mtb populations residing in each compartment
  - Correlate lesion PK, lesion PD and efficacy



1. How much drug reaches each compartment?

PK

2. How much drug does it take to kill the resident bugs?

PD

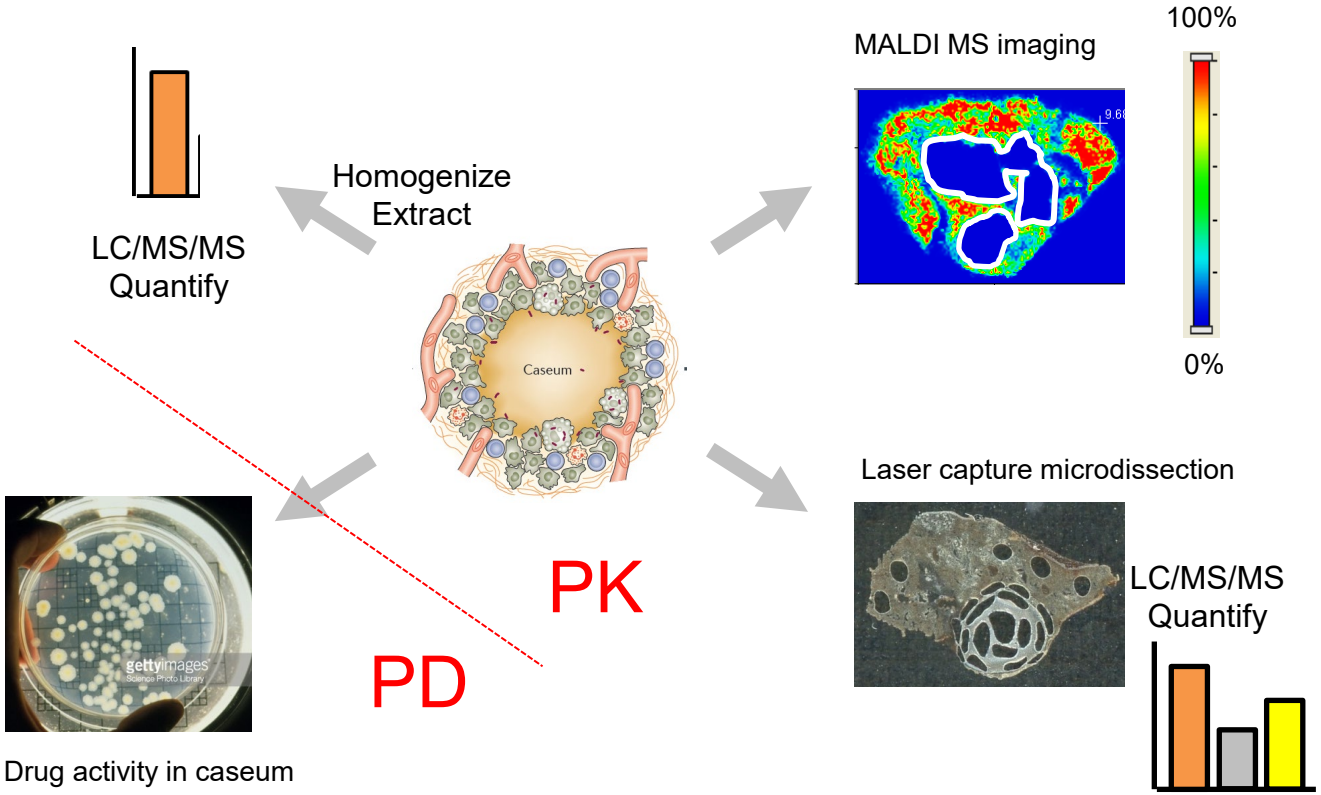
3. How does that translate into lesion sterilization in an in vivo model?

PK-PD

↓ log CFU?
Sterilization?

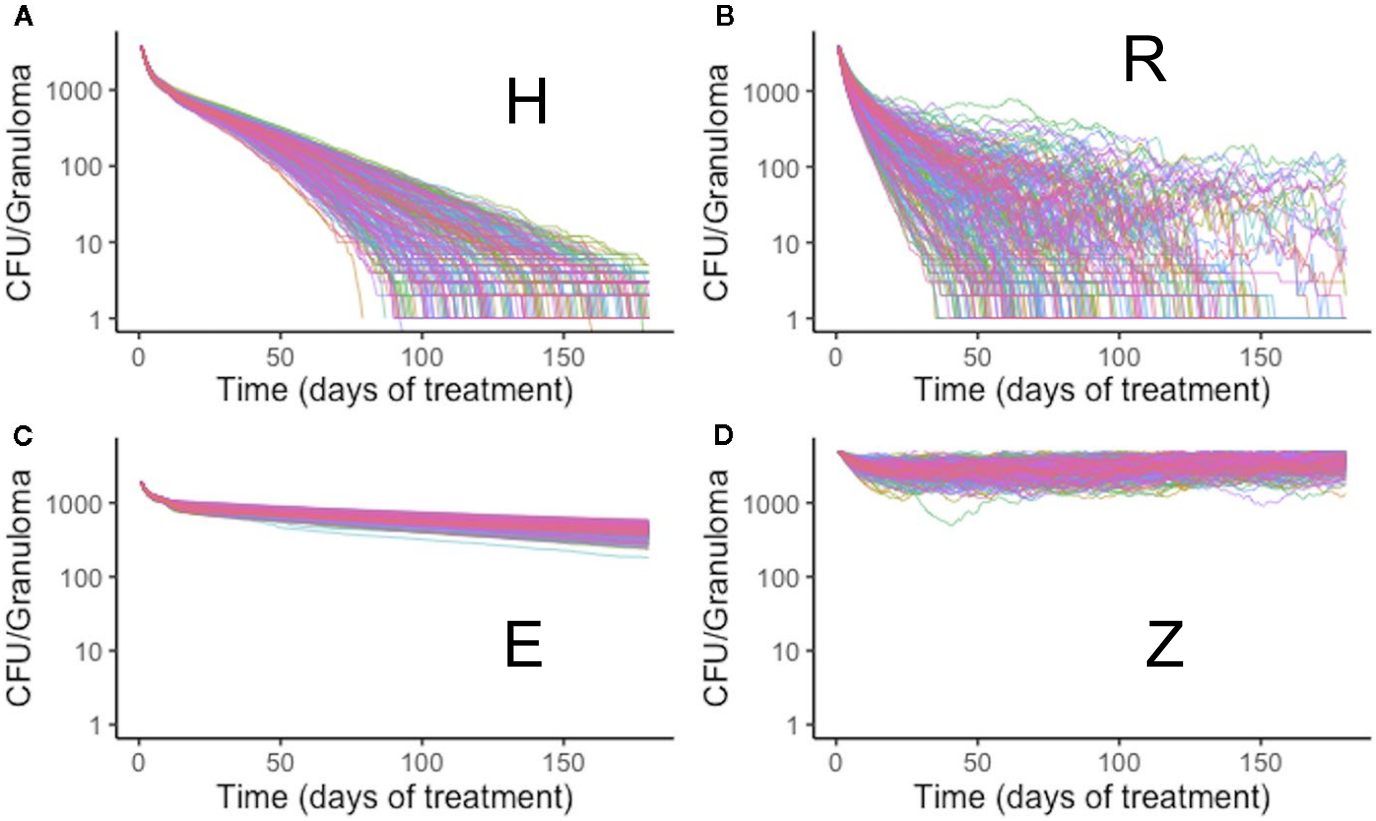
V Dartois

Lesion PK-PD methods



V Dartois

Sterilization



Cicchese JM, Frontiers in Pharmacology, 2020

Site of disease exposures

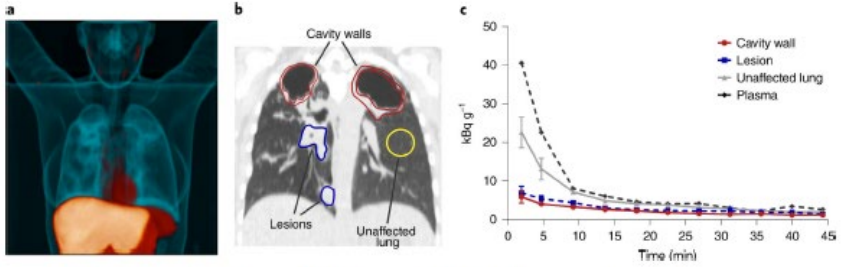
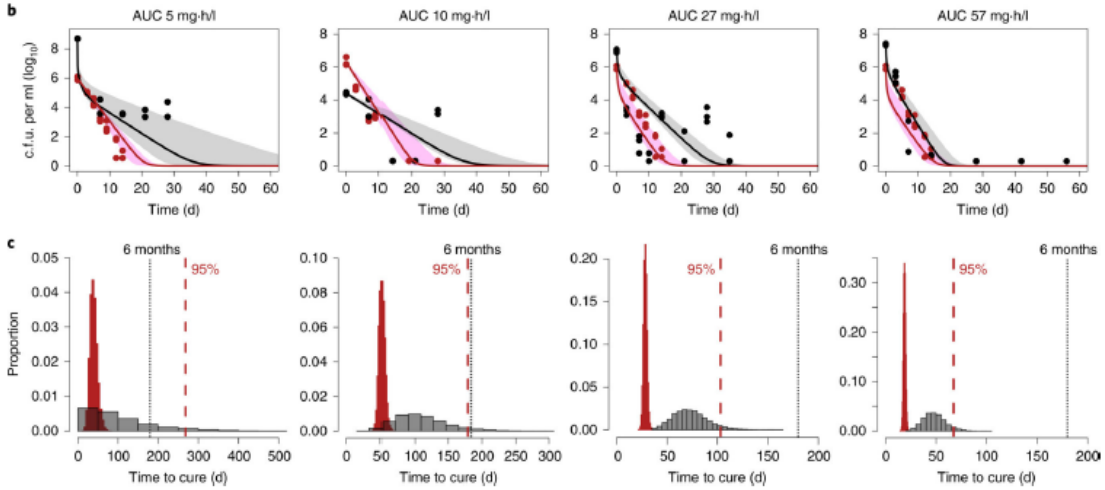


Fig. 1 | First-in-human dynamic [^{11}C]rifampin PET–CT studies in patients with TB.



Dynamic imaging in patients with TB reveals heterogeneous drug exposures in pulmonary lesions.

Ordonez et al.
Nat Med. 2020
April

PaediatricTB: spectrum of disease

- Paucibacillary
- Predominantly a disease of mediastinal lymph nodes in young children
- Spectrum of disease: extremely diverse and age-dependent