The pharmacokinetics of fosfomycin in urine

Evaluation of the effectiveness of the treatment of uncomplicated urinary tract infections based on urinary concentrations

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Fosfomycin background

- Urinary tract infections (UTIs) are the most common bacterial infections among otherwise healthy, nonpregnant woman.[1]
- Antimicrobial resistance is increasing among uropathogens.[2]
- Oral fosfomycin remains one of the most effective antibiotics in the treatment of UTIs.
- Surprisingly, little is known about the pharmacokinetics (PK) of fosfomycin in urine.

The **FUEL** study was born!

(**F**osfomycin **U**rine concentrations in h**E**althy vo**L**unteers)

[1]. Araj GF et al. Leban. Med. J. 2012

[2]. Naber KG et al. Eur Urol. 2008

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Aim of the FUEL study

An evaluation of the effectiveness of the current treatment of uncomplicated urinary tract infections with fosfomycin

Measuring fosfomycin concentrations in urine during 7 days in healthy volunteers after a single, oral dose of 3 grams

April 2016:	Approval of ethical committee
July 2016:	First volunteer was included
Sept 2016:	End of inclusion

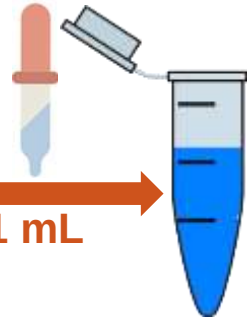
FUEL – study design (1)

Erasmus MC

x 40

3 grams fosfomycin

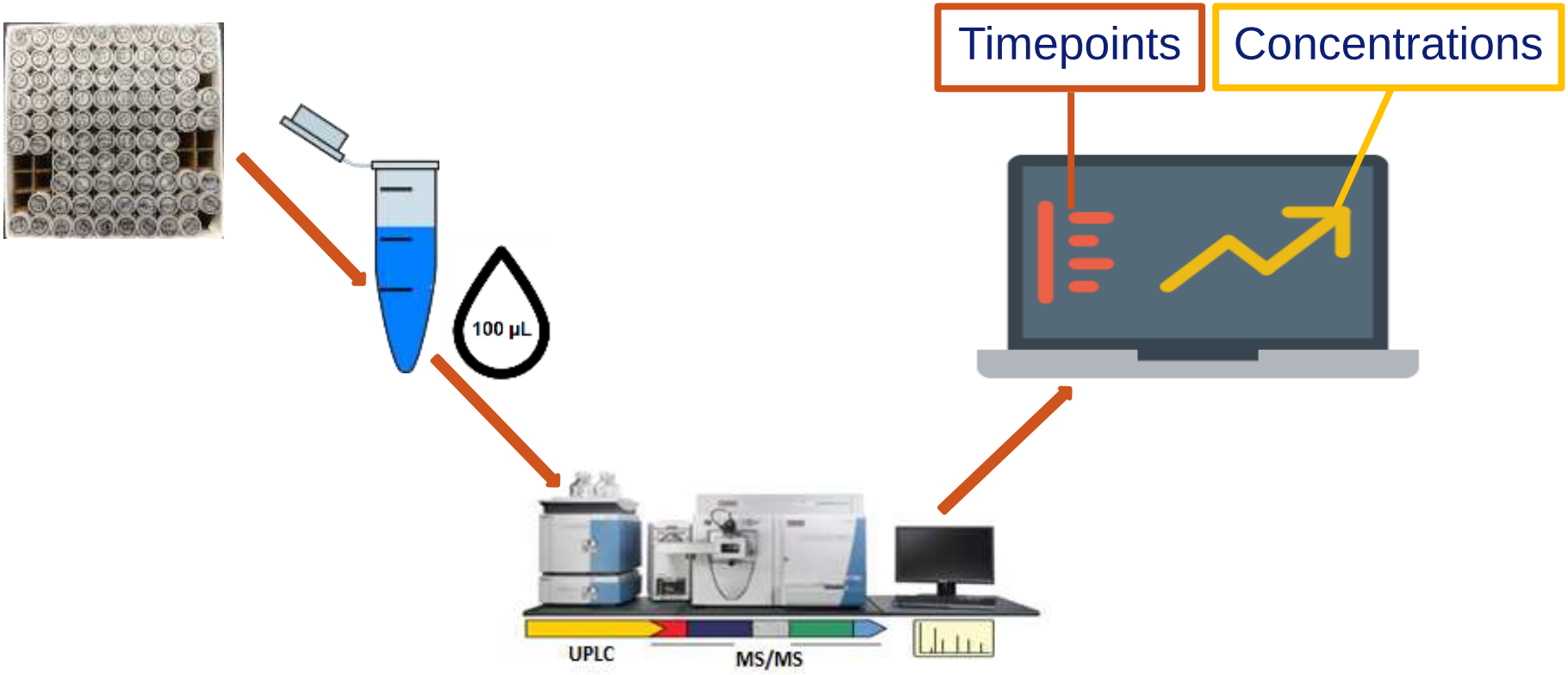
1 mL



0-48h **EVERY**

48h – 7 days **2x daily**

– study design (2)



Wijma, RA et al. 2017 (paper submitted)

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FUEL – study design (3)

- The following **PK parameters** were calculated:
  - Maximum concentration (mg/L) C_{max}
  - Time to C_{max} (h) T_{max}
  - Concentration half-life (h) $T_{1/2}$
  - Fosfomycin clearance (mg/h) CL_{fos}
  - Recovery (%)
- The following **PK/PD indices** were calculated:
  - **T>MIC**: Time > Minimal Inhibitory Concentration [1]
  - **AUC/MIC**: Area Under the Concentration-time curve / MIC [1]

[1]. MICs of the most common uropathogen, E.coli

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Demographics & Sample collection

Demographics of the 40 healhy, female volunteers:

- Age: 24.3 ± 7.9 years
- Length: 170 ± 6.4 cm
- BMI: 22.1 ± 2.4
- eGFR: 119.7 ± 24.0 mL/min

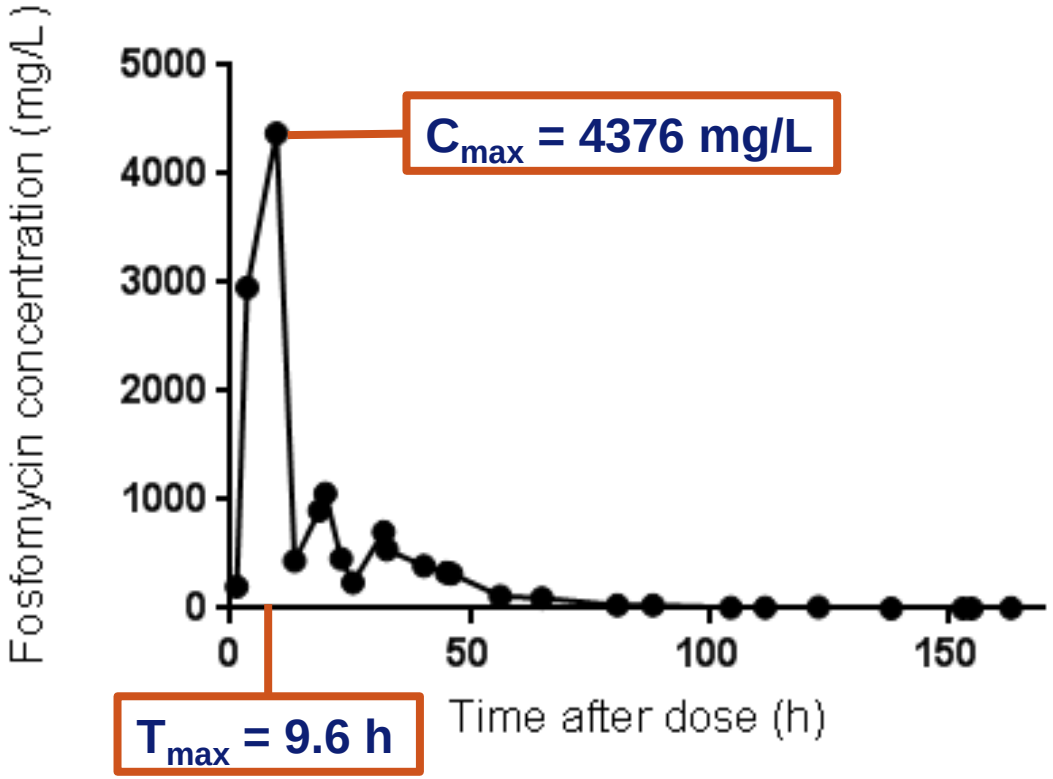
Sample collection:

- **891 samples** were collected
- Mean number of samples for each volunteer: **22 (± 3)**
- Mean **pH** of all samples: **5.5 (± 0.5)**

Example of a concentration-time curve *(n=1)*

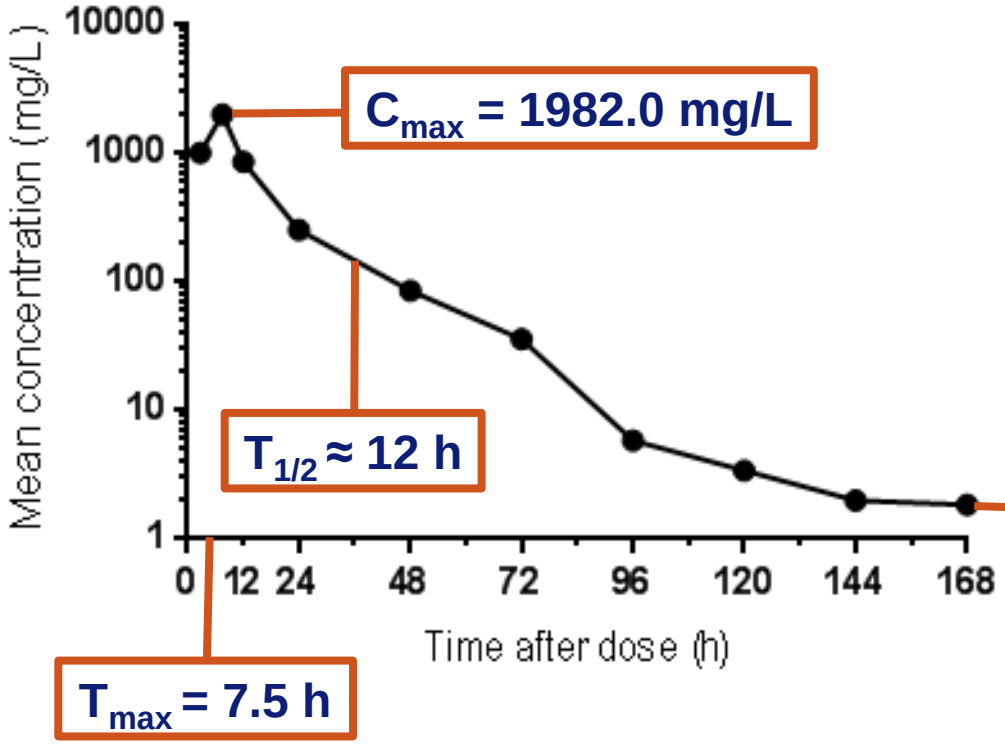
Erasmus MC

PK



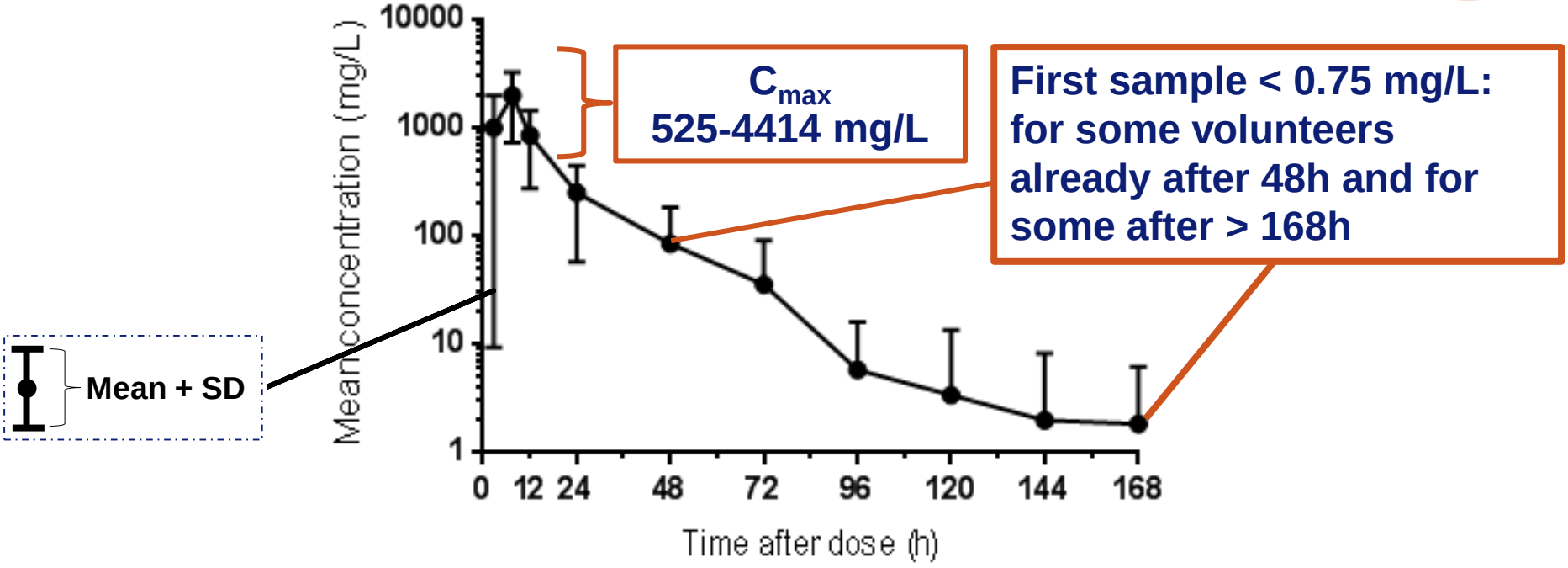
Mean concentrations over time *(n=40)*

PK



Mean concentrations over time *(n=40)*– *with variance*

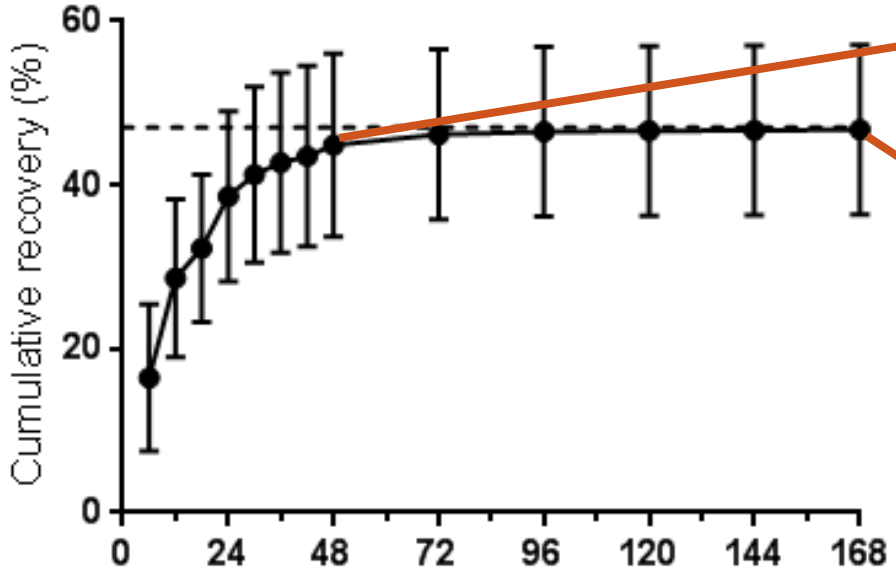
PK



High interindividual variability (IIV) in urinary concentrations

Mean cumulative recovery *(n=40)* – ***with variance***

PK



Recovery$_{48h}$ = 44.5%
(26.2% - 65.1%)

Recovery$_{7days}$ = 47.0%
(26.4% - 67.1%)

Mean + SD

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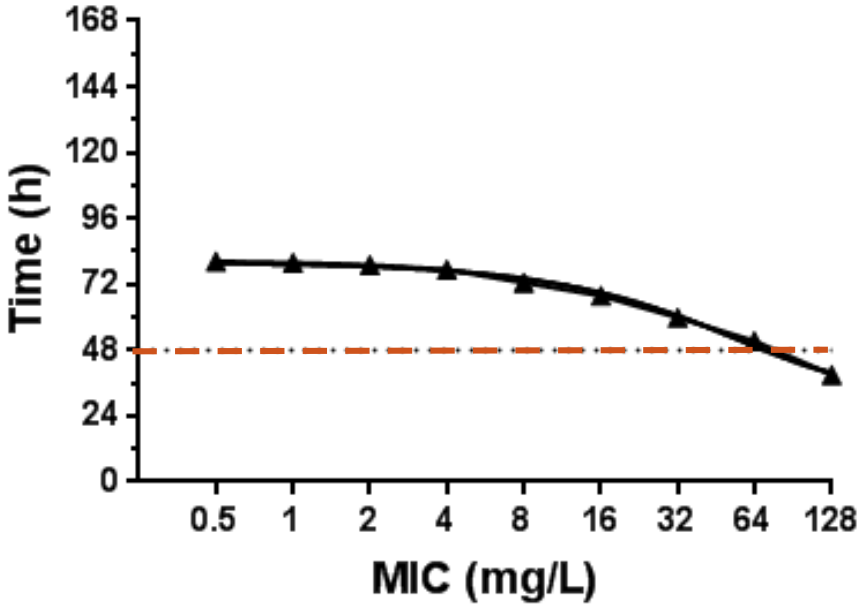
T>MIC for all MICs *(n=40)*

PD



- All strains with MIC 0.5 - 64 mg/L are covered for at least **48 hours**
- Only strains with MIC of **128 mg/L** are not covered during the first **48 hours**

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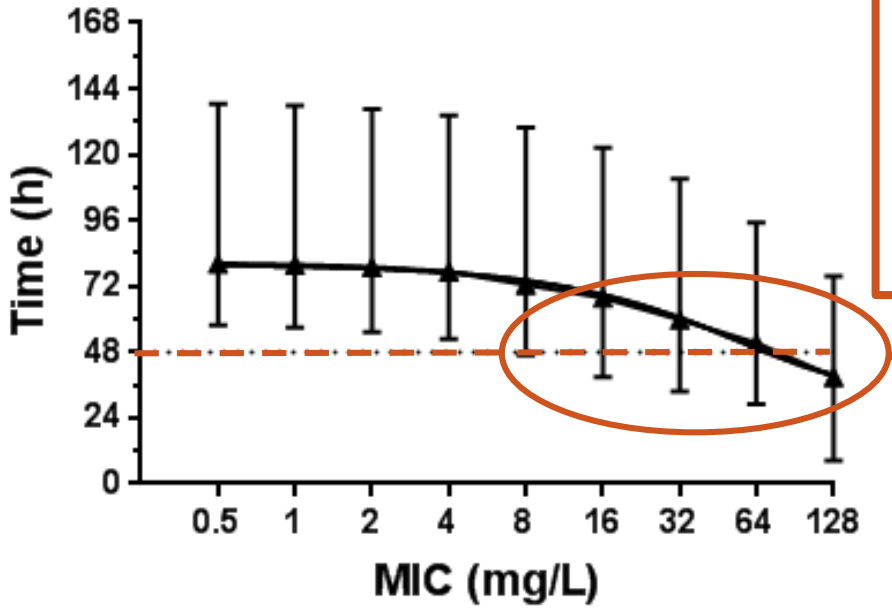
T>MIC for all MICs *(n=40)* – *with variance*

Erasmus MC

PD



These strains could also have T>MIC of less than 48 hours so only MICs 0.5-4 mg/L are covered

Mean + Range

- ~~All strains with MIC 0.5 - 64 mg/L are covered for at least **48 hours**~~
- ~~Only strains with MIC of **128 mg/L** are not covered during the first **48 hours**~~
- But this conclusion is incorrect if the variance is taken into account

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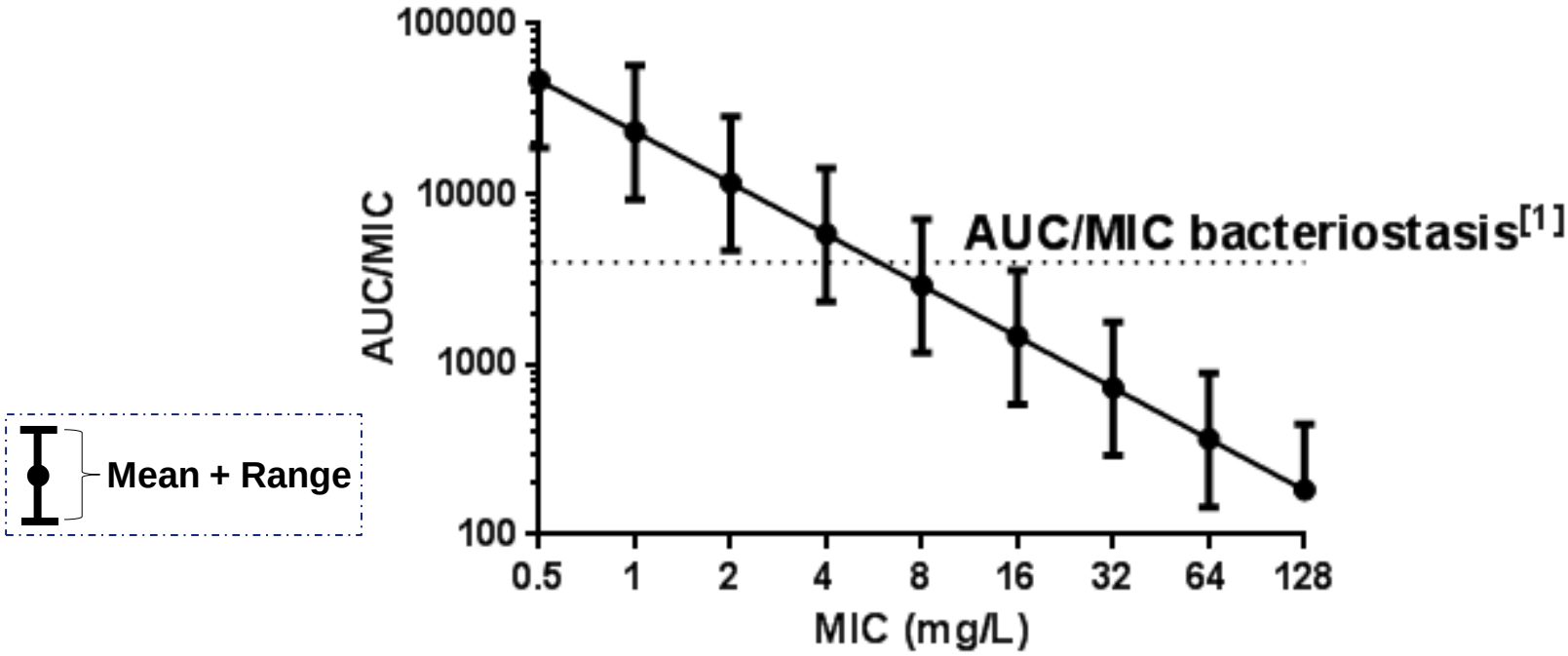
AUC_{7days} /MIC for all MICs *(n=40)* – ***with variance***



- MIC 0.5 - 2 mg/L: Covered
- MIC 4 – 8 mg/L: Uncertain due to high variability in urinary concentrations
- MIC 16 - 128 mg/L: Not covered

[1]. fAUC/MIC for bacteriostasis in urine (3994) conform 'Rationale for the EUCAST clinical breakpoints, version 1.0

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Conclusions

- Concentration over time:
  - Large variability is present in healthy volunteers with normal renal function, BMI, and urinary pH **(C_{max} 525 - 4414 mg/L)**
- Excretion:
  - Recovery over 48 h **(44.5%)** ≈ Recovery over 7 days **(47.0%)**
- PK/PD index:
  - **Time > MIC:** Only MICs of 0.5 – 4 mg/L are covered during 48 h
  - **AUC / MIC:** MIC's of 0.5 – 2 mg/L are covered for bacteriostasis
  - Difficult to evaluate effectiveness due to large variability

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  - For participation
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- Johan Mouton, Birgit Koch and Teun van Gelder
  - For the support and guidance

Overview PK parameters and PK/PD indices

PK parameter		Population mean	SD
C_{max}	(mg/L)	1982.0	1257.4
T_{max}	(h)	7.5	4.2
$T_{1/2}$	(h)	12.4	5.7
Recovery $_{0\text{-}7\ days}$	(%)	47.0	10.4
$_{0\text{-}48\ h}$	(%)	44.5	12.6
PK/PD index		**Population mean**	**Range**
*T>MIC $_{32\ mg/L}$	(h)	60	36-120
AUC $_{7days}$/MIC	MICs	0.5-2.0 mg/L covered	-

** ECOFF E.coli (32 mg/L) conform EUCAST*

- T_{max} was found to be higher compared to literature (< 4h)
- Large variability between subjects for all parameters/indices

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