Pharmacokinetics and pharmacodynamics of anti-tuberculosis drugs in patients with tuberculosis

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The PhD project was carried out at the International Reference Laboratory of Mycobacteriology, 2010-2014

Supervisors:

Consultant, professor Niels Frimodt-Møller, DMSc
(principal supervisor)

Consultant, professor Åse Bengård Andersen, DMSc
(project supervisor)

Laboratory manager Arieh S Cohen, MSc, PhD
(project supervisor)

Papers

The thesis is based on three papers:

Simultaneous quantification of isoniazid, rifampicin, ethambutol and pyrazinamide by liquid chromatography/tandem mass spectrometry

[submitted APMIS]

Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study

[J Antimicrob Chemother 2014;69:2841-7]

Pharmacokinetics of isoniazid and rifampicin in patients with pulmonary tuberculosis: population PK-modeling and Monte Carlo simulation studies

[in preparation]

First-line TB treatment

Preferred regimen on a daily basis		Rationale
Initial Phase 56 doses (8 weeks)	**isoniazid** 5 mg/kg (maximum 300 mg) [children 10 mg/kg]	Clinical studies on mono-therapy and early bactericidal activity (EBA)
	rifampicin 10 mg/kg (maximum 600 mg) [children 15 mg/kg]	Plasma concentration > MIC* Adverse effects dose related? Cost
	ethambutol 15 mg/kg [children 20 mg/kg]	Optic neuritis Plasma concentration > MIC*
	pyrazinamide 25 mg/kg [children 35 mg/kg]	Adverse effects dose related?
Continuation Phase 126 doses (18 weeks)	**isoniazid** 5 mg/kg [10 mg/kg] (maximum 300 mg)	
	rifampicin 10 mg/kg [15mg/kg] (maximum 600 mg)	

* MIC; minimum inhibitory concentration

First-line TB treatment

- Multi-drug treatment
- Directly observed therapy (DOT)

→ **WHO Stop TB strategy**

Issue:

- 1.5 million died from TB in 2013
- Resistance to standard TB drugs is growing and multi-drug resistant TB (MDR-TB) is present in virtually all countries
- 480.000 people developed MDR-TB in 2013

Questions:

- What levels/patterns of non-adherence is predictive of acquired drug resistance and bacteriological failure?
- What ***other*** modifiable factors are associated with acquired drug resistance and bacteriological failure?

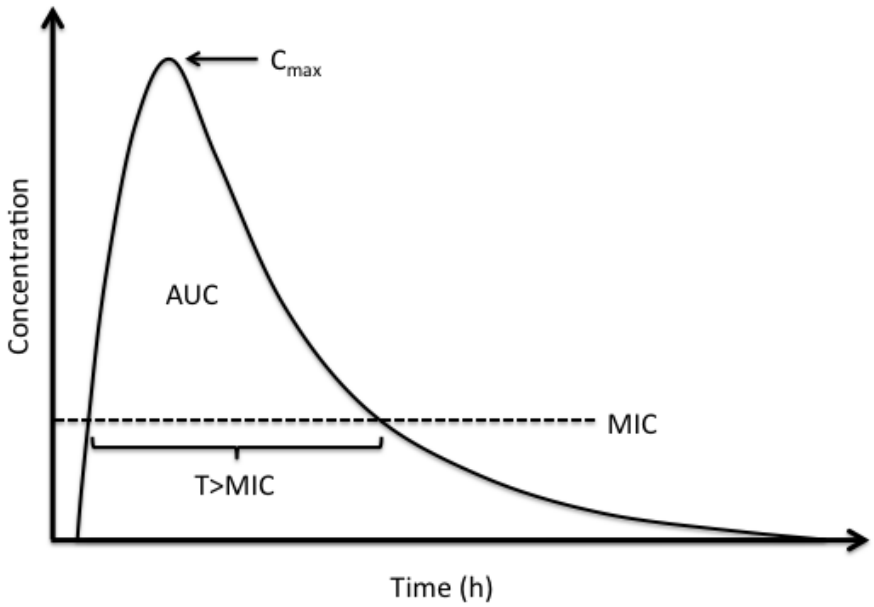
Treatment optimisation

Drug pharmacokinetics (PK)

serum concentration vs. time (C_{max}, AUC, $T_{½}$ etc.)

Drug pharmacodynamics (PD)

serum concentration vs. drug activity (minimum inhibitory concentration (MIC))



Three key PK/PD indices:

C_{max}/MIC **T>MIC**

AUC/MIC

Treatment optimisation

Strongly concentration-dependent antibiotic

AUC/MIC and C_{max}/MIC correlates the best to antimicrobial activity

Optimal dosage regimens;

Maximises plasma concentrations

Minimal concentration-dependent antibiotic

T>MIC correlates the best to antimicrobial activity

Optimal dosage regimens;

Maximises the duration of time above the MIC

Treatment optimisation

Strongly concentration-dependent antibiotic

AUC/MIC and C_{max}/MIC correlates the best to antimicrobial activity

Optimal dosage regimens;

Maximises plasma concentrations

Isoniazid, rifampicin, ethambutol and pyrazinamide

Minimal concentration-dependent antibiotic

T>MIC correlates the best to antimicrobial activity

Optimal dosage regimens;

Maximises the duration of time above the MIC

Does PK variability lead to low drug concentrations in some patients?
Does plasma concentration levels influence on treatment efficacy?

Therapeutic ranges?

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Normal ranges in healthy volunteers

	T_{max} (h)	$T_{½}$ (h)	C_{max} (mg/L)
Isoniazid 300 mg	0.75-2	3.5-4 / 1.5-2	3-5
Rifampicin 600 mg	2	2-4	8-24
Ethambutol 1200 mg	2-3	4-5 / 10-15	2-6
Pyrazinamide 2000 mg	1-2	9-11	20-60

Peloquin 1996 and 2002

Targets for optimal efficacy in mouse studies

	AUC/MIC (h)
Isoniazid 300 mg	500
Rifampicin 600 mg	271

Jayaram 2003, 2004

Neither normal C_{max} ranges nor AUC/MIC targets have been validated clinically

Aims

To develop a rapid, precise and accurate method for simultaneous quantitation of all four first-line TB drugs in human plasma samples, and to study plasma concentration levels of first-line TB drugs in groups of TB patients in Denmark

Main hypothesis:

Inter-patient pharmacokinetic variability is not recognized and standard dosing therefore leads to insufficient plasma concentration levels in some patients and consequently reduced treatment efficacy

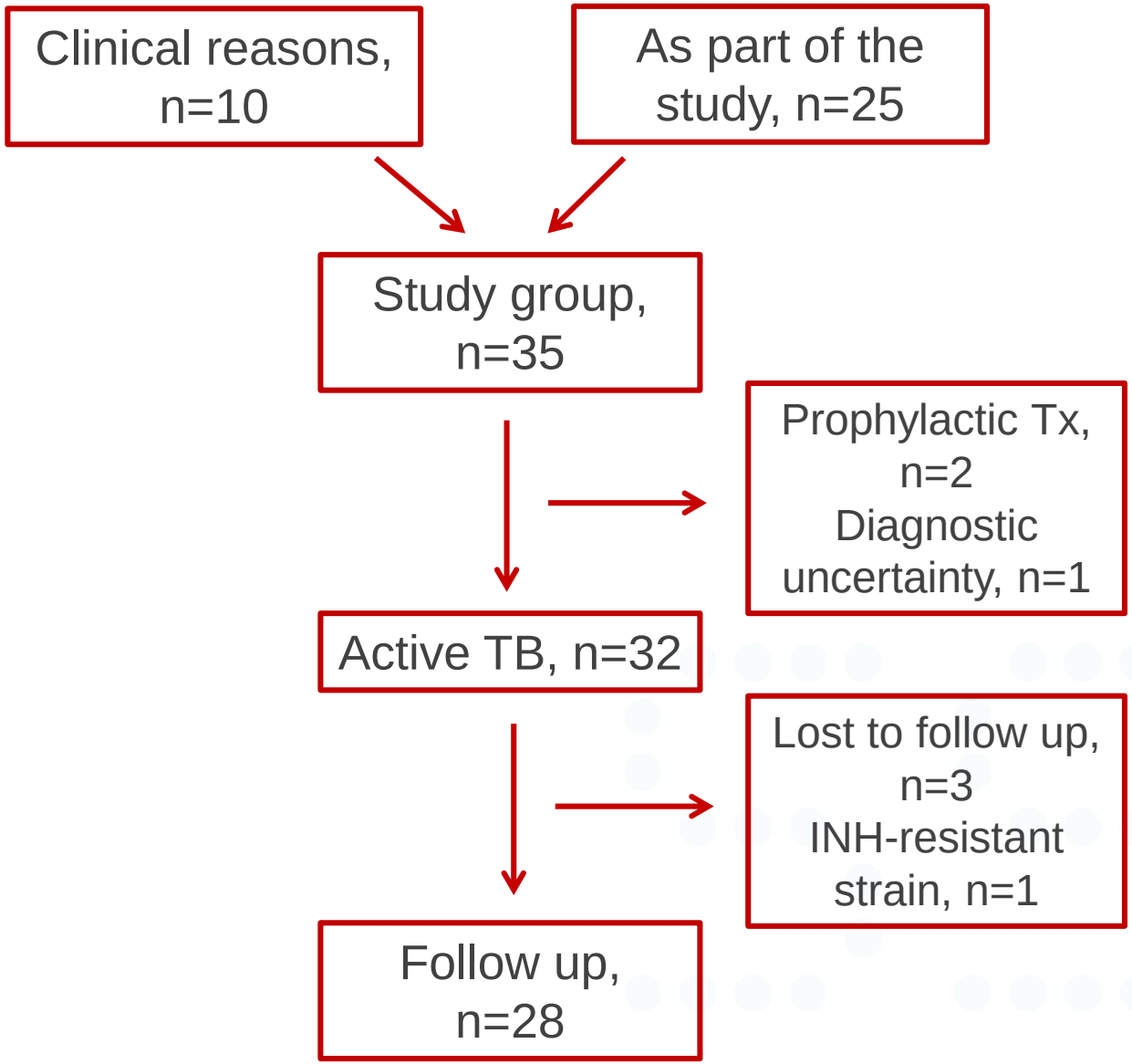
Study I: Aim

To study two-hour plasma concentration levels of first-line tuberculosis drugs in a cohort of patients from the eastern part of Denmark and to determine the relationship to clinical outcome.

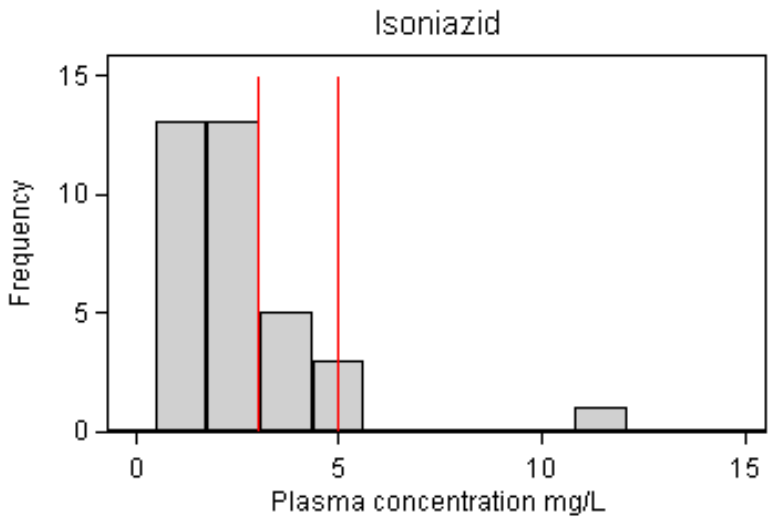
C_{2h} < normal ranges

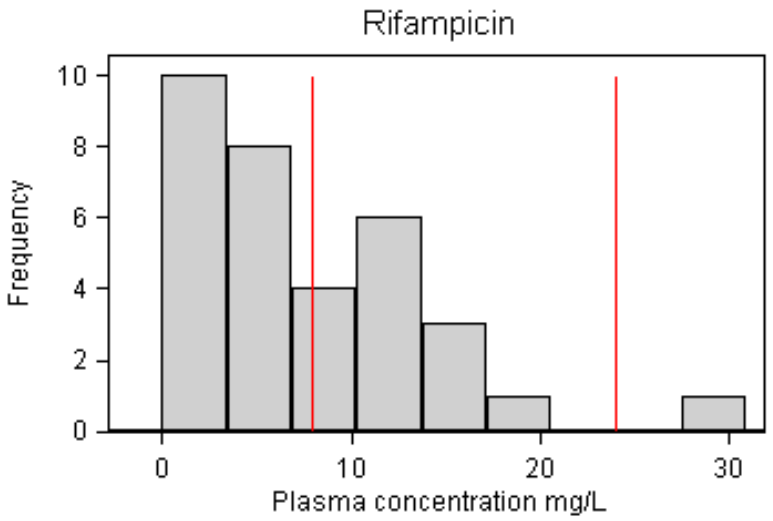
- Prevalence
- Association to therapy failure (death/relapse) at 1 year follow-up

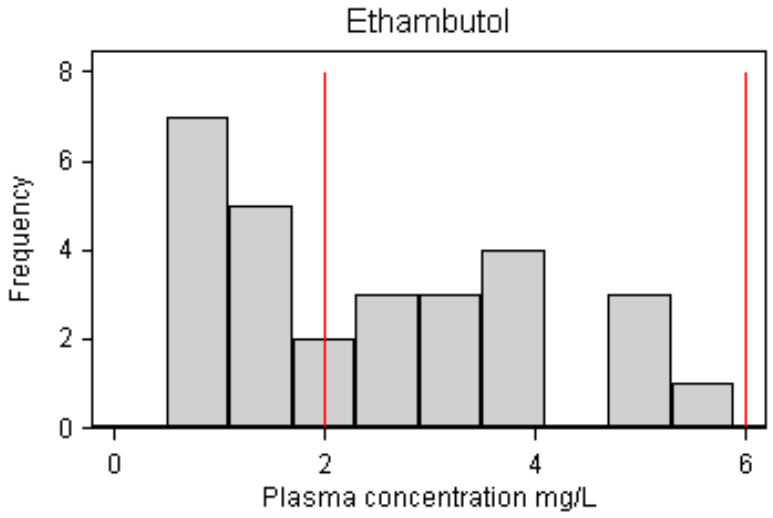
Study I: Methods

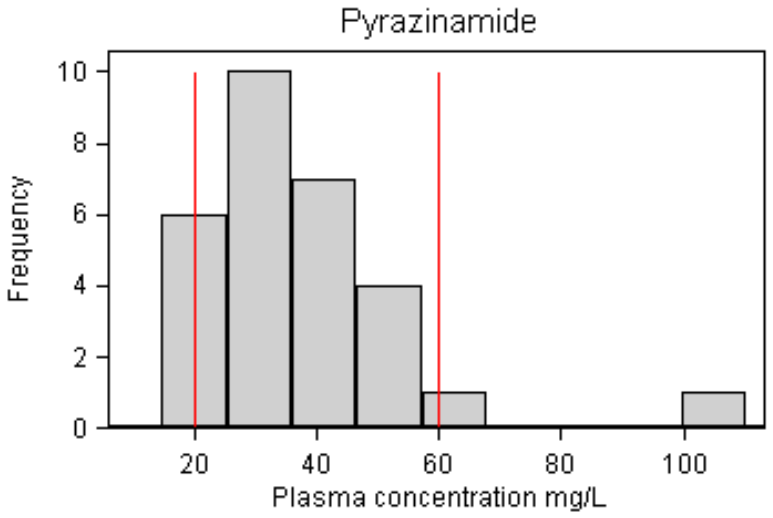


Study I: Results

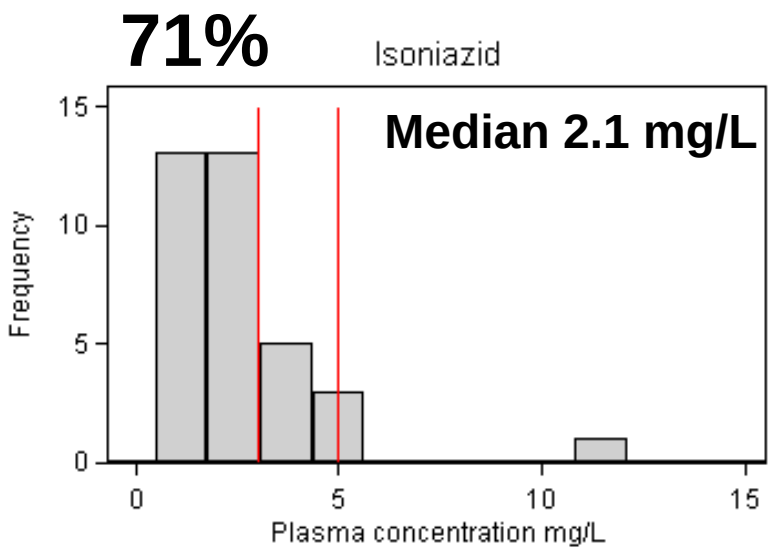


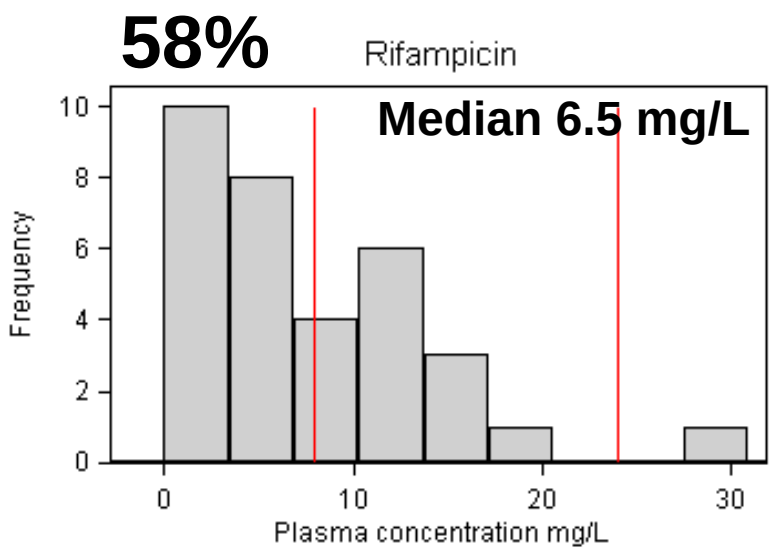


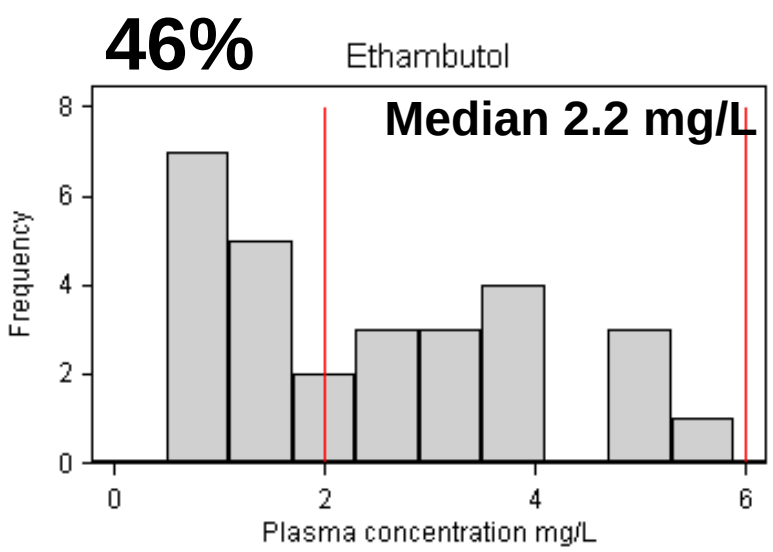


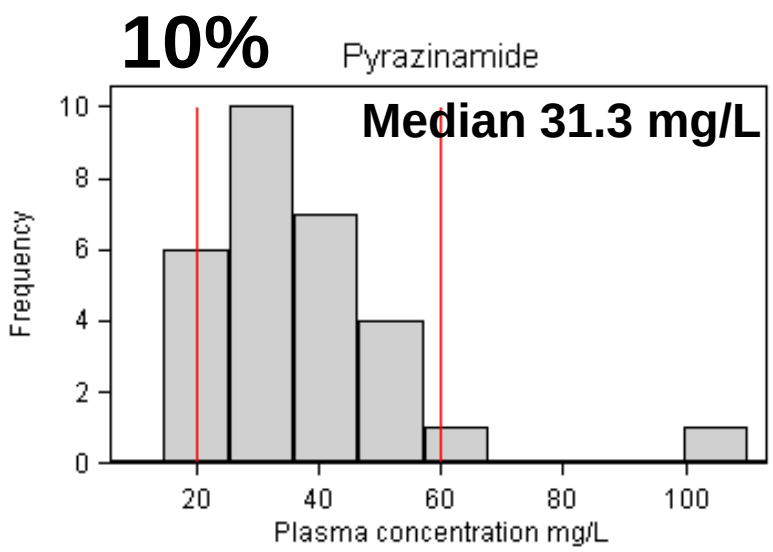


Study I: Results









Study I: Results

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Plasma concentration in mg/L

	Therapy failure (n=5)	Succesful (n=23)	P value for diff.*
Isoniazid, mean† (95% CI)	1.0 (0.4-2.2)	2.6 (2.0 -3.3)	0.004
Rifampicin, mean† (95% CI)	4.0 (2.2-7.6)	7.3 (5.1-10.5)	0.129
Ethambutol, mean† (95% CI)	2.5 (0.7-9.2)	2.0 (1.4-2.8)	0.551
Pyrazinamide, mean† (95% CI)	26.4 (14.0-50.0)	35.2 (28.8-43.1)	0.232

* t-test. † geometric mean.

Study I: Results

- Therapy failure was observed more frequently in patients with:
  - isoniazid & rifampicin < normal ranges (5/13 vs. 0/15, p=0.013)
  - isoniazid < median value (5/14 vs. 0/14, p=0.041)
  - rifampicin < median value ((5/15 vs. 0/13, p=0.044)
  - isoniazid & rifampicin < median values (5/11 vs. 0/17, p=0.005)

- Isoniazid plasma concentrations correlated inversely with CRP at time of sampling ($p<0.001$, $R^2=0.35$), also when adjusted for CRP at baseline ($p=0.041$, $R^2=0.59$). This could indicate less treatment effect of isoniazid at lower drug concentrations

Study II: Aim

To investigate the pharmacokinetics of isoniazid and rifampicin in a group of adult TB patients in Denmark, and to determine probability of target attainment (PTA) of suggested AUC/MIC levels for optimal killing effect by use of population PK-modeling and Monte Carlo simulation

PTA
- Isoniazid AUC/MIC ≥ 500h
- Rifampicin AUC/MIC ≥ 271h

Study II: Methods

20 patients; Drug susceptible pulmonary TB, standard TB therapy
2 days of study; After 1 and 4 weeks of Tx
Sampling; 0, 30, 60, 90, 120, 150, 180, 240 and 360 min. after oral intake

Total plasma concentrations; Determined by LC-MS/MS
Noncompartmental analysis; C_{max}, AUC, $T_{½}$ each patient each study day

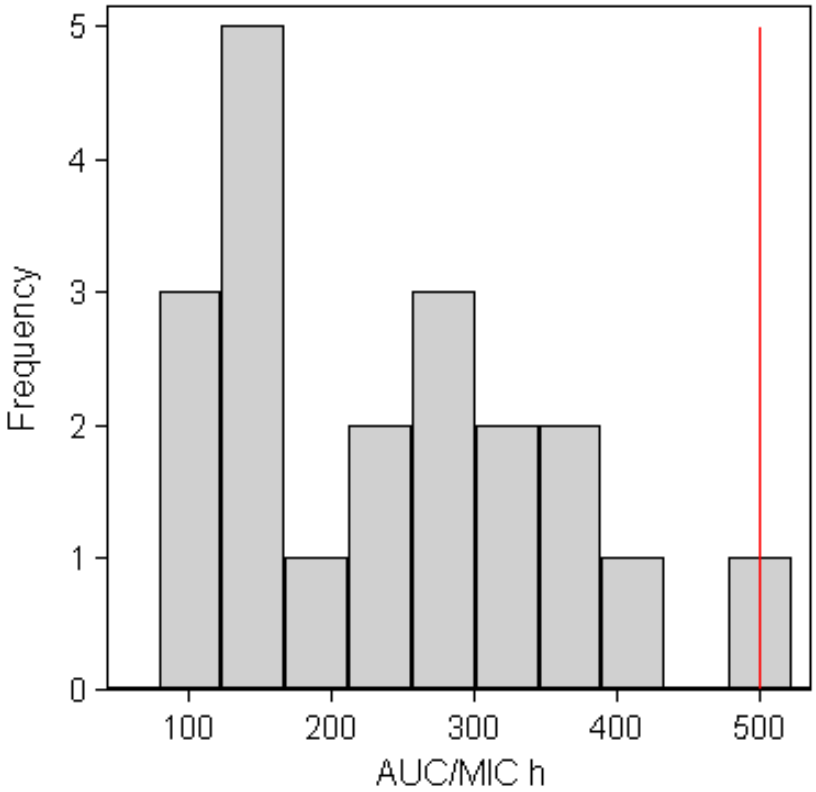
Six PK parameter linear model fit; Population PK parameter distributions
Monte Carlo simulation; 50.000 individuals

PTA analysis; isoniazid AUC/MIC ≥ 500h, rifampicin AUC/MIC ≥ 271h
Fixed MIC value; INH 0.05 mg/L, RIF 1 mg/L

Study II: Results

Isoniazid dosage regimen; 300 mg every 24 hours

Population level:
5 % obtained an AUC/MIC ≥ 500 h
(MIC = 0.05mg/L)



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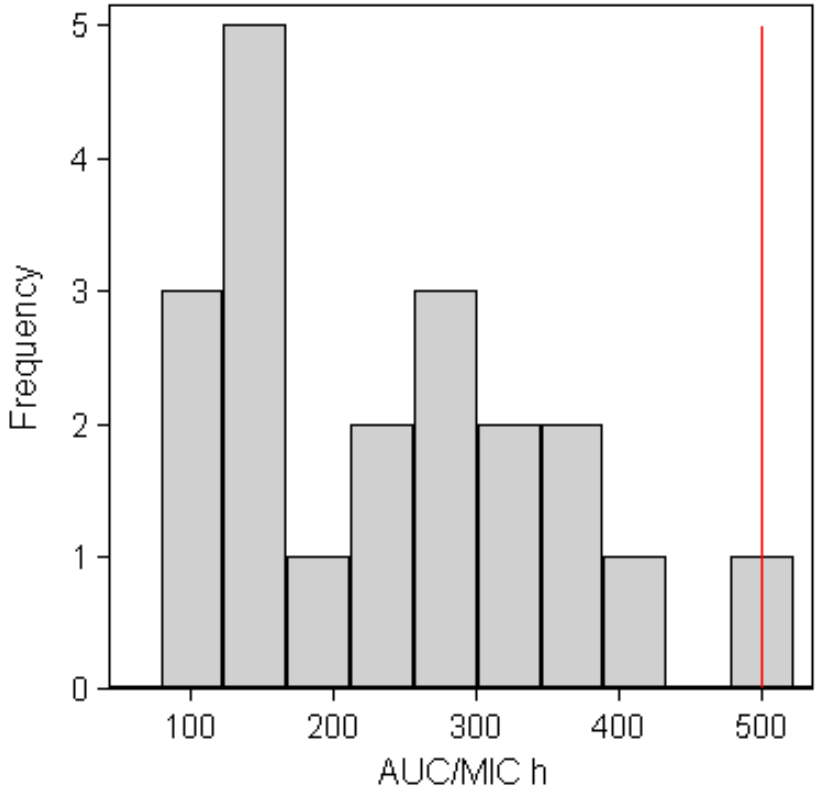
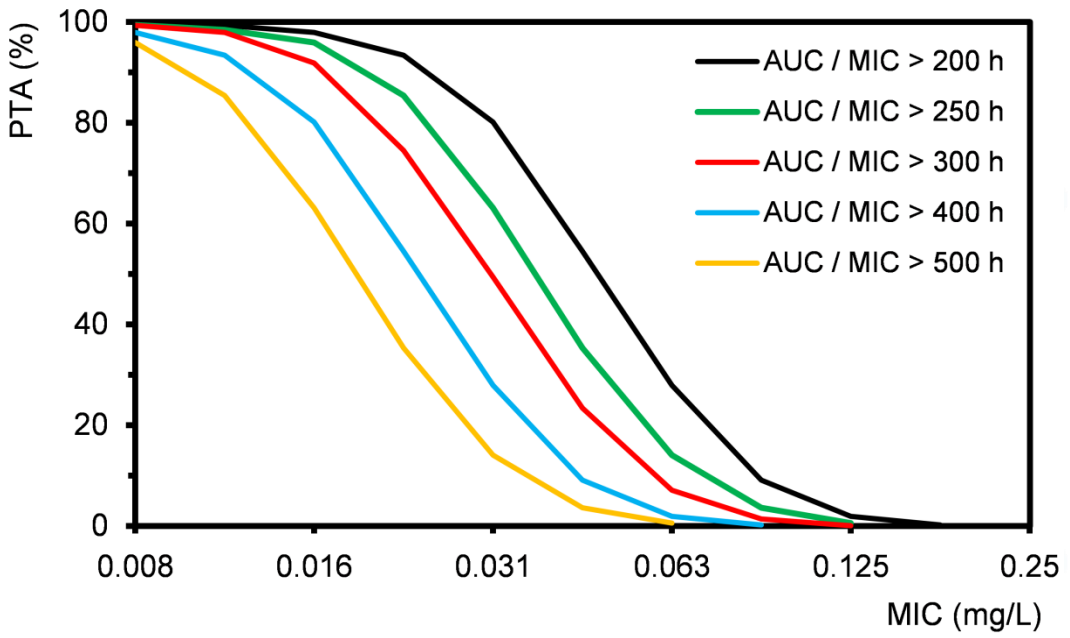


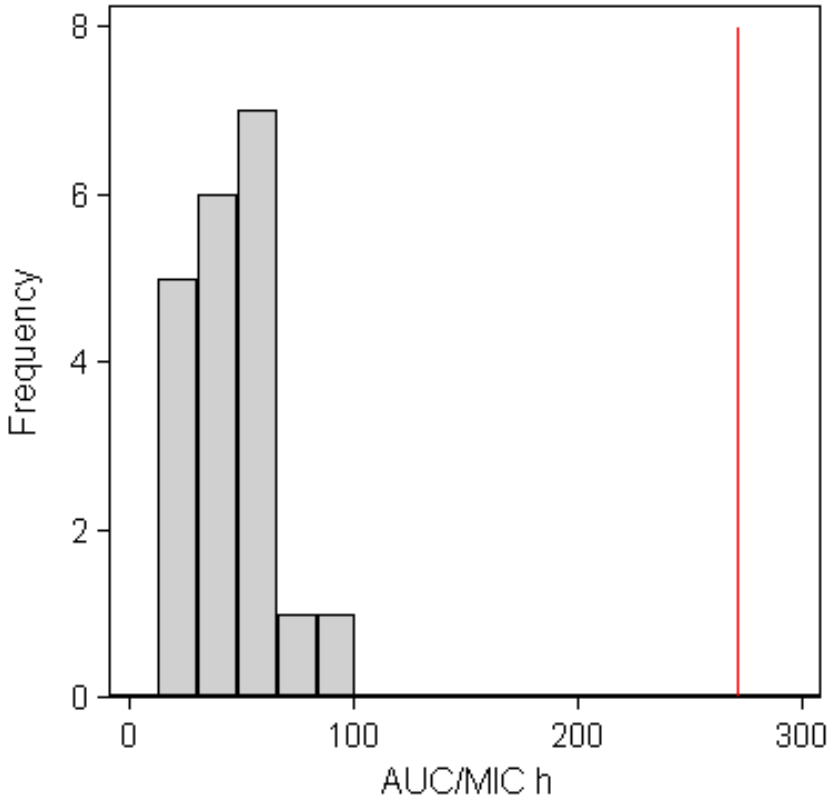
Monte Carlo simulation, n_{indiv} = 50.000:
AUC/MIC ≥ 500 h (MIC = 0.05 mg/L)
PTA = 1.4 %



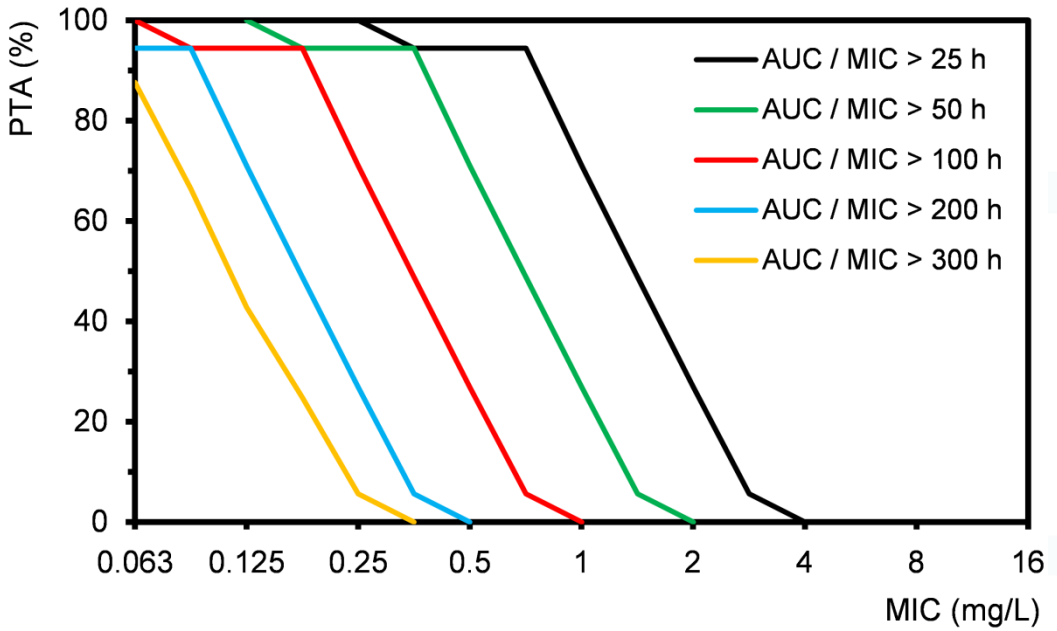
Study II: Results

Rifampicin dosage regimen; 600 mg every 24 hours

Population level:
Non obtained an AUC/MIC ≥ 271 h (MIC = 1.0 mg/L)



Monte Carlo simulation, n_{indiv} = 50.000:
AUC/MIC ≥ 271 h (MIC = 1.0 mg/L)
PTA = 0 %



Summary

Using standard dosis regimens:

- a considerable interpatient pharmacokinetic variability was observed
- C_{2h} and /or C_{max} lower than normal C_{max} ranges were frequently observed
- AUC/MIC levels below suggested targets were frequently observed

Summary

Study I suggests:

- An association between therapy failure and isoniazid and/or rifampicin plasma concentration levels
- That slightly lower threshold targets of C_{2h} and /or C_{max} of isoniazid and rifampicin might be more predictive of treatment outcome

Acknowledgements

Supervisors

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- Åse Bengaard Andersen (project supervisor)
- Arieh S Cohen (project supervisor)

Evaluation Committee

- Staff Specialist, associate professor Christian Wejse, (chairman)
- Regional Medical Officer, associate professor Håkan Miörner, Sweden
- Consultant, associate Professor, Ole Kirk, Denmark

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- Colleagues and fellow PhD students

All collaborators and co-authors

Pharmacokinetics and pharmacodynamics of anti-tuberculosis drugs in patients with tuberculosis

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International Reference Laboratory of Mycobacteriology, Diagnostics and Infection Control
Statens Serum Institut

Taget ud

Summary

- Considerable interpatient pharmacokinetic variability was observed, and C_{2h} and /or C_{max} lower than normal C_{max} ranges were frequently observed

- AUC/MIC ratios above suggested targets for optimal killing effect of isoniazid and rifampicin are generally not attained

- Study I suggests an association between treatment outcome and isoniazid and/or rifampicin plasma concentration levels

Study II: Limitations

- Small sample size
- Both patients receiving directly observed therapy (DOT) and self-administered therapy (SAT) were included
- Time of sampling during treatment was not standardized
- Patients not necessarily fasting
- Measured C_{2h} and not C_{max}

Study III: Limitations

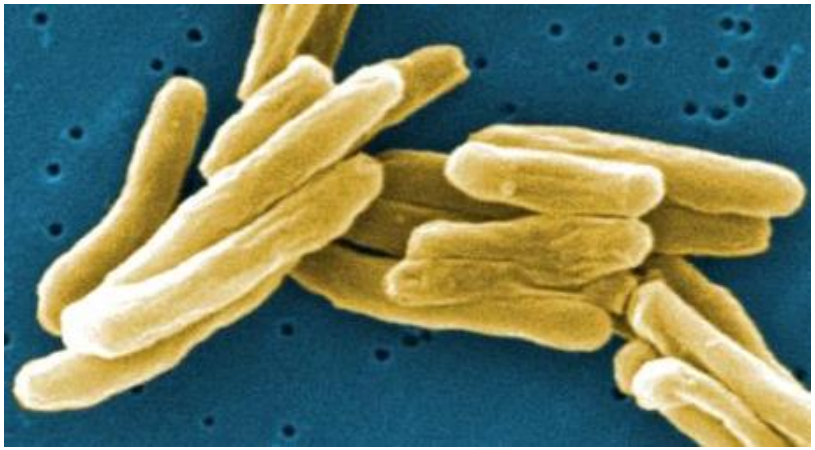
- Isoniazid PK data of one patient and rifampicin PK data of two patients were left out of the population PK-modeling
- Focus on the typical male, HIV negative, TB patient in Denmark

Mycobacterium tuberculosis

Etiological agent of tuberculosis

Airborne

Aerobe
Intra- and extracellular



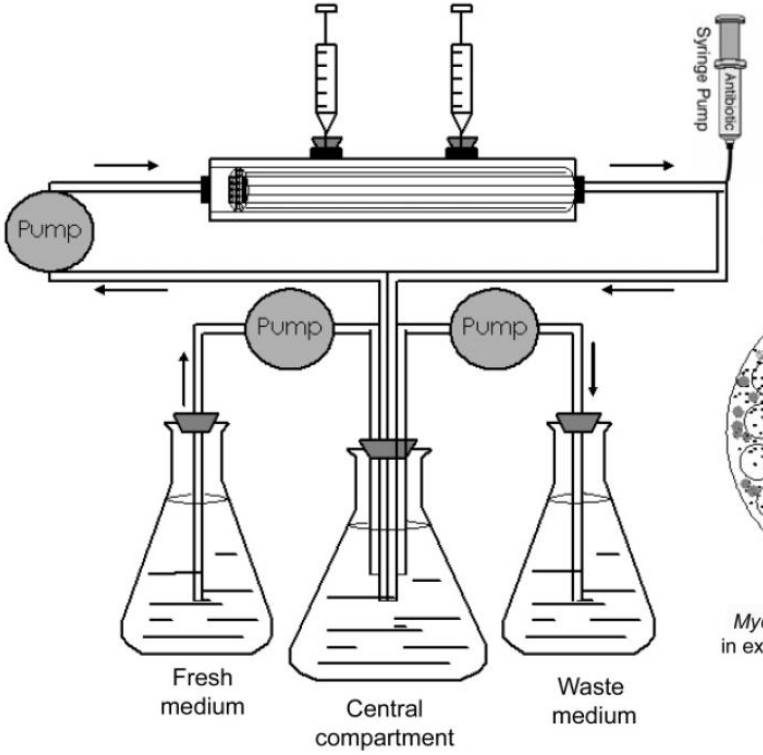
Slowly growing may even lie domant

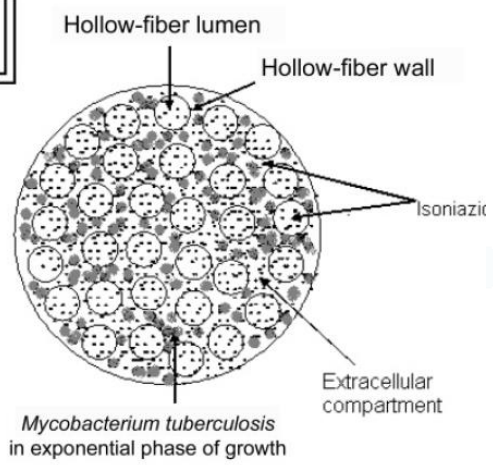
Thick cell membrane rich on lipids

Complex cell-mediated immune response

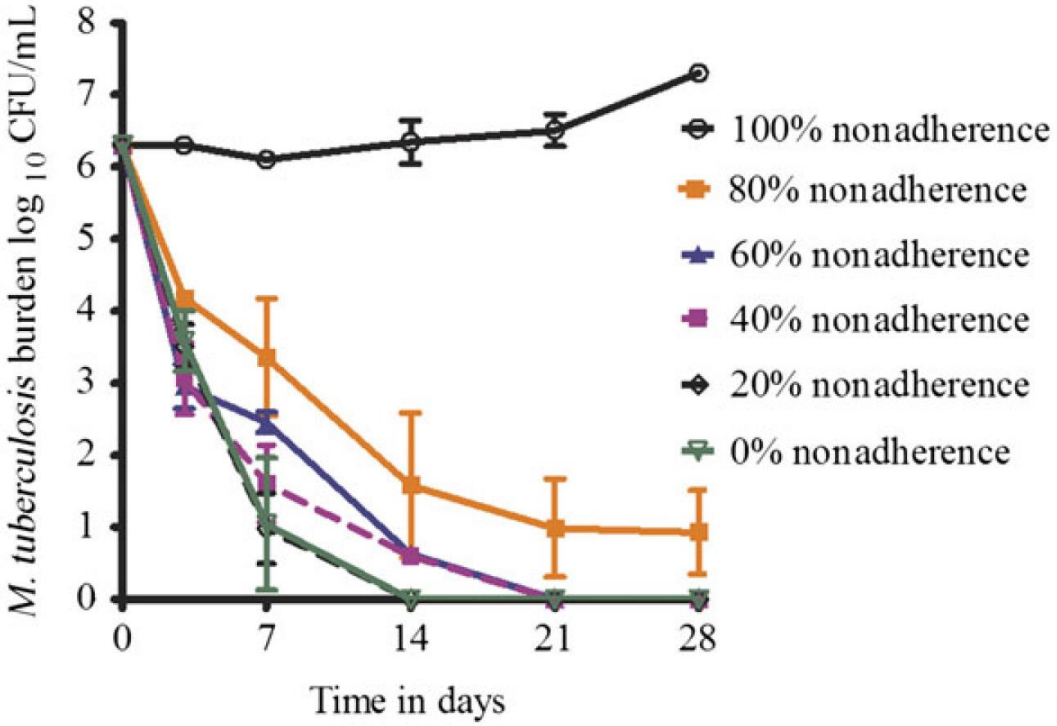
In vitro model

Hollow fiber model





Non-adherence



In vitro hollow fiber model

- ***Non-adherence only leads to failure of therapy after very high cumulative non-adherence >60% of doses***
- ***Non-adherence does not lead to MDR-TB***

Multidrug-Resistant Tuberculosis Not Due to Noncompliance but to Between-Patient Pharmacokinetic Variability

Shashikant Srivastava,[1] Jotam G. Pasipanodya,[1] Claudia Meek,[2] Richard Leff,[2] and Tawanda Gumbo[1]
The Journal of Infectious Diseases 2011;204:1951–9

Study II: Results

Characteristics		Therapy failure (n=5)	Succesful (n=23)	P value for diff.
Male sex, n(%)		3(60)	13(57)	1.0§
Age in years, median		49	38	0.401∞
BMI in kg/m^2, median		18.6	20.3	0.266∞
Inpatient, n(%)		4(80)	13(57)	0.620§
Focus, n(%)	Pulmonary Extrapulmonary Both	5(100) - -	12(52) 10(44) 1(4)	0.211§
Diabetes mellitus, n(%)		2(40)	3(13)	0.207§
HIV infection, n(%)		0(0)	2(9)	1.0§
Excessive alcohol use, n(%)		4(80)	4(17)	0.015§
FDC product, n(%)		2(40)	16(70)	0.315§
$CRP_{baseline}$ in mg/L, median		155	44	0.029∞

§ Fischer exact test. ∞ Mann-Whitney. Abbreviations: FDC = fixed dose combination.

Study II: Results

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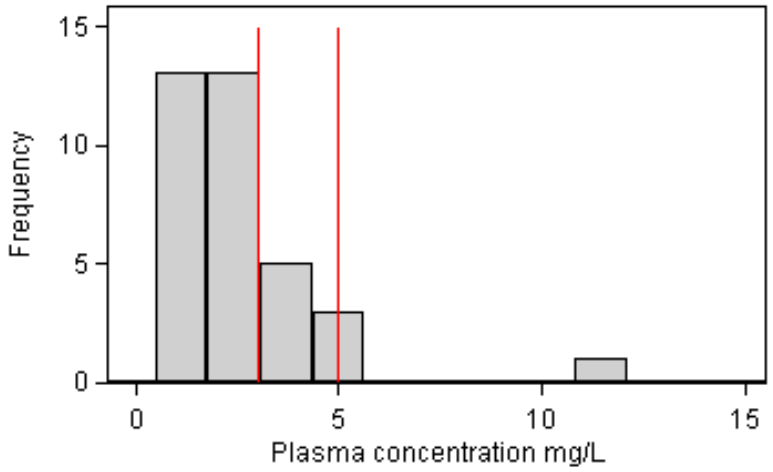
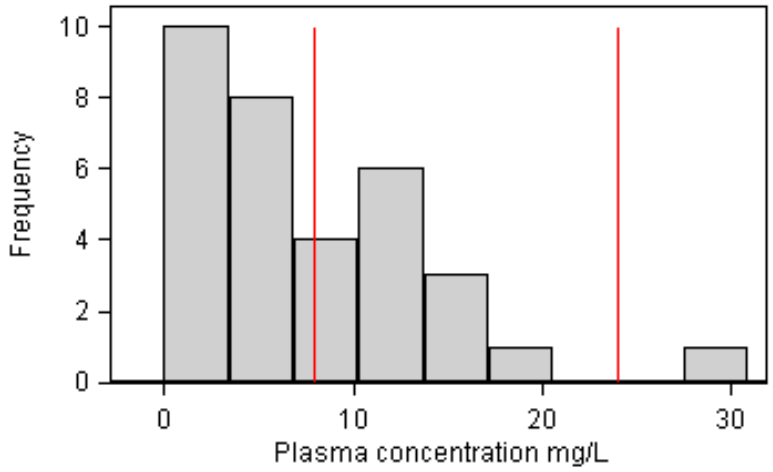
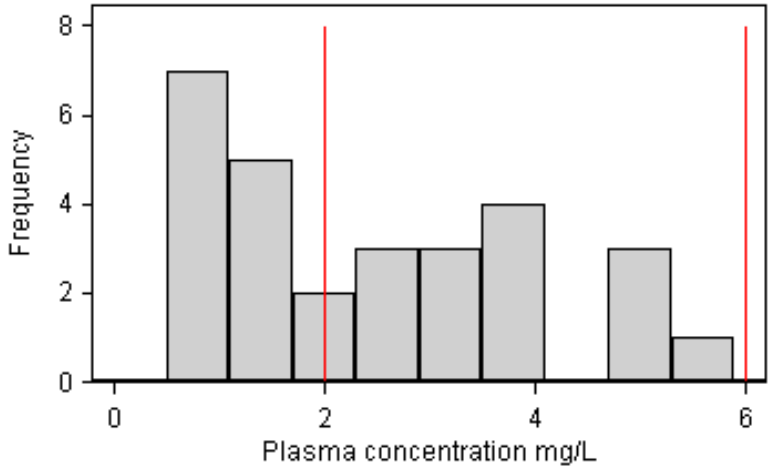
71% Isoniazid



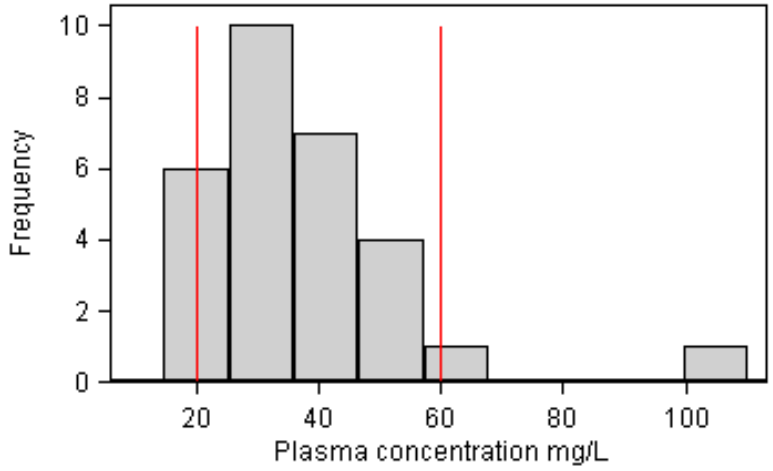
58% Rifampicin



46% Ethambutol



10% Pyrazinamide



Perspectives

In order to optimise the use of TDM :

- To optimise sampling and analysis;
  - when and how to sample
  - Use of filter paper
  - detemine the unbound drug concentrations

- Evidence based guidelines for TDM
  - relationship btw. doses, plasma concentrations, treatment efficacy and side effects
  - develope clinically validated target ranges of the drugs

- Individualise TB therapy:
  - measure individual MIC values
  - causes of interpatient pharmakokinetic variability

Study I: Aim

To develop a rapid, precise and accurate liquid chromatography tandem mass spectrometry (LC-MS/MS) method for simultaneous quantitation of isoniazid, rifampicin, ethambutol and pyrazinamide

- Clinically relevant ranges
- Rapid and simultaneous quantitation of all four first-line drugs
- Precision estimated by the coefficient of variation; CV <15%
- Accuracy estimated by the relative error; relative error % <15%

Study I: Methods

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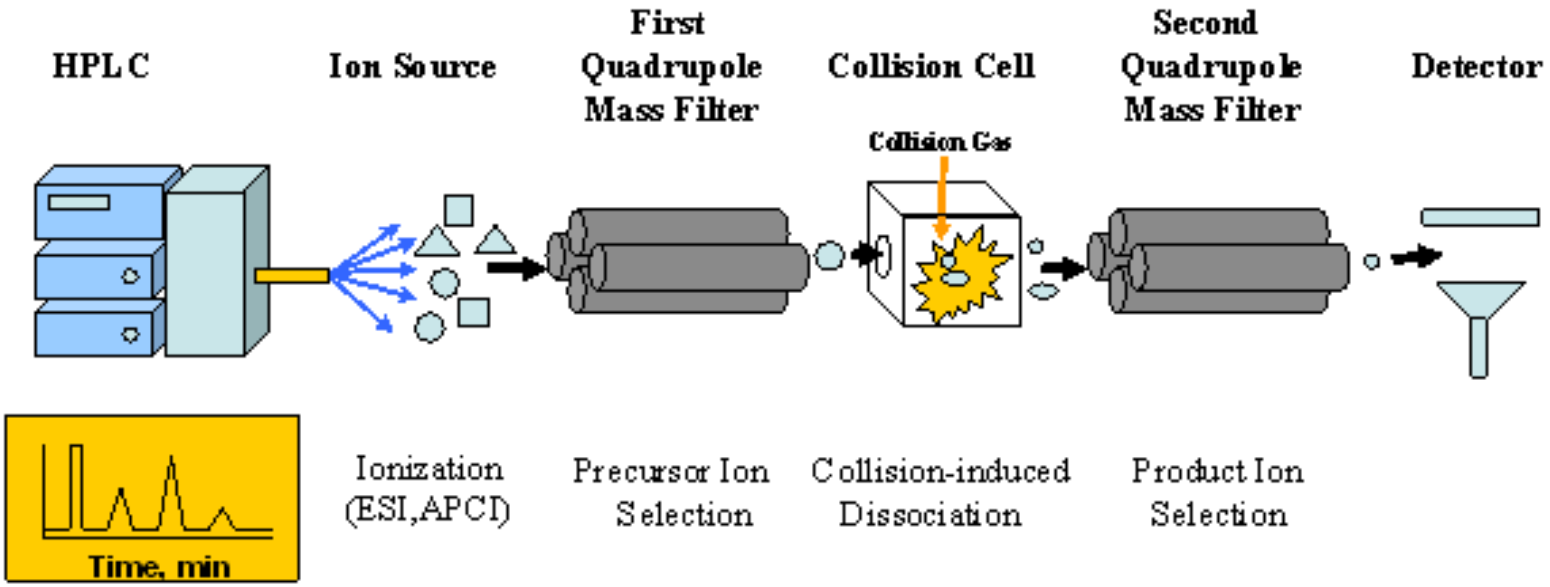
Mass spectrometry (MS):

- Analytical technique to quantitate each type of molecules in a sample
- Separates molecules by mass to charge ratio
- Tandem mass spectrometry (MS/MS); selects and fragments precursor ions and selects product ions

Liquid chromatography (LC):

- Method for physical separation of components in a complex mixture
- Different components are retained to varying degrees
- Compounds are introduced into the MS sequentially



Study I: Methods

LC-MS/MS:

For a compound to be determined it must:

- have the right retention time
- have the right mass/charge ratio
- form the right fragments

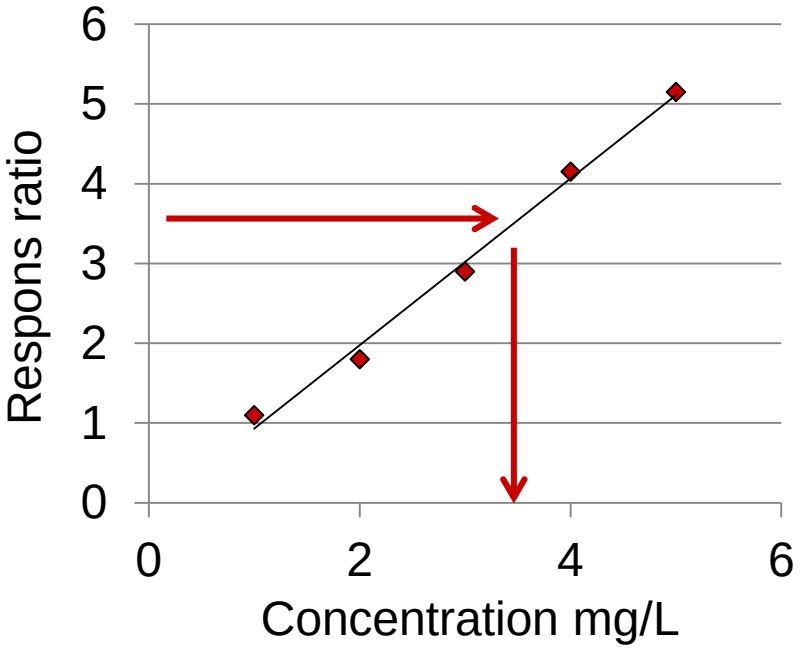
Thus, LC-MS/MS has a high degree of selectivity

Study I: Methods

Calibration curves
Linear plot of the analyte respons/internal standard respons (respons ratio) against the analyte concentration

7 calibration standards (clinically relevant ranges)

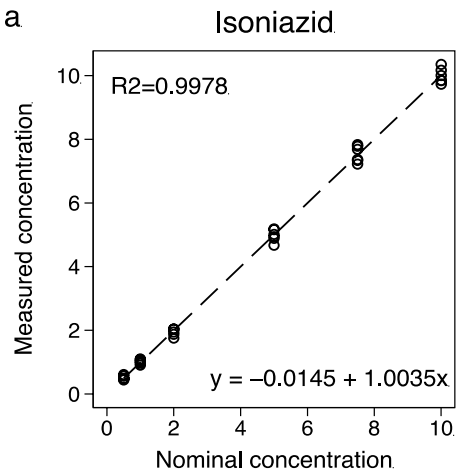
4 isotopically labeled internal standards



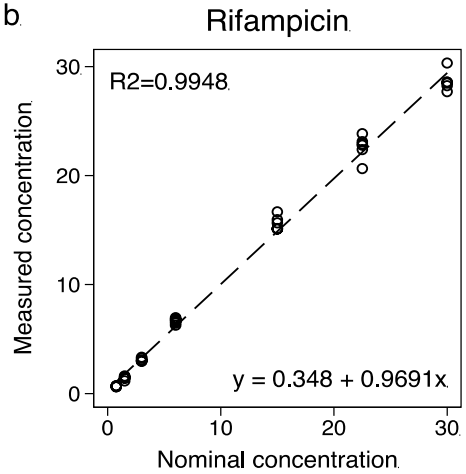
The analyte concentration in an unknown sample can be determined by measuring the analyte respons/internal standard respons which can be converted to a corresponding concentration

Study I: Results

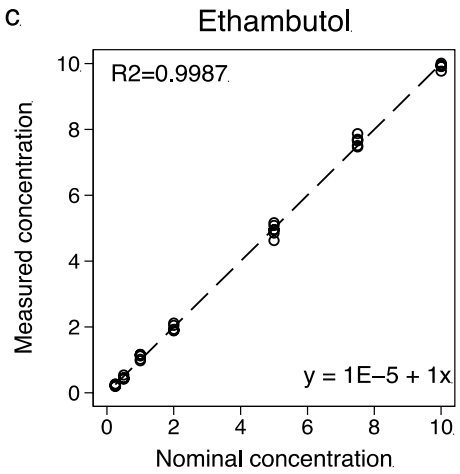
Linearity test



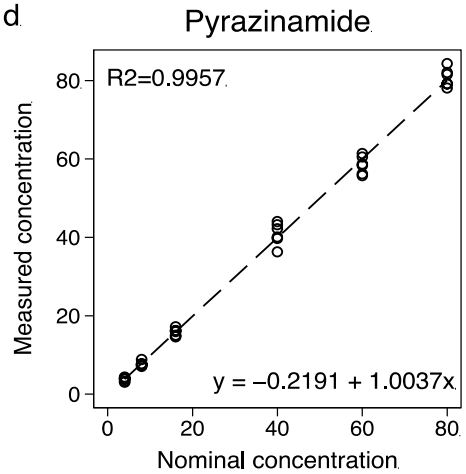
Isoniazid
Linear range
0.5-10 mg/L



Rifampicin
Linear range
0.75-30 mg/L



Ethambutol
Linear range
0.25-10 mg/L



Pyrazinamide
Linear range
4.0-80 mg/L

Coefficient of variation and relative error <15%

Study I: Results

Quality controls at two levels, low and high:

	CV (%)	Accuracy (relative error %)
INH	5.1 - 7.8	-13.7 - -13.2
RIF	4.3 - 4.8	-7.7 - -3.4
EMB	1.6 - 3.5	8.2 - 15.0
PZA	6.0 - 11.0	-8.6 - -6.9

Data represent 6 observations

Proficiency test samples at two levels, low and high:

	CV (%)	Accuracy (relative error %)
INH	11.3 - 12.4	-2.2 - -0.6
RIF	12.4 - 12.7	-5.2 - -2.8
EMB	5.6 - 6.9	1.5 - 7.8
PZA	5.7 - 8.5	7.9 - 9.6

Data represent 12 observations

Study I: Conclusions

The developed LC-MS/MS method:

- provides a rapid and simultaneous quantitation of first-line TB drugs
- has clinically relevant quantitation ranges
- performs within accepted standards of LC-MS/MS analysis in terms of precision and accuracy
- is suitable for therapeutic drug monitoring (TDM) and PK/PD studies

Study I: Limitations

- Precision and accuracy were compromised to be able to quantitate all four TB drugs rapidly and simultaneously
- Lack of golden standards for comparison

Treatment optimisation

Strongly concentration-dependent antibiotic

AUC/MIC and C_{max}/MIC correlates the best to antimicrobial activity

Optimal dosage regimens;

Maximises plasma concentrations

Isoniazid, rifampicin, ethambutol and pyrazinamide

Minimal concentration-dependent antibiotic

T>MIC correlates the best to antimicrobial activity

Optimal dosage regimens;

Maximises the duration of time above the MIC

Therapeutic ranges?

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Normal ranges in healthy volunteers

	T_{max} (h)	$T_{½}$ (h)	C_{max} (mg/L)
Isoniazid 300 mg	0.75-2	3.5-4 / 1.5-2	3-5
Rifampicin 600 mg	2	2-4	8-24
Ethambutol 1200 mg	2-3	4-5 / 10-15	2-6
Pyrazinamide 2000 mg	1-2	9-11	20-60

Peloquin 1996 and 2002

Targets for optimal efficacy in mouse studies

	AUC/MIC (h)
Isoniazid 300 mg	500
Rifampicin 600 mg	271

Jayaram 2003, 2004

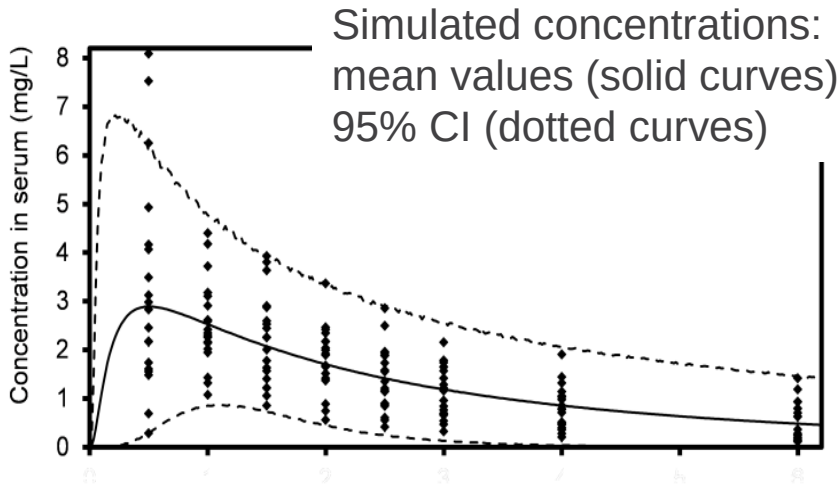
Study II: Conclusions

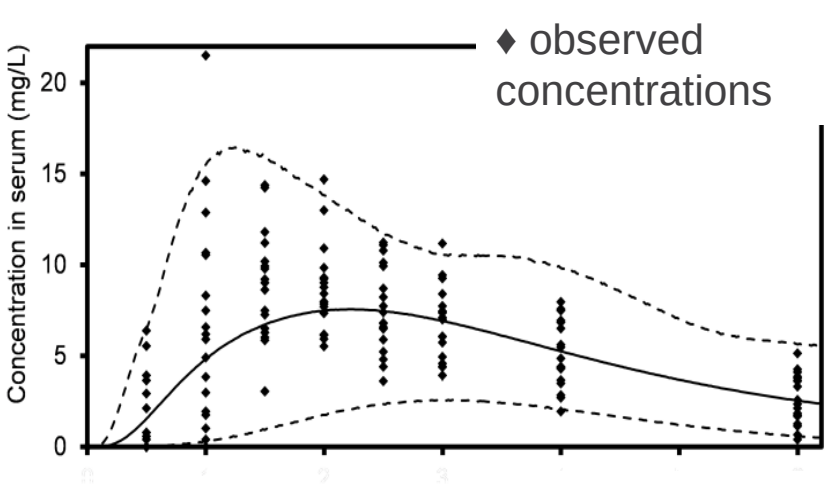
Two-hour plasma concentrations of rifampicin and isoniazid below normal values were:

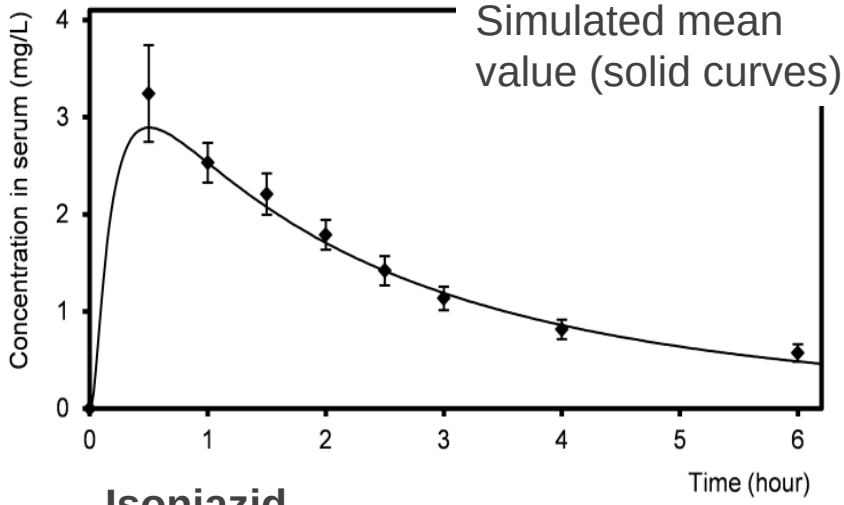
- frequently observed in adult TB patients
- associated with an increased risk of death or relapse

Study III: Results

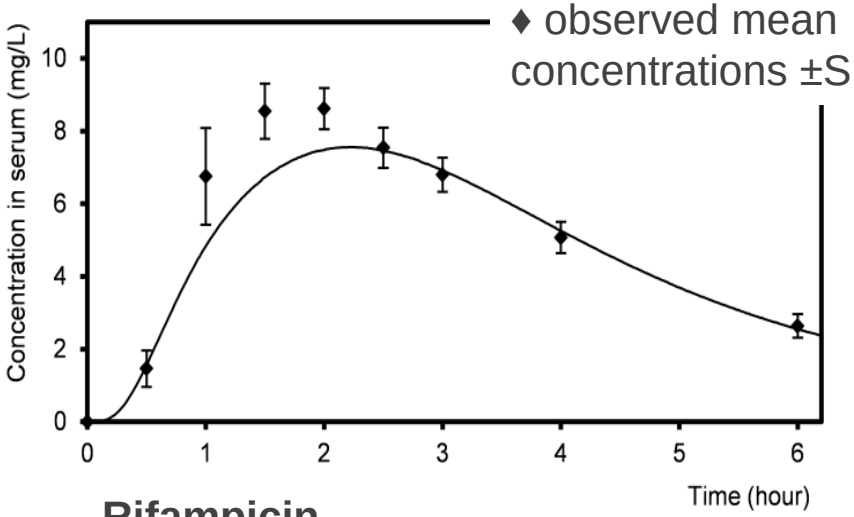
Monte Carlo simulation; Evaluation of model fit on the population level





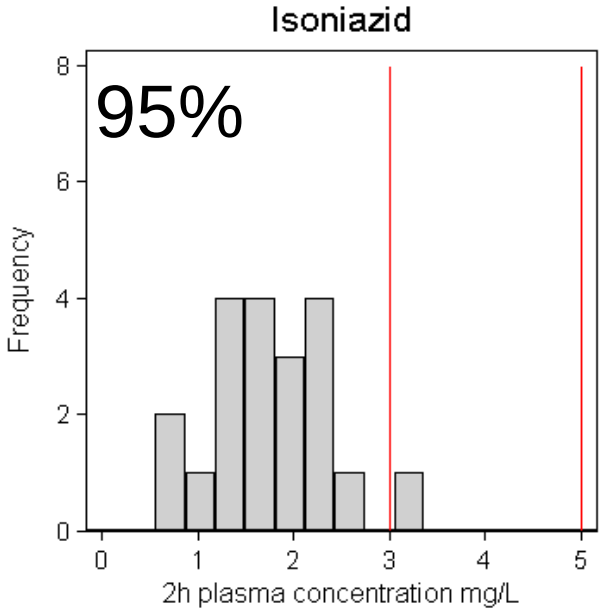


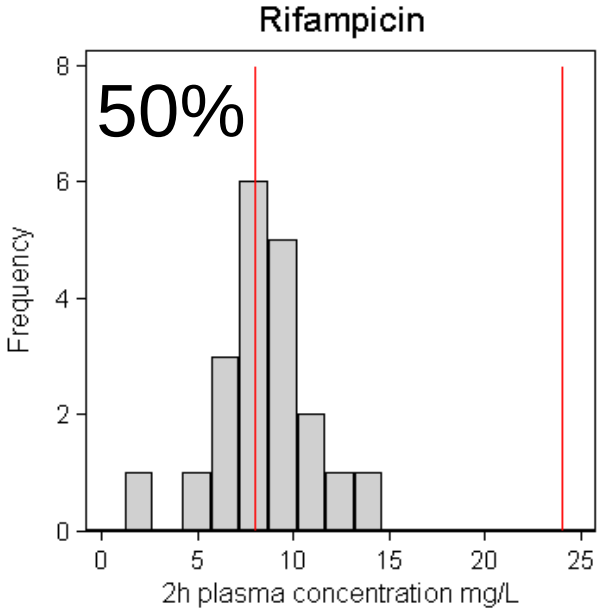
Isoniazid

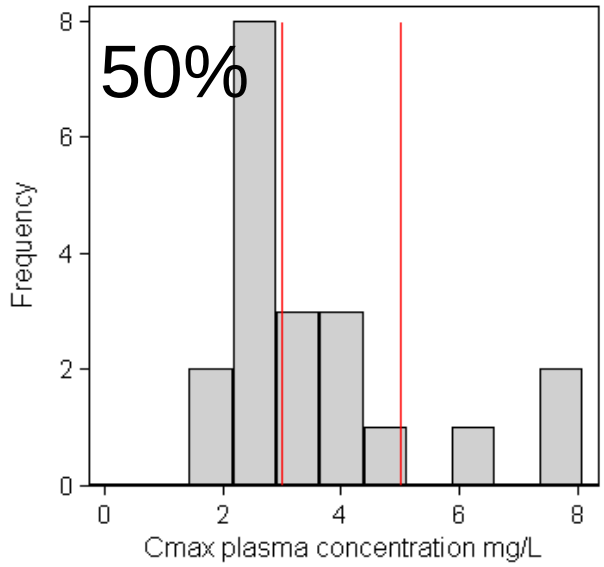


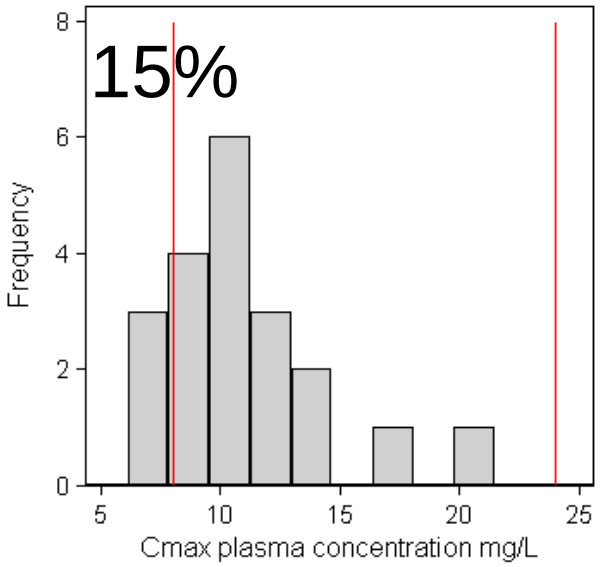
Rifampicin

Study III: Results

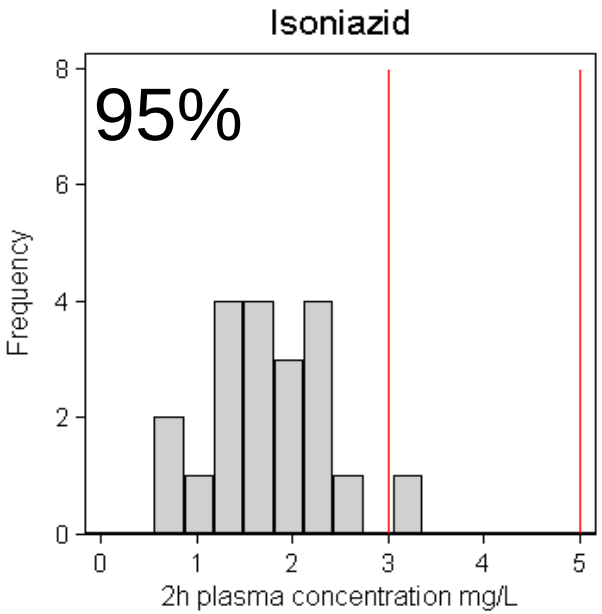


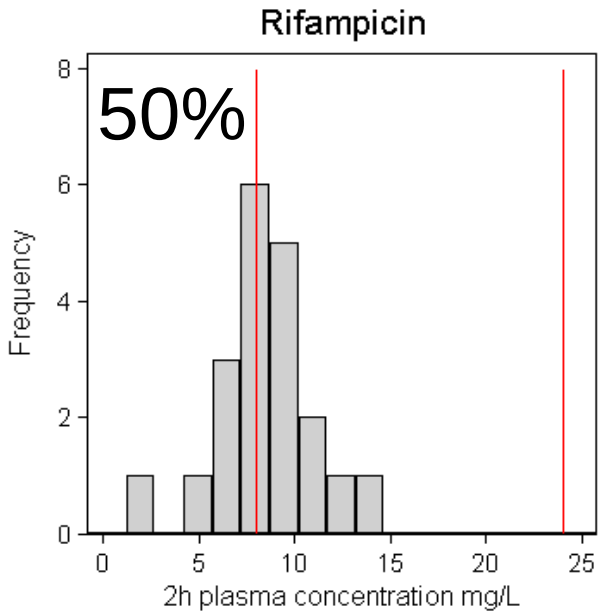


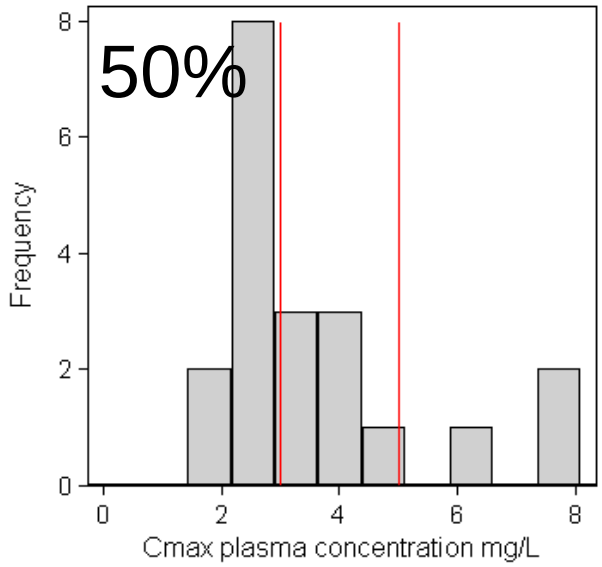


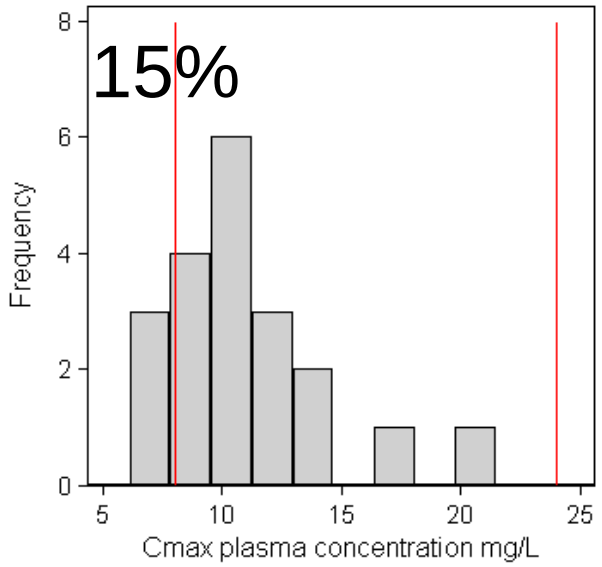


Study II: Results









Monte Carlo simulation, n_{indiv} = 50.000:

Isoniazid C_{2h} > 3.0 mg/L
PTA = 5 %
(95% CI: 0.4 - 3.4 mg/L)

Rifampicin C_{2h} > 8.0 mg/L
PTA = 42 %
(95% CI: 1.7 - 13.6 mg/L)

For both isoniazid and rifampicin:
T_{max} < 2 h
therefore
C_{2h} did not equal C_{max}

Study III: Conclusions

Standard doses of 300 mg isoniazid and 600 mg rifampicin are not sufficient to attain the suggested AUC/MIC targets of:

- 500 h for isoniazid
- 271 h for rifampicin

Agenda

Background

Study I-III

Summary

Perspectives

Agenda

Background

Study I-III

Summary

Perspectives

Rester

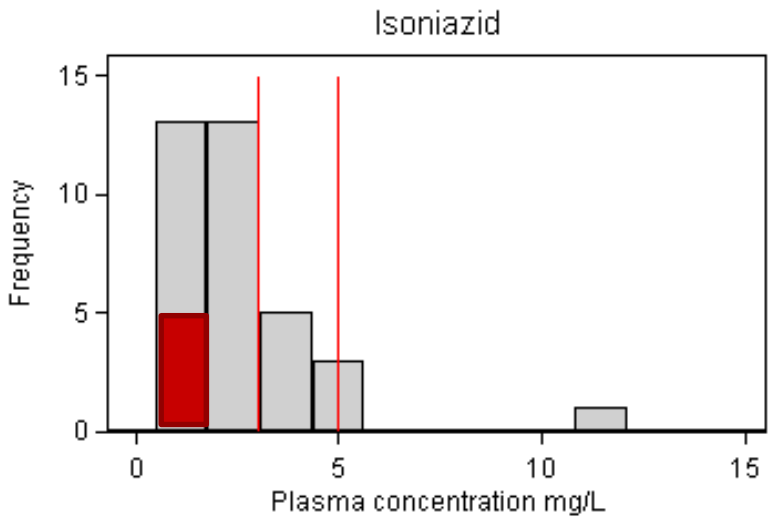
Summary

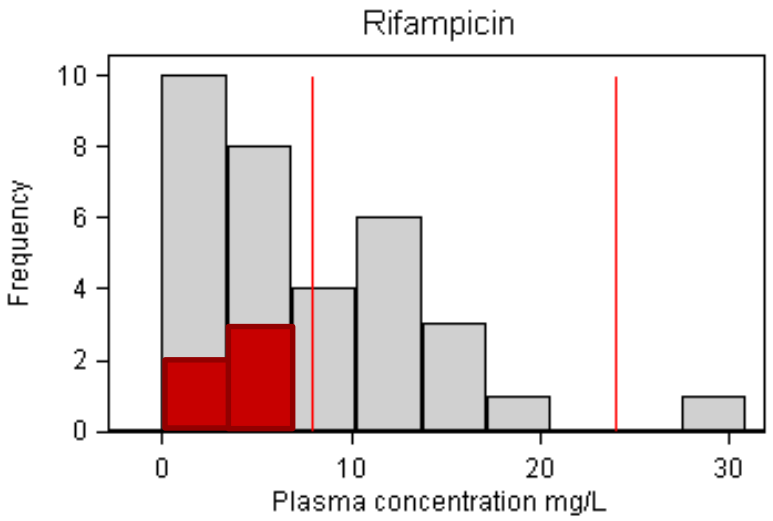
- The LC-MS/MS method developed provides simultaneous, precise and accurate quantitation of all four first-line TB drugs
  - Only few other LC-MS/MS methods use isotopically labeled internal standards and most only quantitate a few drugs simultaneous

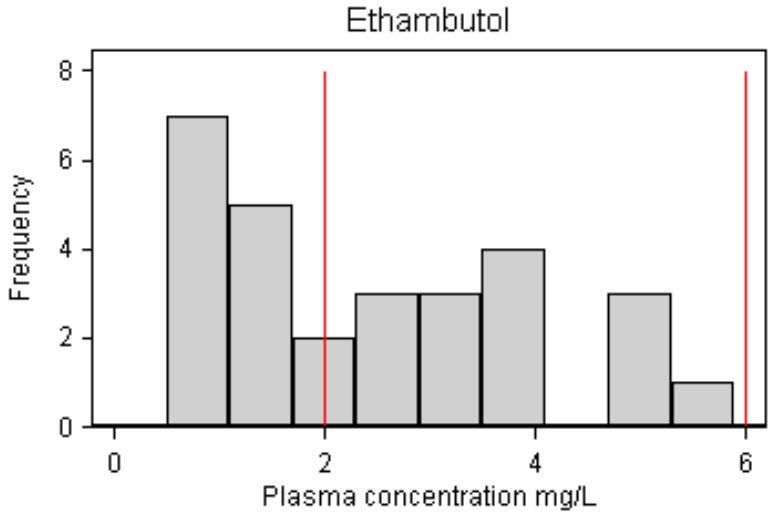
- considerable interpatient pharmacokinetic variability was observed, and C_{2h} and /or C_{max} lower than normal C_{max} ranges were frequently observed
  - C_{2h} levels lower than normal C_{max} ranges have previously been observed [Tappero 2005]

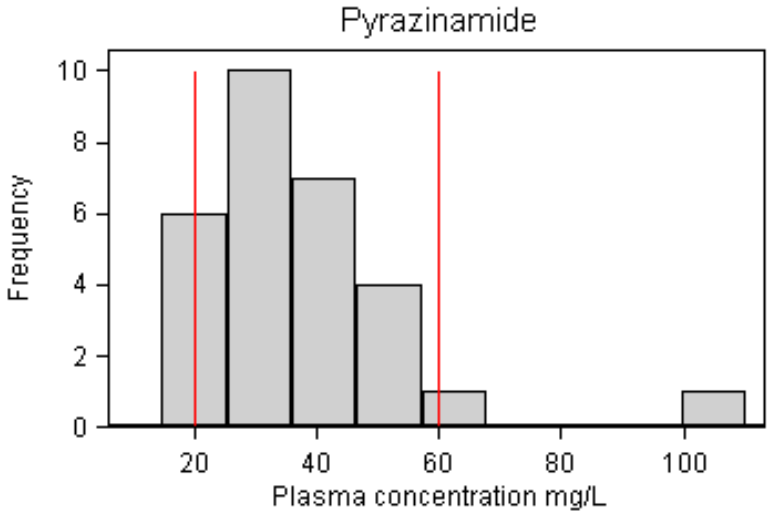
- AUC/MIC ratios above suggested targets for optimal killing effect of isoniazid and rifampicin are generally not attained
  - One study has previously investigated PTA of an AUC/MIC ≥ 271 h for rifampicin [Goutelle 2009]

Study II: Results

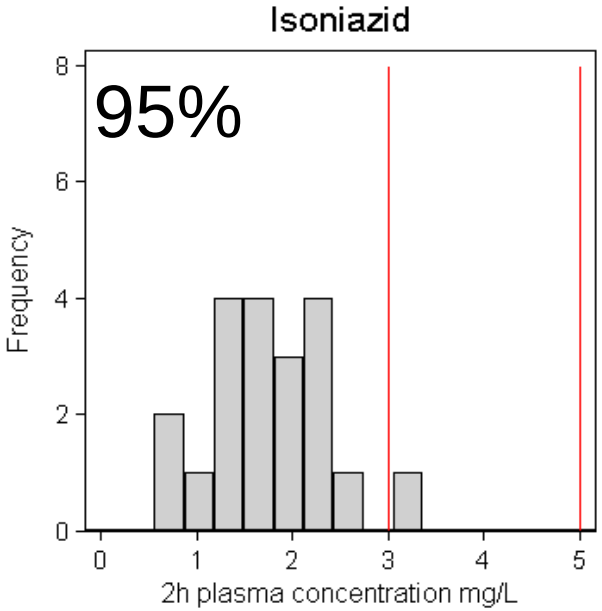


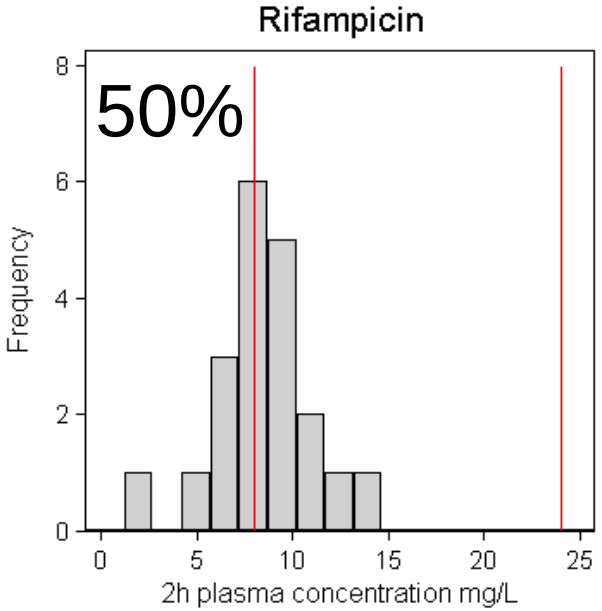






Study III: Results





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Rifampicin C_{2h} > 8.0 mg/L
PTA = 42 %
(95% CI: 1.7 - 13.6 mg/L)

Study II: Methods

	Group A (n=10)	Group B (n=25)	P value for diff.
Isoniazid C_{2h} in mg/L, median	2.0	2.2	0.32*
Rifampicin C_{2h} in mg/L, median	6.5	6.6	0.98*
Ethambutol C_{2h} in mg/L, median	2.4	1.9	0.40*
Pyrazinamide C_{2h} in mg/L, median	37.8	31.1	0.42*
CRP baseline in mg/L, median	74	57	0.62*
CRP sampling time in mg/L, median	39	14	0.37*
Therapy failure	3/8	2/20	0.12†

*Mann-Whitney, † Fisher exact

Study III: Results

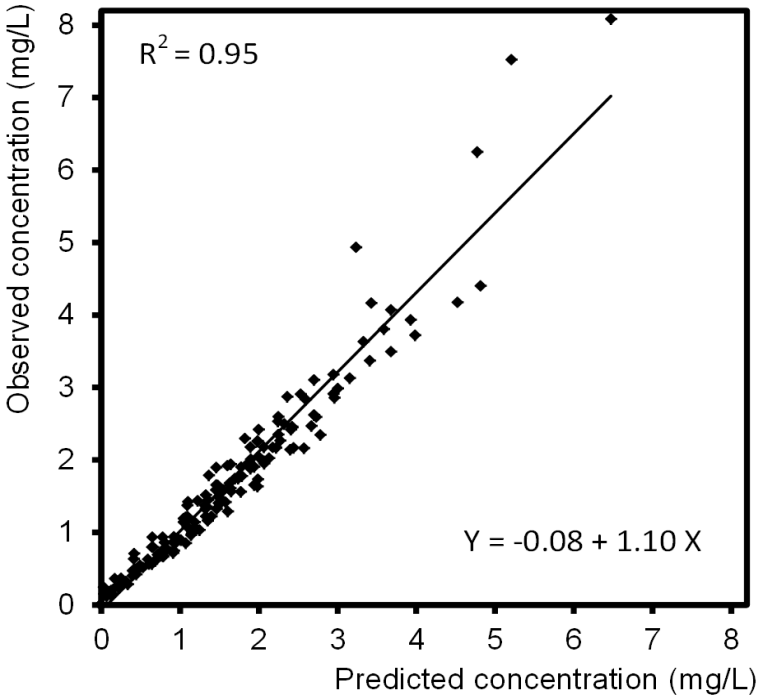
Pharmacokinetics of isoniazid and rifampicin, median value (range)

	Isoniazid			Rifampicin		
	One week	Four weeks	P-value*	One week	Four weeks	P-value*
C_{2h} (mg/L)	**1.7** (0.6-3.4)	**1.6** (0.5 - 3.2)	**0.49**	**8.2** (1.3 - 14.7)	**7.9** (0 - 16.1)	**0.98**
C_{max} (mg/L)	**3.0** (1.4-8.1)	**3.1** (0.8- 6.6)	**0.28**	**10.4** (6.1 - 21.5)	**9.2** (4.8 - 21.6)	**0.46**
AUC (mg*h/L)	**11.4** (4.0-26.1)	**9.2** (2.8 - 23.6)	**0.08**	**42.4** (13.2-101.4)	**37.8** (16.8 -80.3)	**0.80**
T_{max} (h)	**0.5** (0.5 - 3.0)	**1** (0.5 - 2.5)	**0.19**	**1.75** (1 - 3)	**2.5** (1 - 4)	**0.02**
$T_{½}$ (h)	**3.3** (1.3 - 6.5)	**2.4** (0.5 - 6.7)	**0.04**	**2.2** (0.9 – 7.1)	**2.1** (1.2 – 4.3)	**0.65**

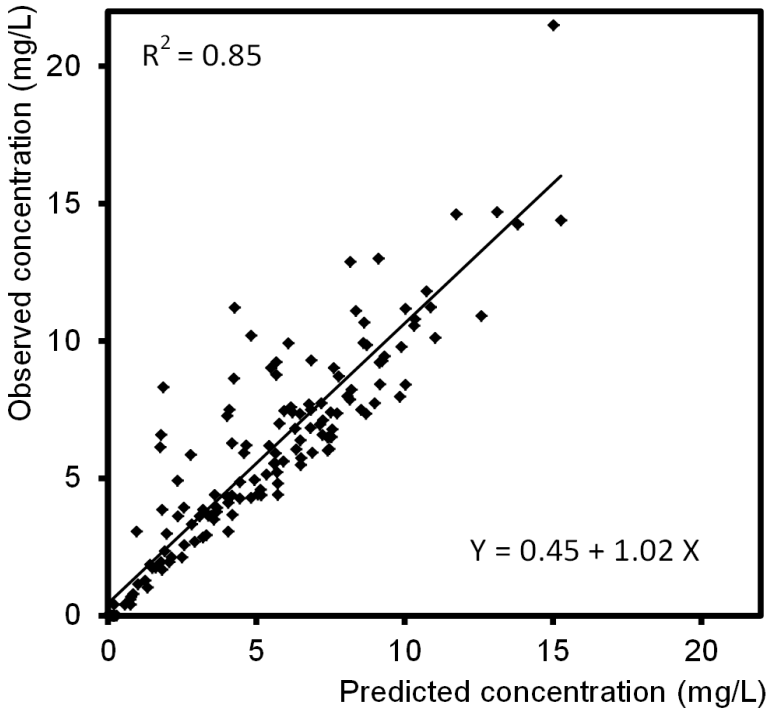
*wilcoxon signed rank test for difference

Study III: Results

Prediction of the observed concentrations when simulations are made with individual model fit (PK parameters) for each patient



Isoniazid
19 patients, 171 data points



Rifampicin
18 patients, 162 data points

Study II: Results

- Therapy failure was observed more frequently in patients with:
  - isoniazid & rifampicin < normal ranges (5/13 vs. 0/15, p=0.013)
  - isoniazid < median value* (5/14 vs. 0/14, p=0.041)
  - rifampicin < median value* ((5/14 vs. 0/14, p=0.041)
  - isoniazid & rifampicin < median values *(5/10 vs. 0/18, p=0.003)

*median amongst the 28 follow-up patients

Perspectives

When to sample?

Treatment start	No significant difference between plasma concentration measured the two days of study on population level (study III)
Single vs. multiple days	To eliminate day-to-day variation (study III)
Ingestion of medication	Quantitating C_{2h} we risk underestimating C_{max} in patients with rapid or delayed absorption (study III)
Single vs. multiple sample points	Multiple sample points (study III) or a limited sample strategy provides a more reliable estimate of C_{max} and AUC
Depends on indication	Non-adherence? TDM and dose adjustment? PK/PD study?

Study II: Results

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Associations:

Rifampicin plasma concentrations

- Decrease with increasing age ($p=0.006$, $R^2=0.23$)
- Lower in patients with low hemoglobin at baseline ($p=0.004$)

No associations were found between plasma concentrations of isoniazid, rifampicin, ethambutol or pyrazinamide and:

- Gender
- Hypoalbuminaemia
- Dose (mg/kg)
- Drug formulation
- Hospital status
- Number of days on treatment at the time of sampling

Study II: Results

- Univariate logistic regression analysis:

  - Therapy failure inversely associated with plasma concentrations of isoniazid (p=0.021)
  - Therapy failure inversely associated with CRP at baseline (p=0.056)
  - Including both, plasma concentration of isoniazid remained borderline significant (p=0.072) whereas the effect of CRP disappeared (p=0.763)

Study II: Results

- Univariate logistic regression analysis:

  - Risk of therapy failure decreased with increasing plasma concentrations of isoniazid (p=0.021)
  - Risk of therapy failure tended to increase with increasing CRP levels at baseline (p=0.056)
  - Including both, the effect of isoniazid levels remained borderline significant (p=0.072) whereas the effect of CRP disappeared (p=0.763)

Study I: Methods

Precision determined by calculating the coefficient of variation:

$$\text{CV (\%)} = \frac{\text{standard deviation}}{\text{mean concentration}} * 100\ \%$$

Accuracy estimated by the relative error calculated as:

$$\text{Relative error (\%)} = \frac{\text{back calculated concentration} - \text{nominal concentration}}{\text{nominal concentration}} * 100\ \%$$

Study I: Results

	Intraday (n=6)		Interday (n=6)	
	CV (%)	relative error (%)	CV (%)	relative error (%)
Isoniazid 0.5 - 10 mg/L	3 - 8	-7.6 - 17.7	2.3 -12.4	-2.6 - 1.7
Rifampicin 0.75 - 30 mg/L	1.9 - 7.9	-4.6 - 11.1	2.8 - 11.5	-12.1 - 9.7
Ethambutol 0.5 - 10 mg/L	2 - 4.3	-0.6 - 5.1	0.8 - 10.9	-9.8 - 10.4
Pyrazinamide 4 - 80 mg/L	2.5 - 13.7	-4.1 - 1.5	2.9 - 13	-6.1 - 2.3

CV, coefficient of variation

Summary

- Using standard dosis regimens a considerable interpatient pharmacokinetic variability was observed, and C_{2h} and /or C_{max} lower than normal C_{max} ranges were frequently observed
  - C_{2h} levels lower than normal C_{max} ranges have previously been observed [Tappero 2005]

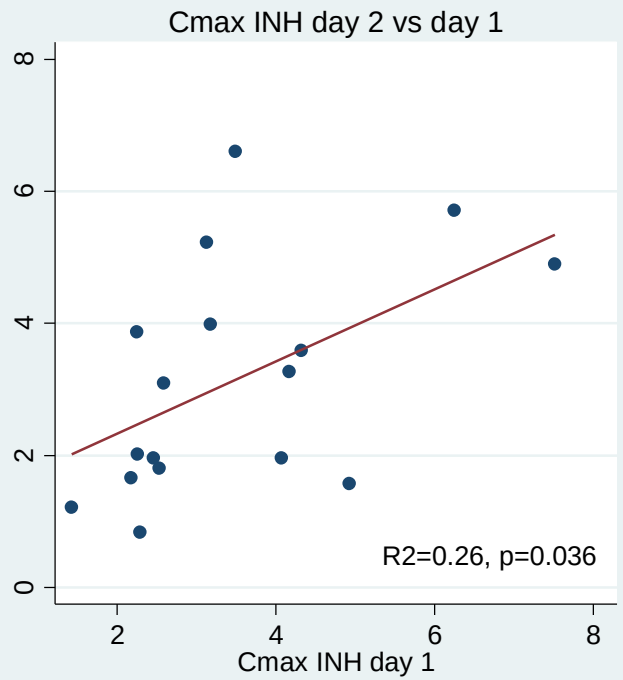
- Using standard dosis regimens AUC/MIC levels below suggested target ranges were frequently observed
  - One study has previously investigated PTA of an AUC/MIC ≥ 271 h for rifampicin [Goutelle 2009]

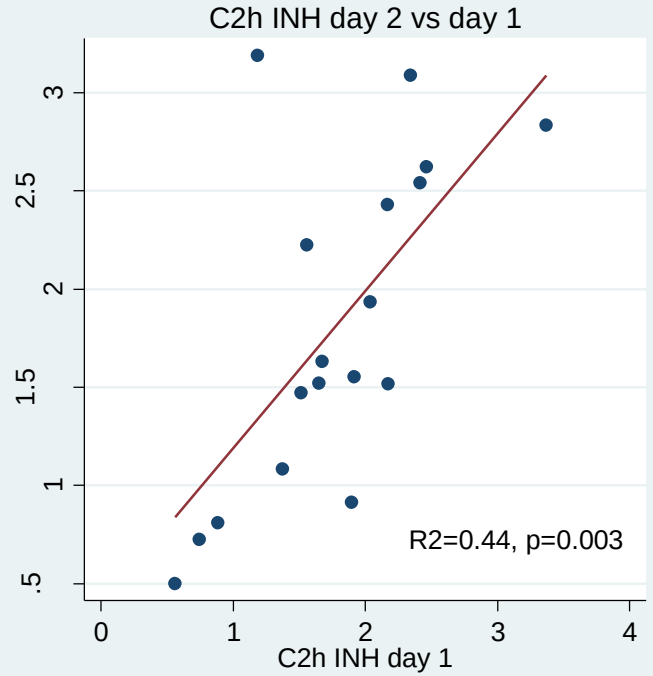
Summary

- Study II suggests an association between therapy failure and isoniazid and/or rifampicin plasma concentration levels
  - Isoniazid and/or rifampicin plasma concentration levels have been suggested to influence on treatment efficacy/outcome in two resent prospective studies [Pasipanodya 2013, Ramachandran 2013]

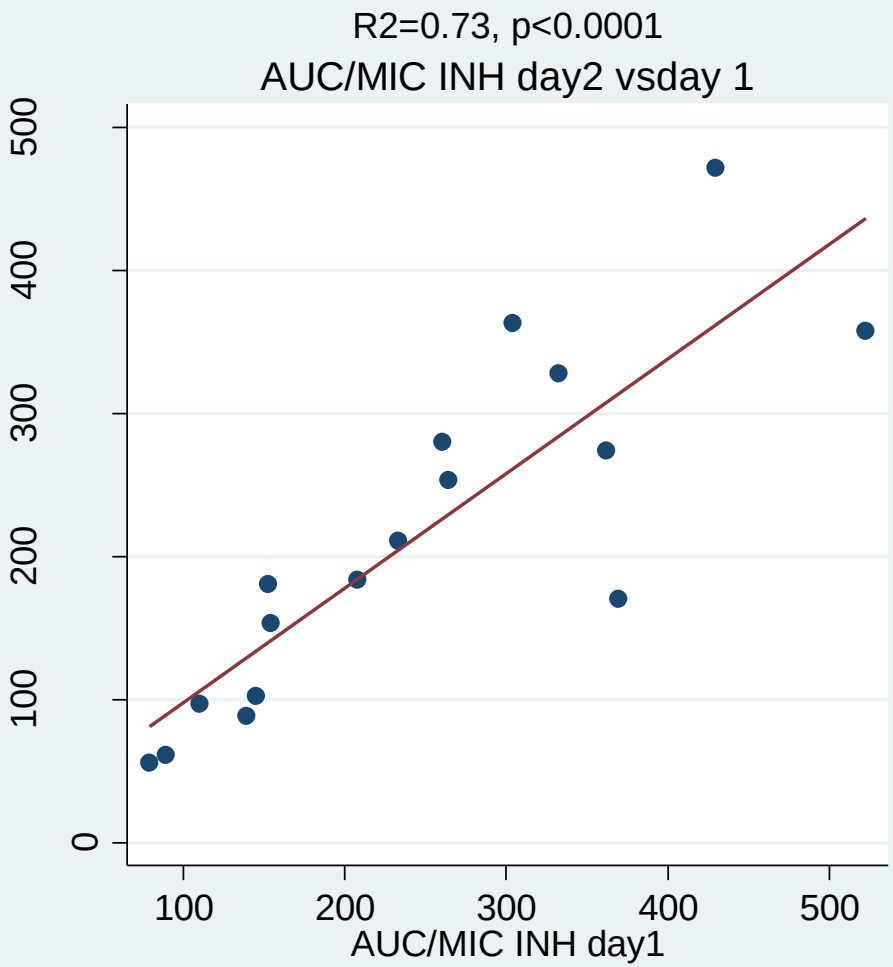
- Lower therapeutic C_{2h} and /or C_{max} targets for isoniazid and rifampicin might be more predictive of treatment outcome
  - New rifampicin C_{max} and isoniazid C_{2h} threshold targets lower than the normal C_{max} ranges have been suggested to be more predictive of therapy failure [Pasipanodya 2013, Donald 2007]

Day-to-day variability C_{max} and C_{2h}

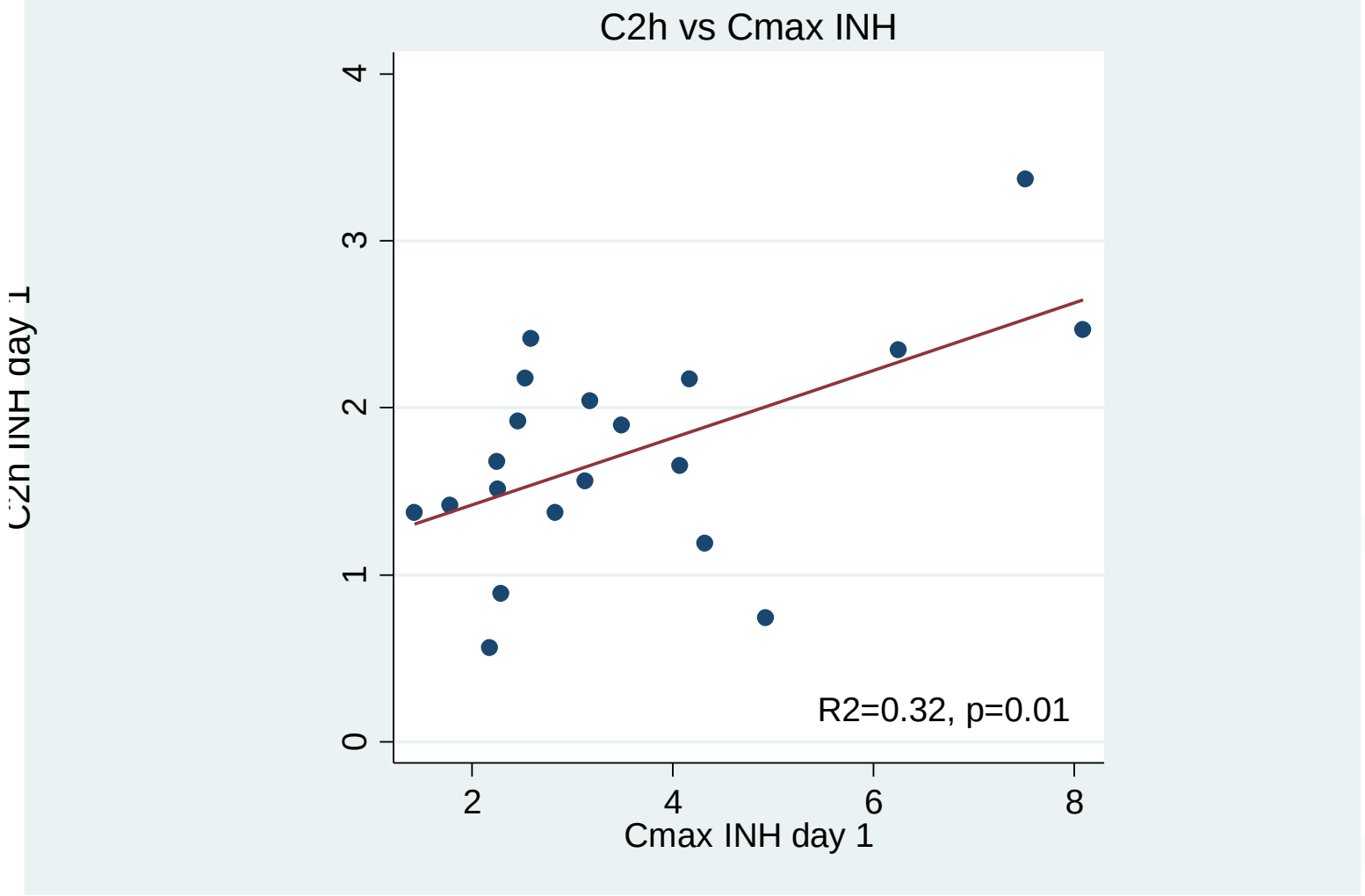




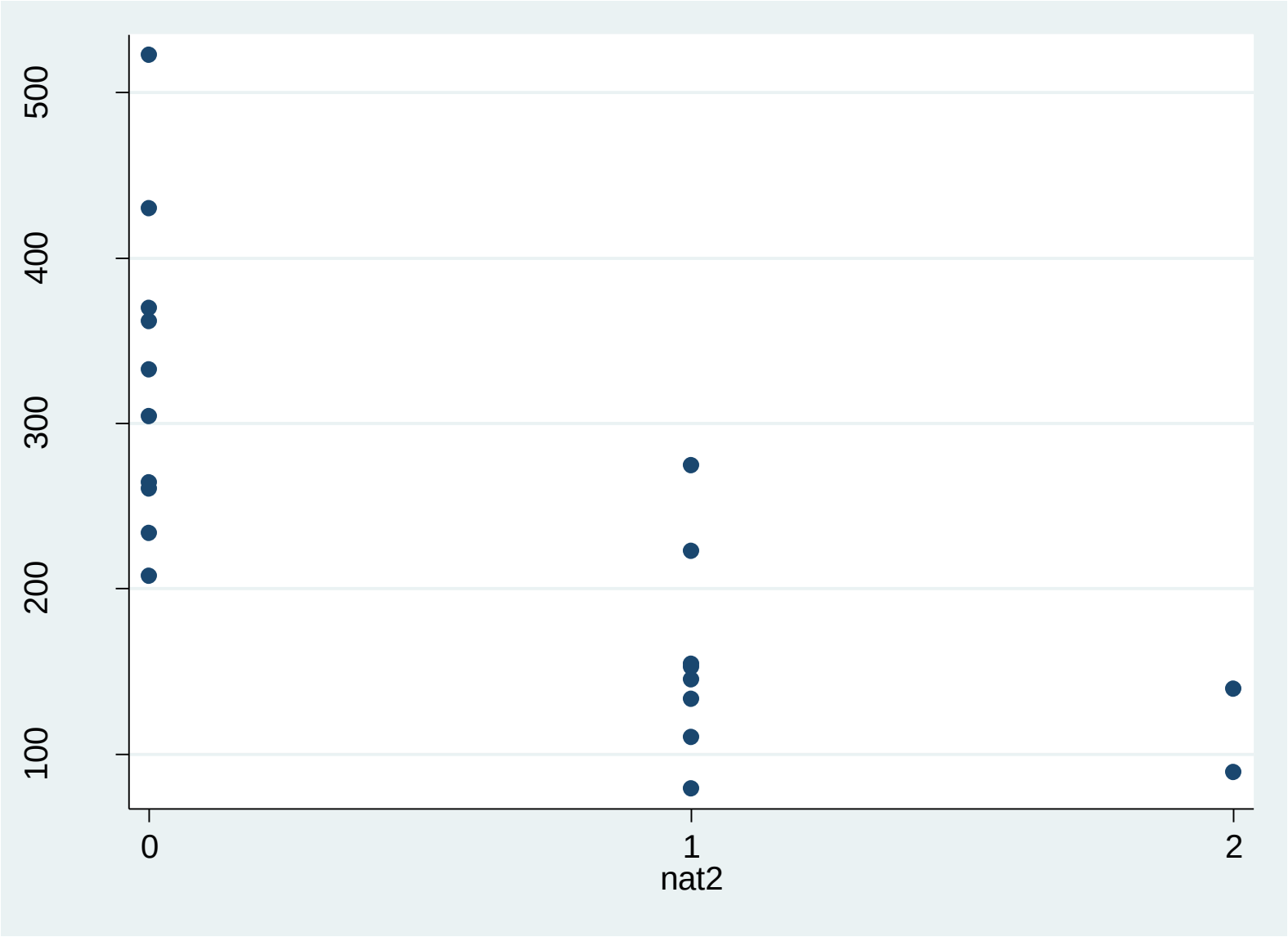
Day-to-day variability AUC



C2h vs Cmax


C2h vs Cmax INH
C2h INH day 1
Cmax INH day 1
R2=0.32, p=0.01
0
1
2
3
4
2
4
6
8

AUC INH vs NAT2



C2h vs Cmax