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Introduction

Isoniazid (INH) is one of the first-line anti-tuberculosis drugs and it has the greatest early bactericidal activity among first-line agents. Its microbial kill against *Mycobacterium tuberculosis* is best explained by the **AUC/MIC** ratio. INH is mainly metabolized by acetylation and two subpopulations are usually identified: slow acetylators (**SA**) and fast acetylators (**FA**). INH PK was extensively studied in plasma but not in lung.

Objectives

- To develop a pulmonary PK model of INH
- To simulate the ability of various dosing regimens to achieve published target exposure of antimicrobial efficacy

Patients and methods

Patients

- 89 subjects who received oral INH [1,2,3]
- INH concentrations available in plasma, epithelial lining fluid (ELF) and alveolar cells (AC)

Methods

- Population PK modeling: Monolix software (SAEM algorithm)
- Simulations: Matlab software, 1000-subject simulations of different dosing regimens for SA and FA
- Probability of target attainment: Day2 AUC/MIC calculated for a range of MICs of susceptible bacteria [4], and comparison to target ratios associated with 50% and 90% maximal killing of *Mycobacterium tuberculosis*

Table 1. Target AUC/MIC ratios associated with 50% and 90% maximal killing in plasma and ELF

	Plasma	ELF
50% killing	AUC/MIC > 63	AUC/MIC > 61.55
90% killing	AUC/MIC > 567	AUC/MIC > 707.13
Model	Mouse	<i>In vitro</i>
Reference	Jayaram, AAC 2004 [5]	Gumbo, AAC 2007 [6]

Results

INH PK model

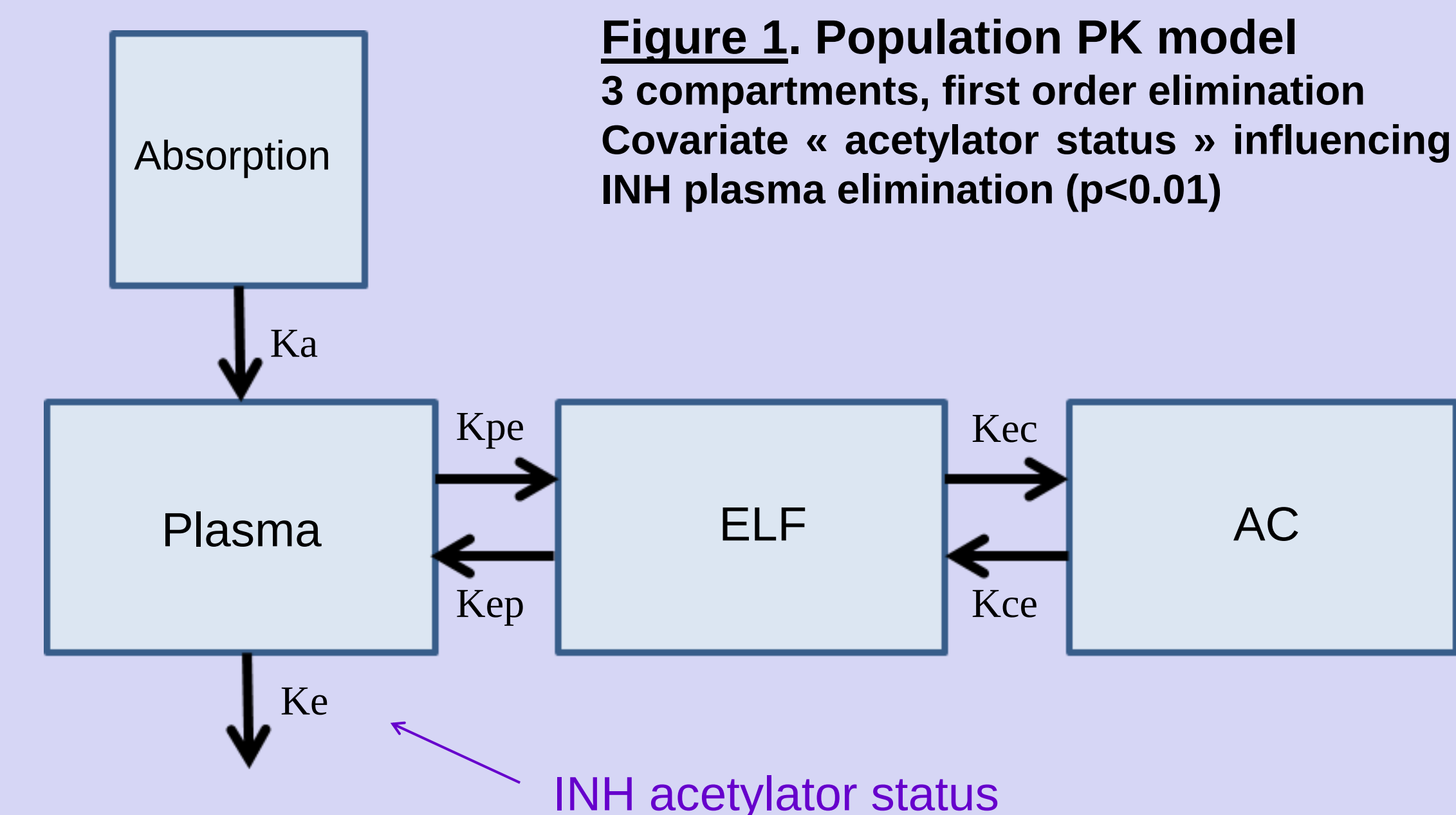


Table 2. Population PK parameters
RSE relative standard error, SD standard deviation

Parameter	K_a (h ⁻¹)	K_e SA (h ⁻¹)	K_e FA (h ⁻¹)	K_{pe} (h ⁻¹)	K_{ep} (h ⁻¹)	K_{ec} (h ⁻¹)	K_{ce} (h ⁻¹)	V (L)	V_{elf} (L)	V_{ac} (L)
Mean	2.57	0.203	0.328	0.061	0.001	0.085	0.213	110	52.2	45.2
RSE (%)	-	14.3	12.5	26.2	100	92.9	122	9.1	47.9	31.0
SD	1.59	0.117	0.189	0.062	0.005	0.310	0.609	75.8	13.3	-

INH PK model performance

Figure 2. Weighted residuals vs time

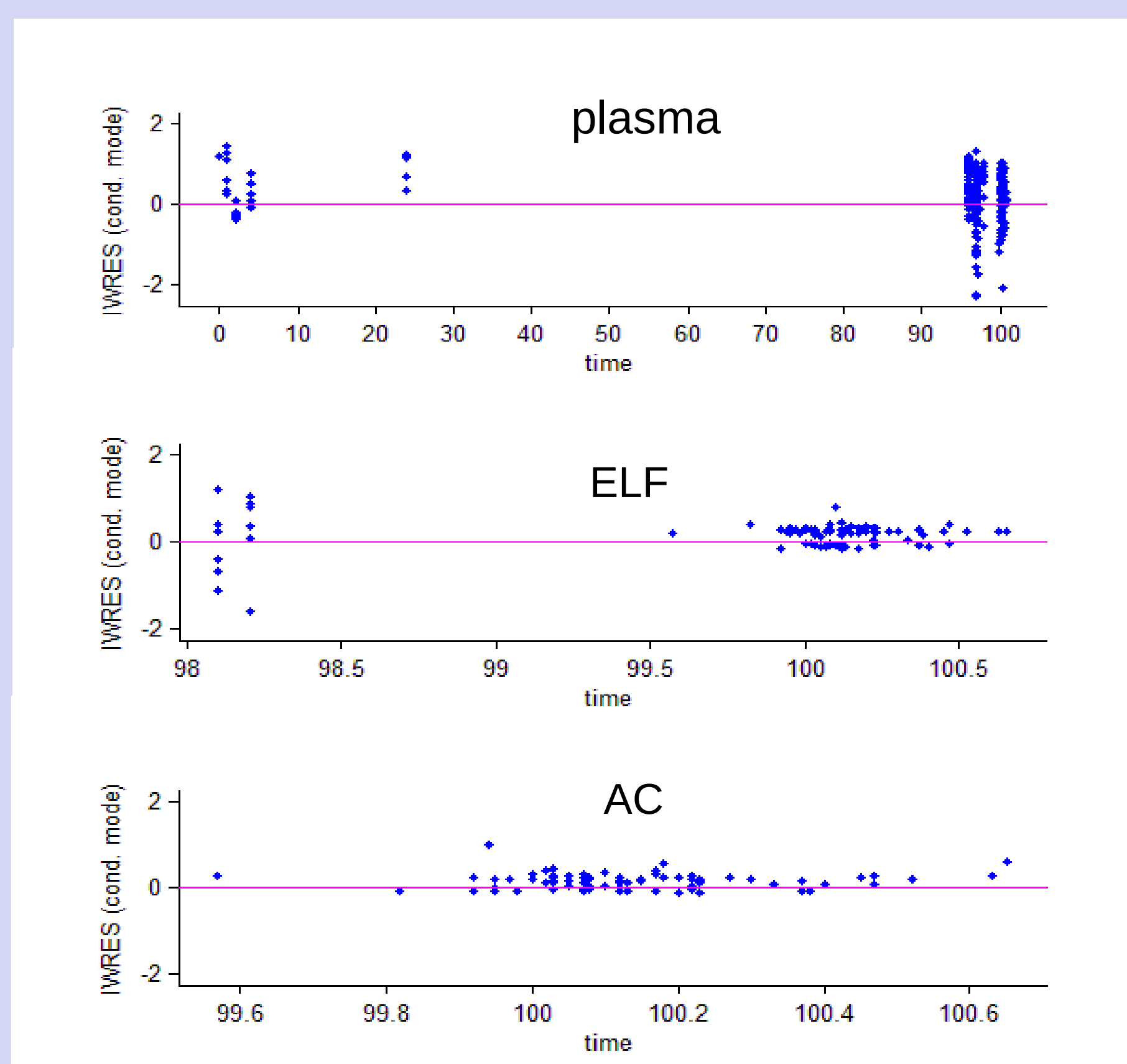


Table 3. Performance of individual predictions
ME mean error, RMSE root mean squared error

	ME (mg/L)	RMSE (mg/L)
Plasma	-0.14	1.17
ELF	0.76	3.77
AC	-1.18	5.24

Simulations

Figure 3. Probability of target attainment
50% and 90% maximal killing rate
2 dosing regimens: 300mg/day (standard) and 600mg/day

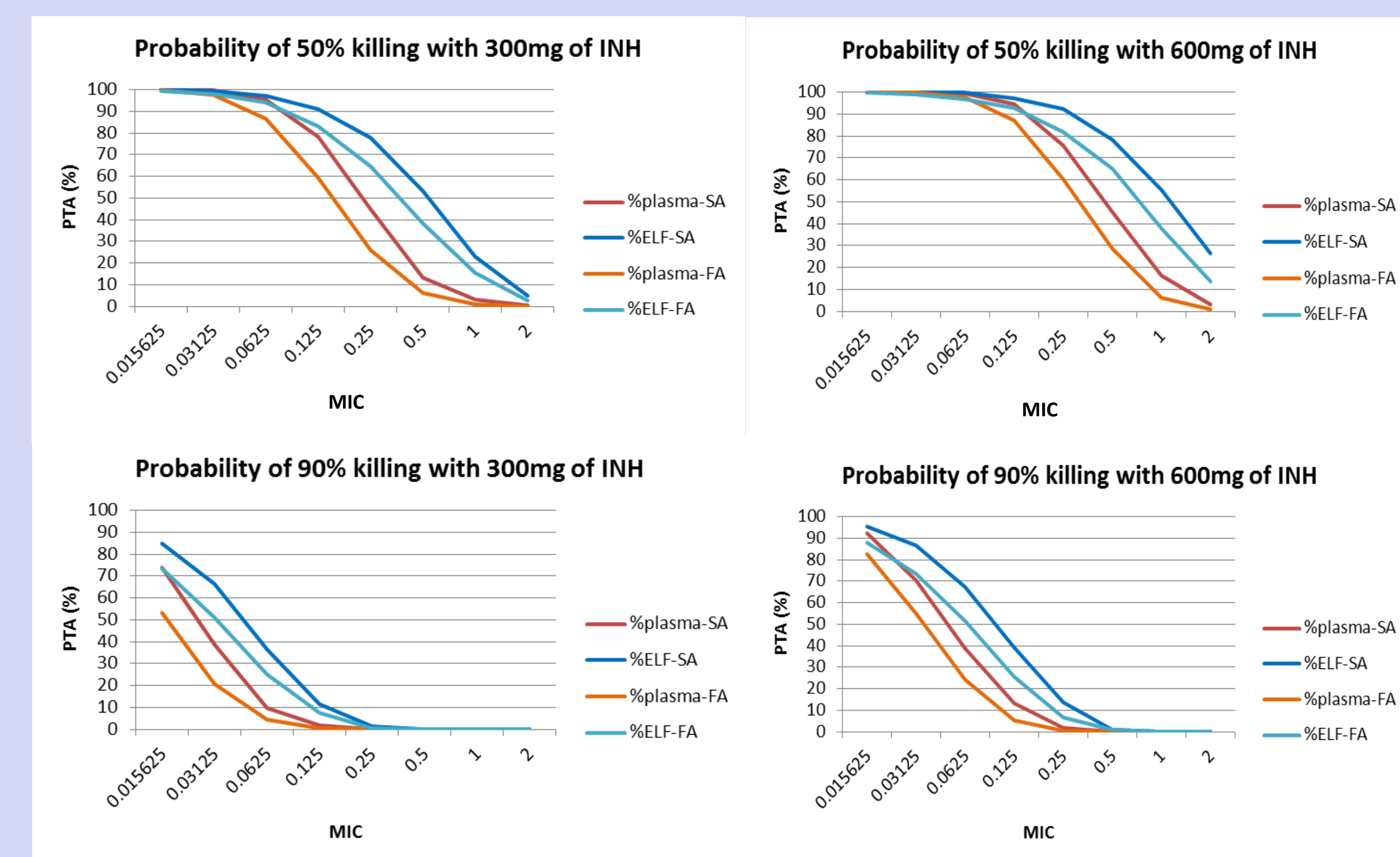


Table 4. Probability of target attainment (in %) associated with the standard 300mg INH dose for a low and an intermediate MIC

50% maximal killing			90% maximal killing		
MIC	0.015625	0.125	MIC	0.015625	0.125
Plasma – SA	100	78.3	Plasma – SA	73.9	2
Plasma – FA	99.8	59.5	Plasma – FA	53.2	0.5
p-value	-	< 10 ⁻¹⁸	p-value	< 10 ⁻⁹	< 10 ⁻²
ELF – SA	100	90.9	ELF – SA	84.7	11.5
ELF – FA	99.4	83.2	ELF – FA	73.4	7.4
p-value	-	< 10 ⁻⁶	p-value	< 10 ⁻⁹	< 10 ⁻²

Discussion

- PK model adequately described INH levels in plasma and lungs.
- PTA in ELF was always higher than in plasma. So plasma exposure may not be predictive of **pulmonary exposure**.
- PTA in fast acetylator subjects was always lower than that in slow acetylator subjects.
- M. tuberculosis* MIC greatly influences target attainment. Low PTA may be observed even for susceptible organism with intermediate MIC
- The standard INH dose of 300mg was associated with **suboptimal killing** especially in fast acetylator subjects.
- INH therapy may be optimized by using **higher INH doses**, if such doses can be tolerated, and by **individualizing** the dose to the acetylator status.

References

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