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Individualization of Cefuroxime Dosage using Pharmacodynamic targets, MIC distributions and Minimization of a Risk Function

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Aim

To further develop the methodology of estimating dosing strategies

and

To develop individualized dosing strategies for cefuroxime

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Cefuroxime

- Cephalosporin
- Intravenous administration
- Renal elimination

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General drug treatment target

- As many patients as possible should be given effective treatment
- As few patients as possible should have side-effects

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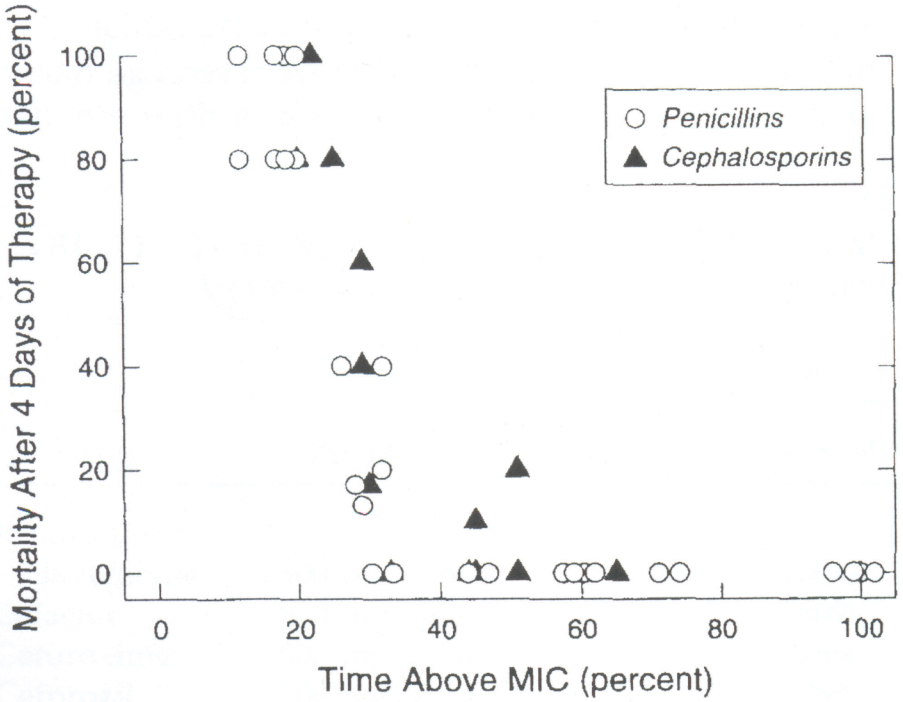
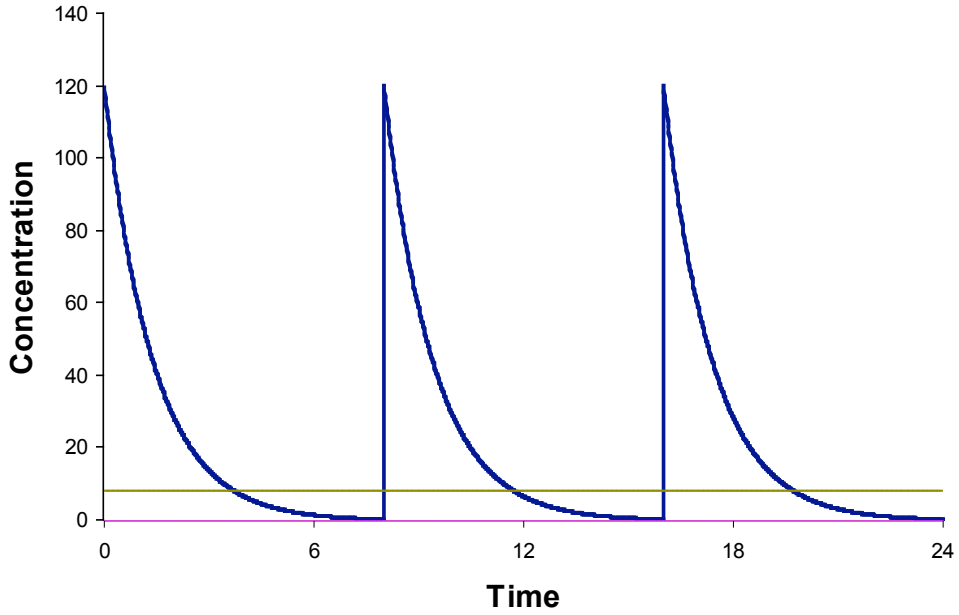
Drug treatment target for cefuroxime





Craig, Clin Infect Dis 26:1-10

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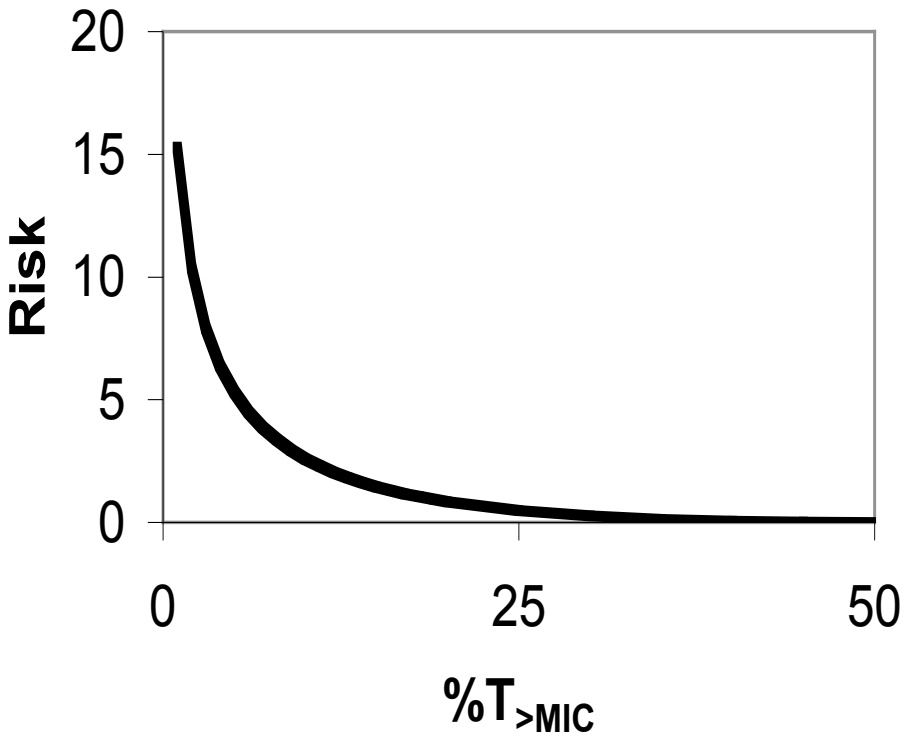
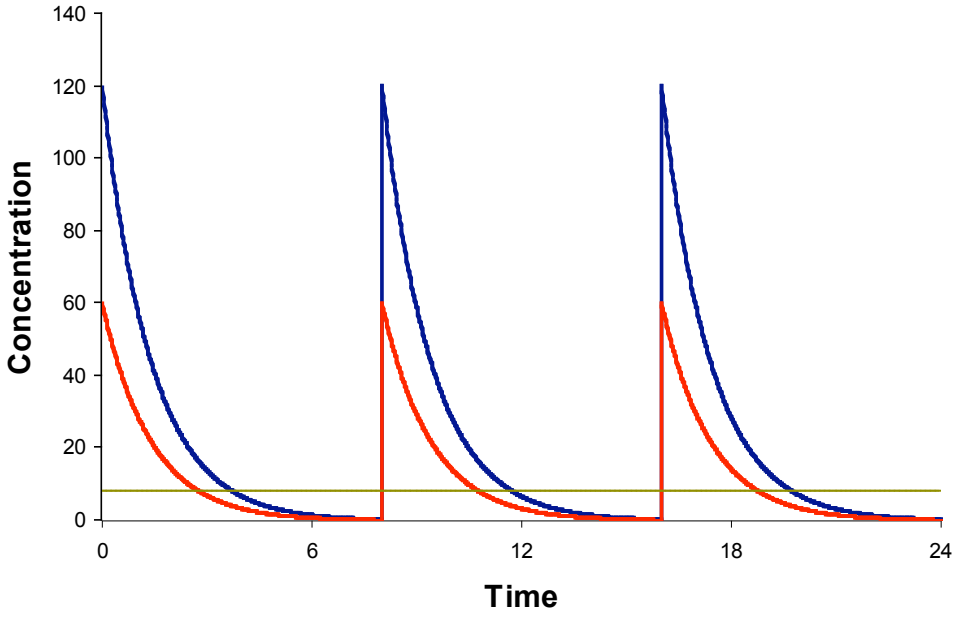
Drug treatment risk function for cefuroxime





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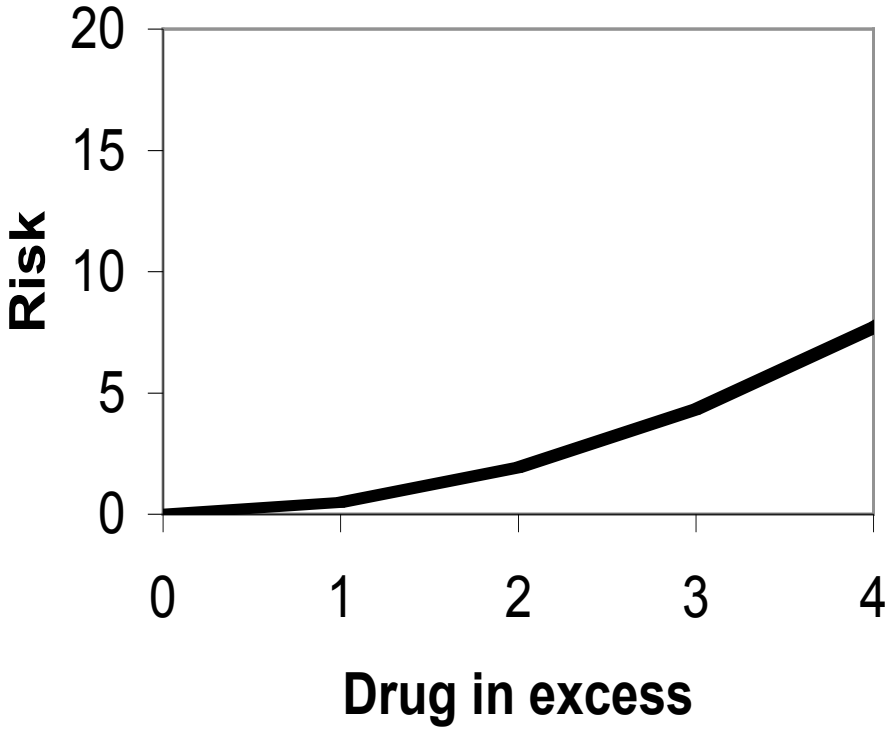
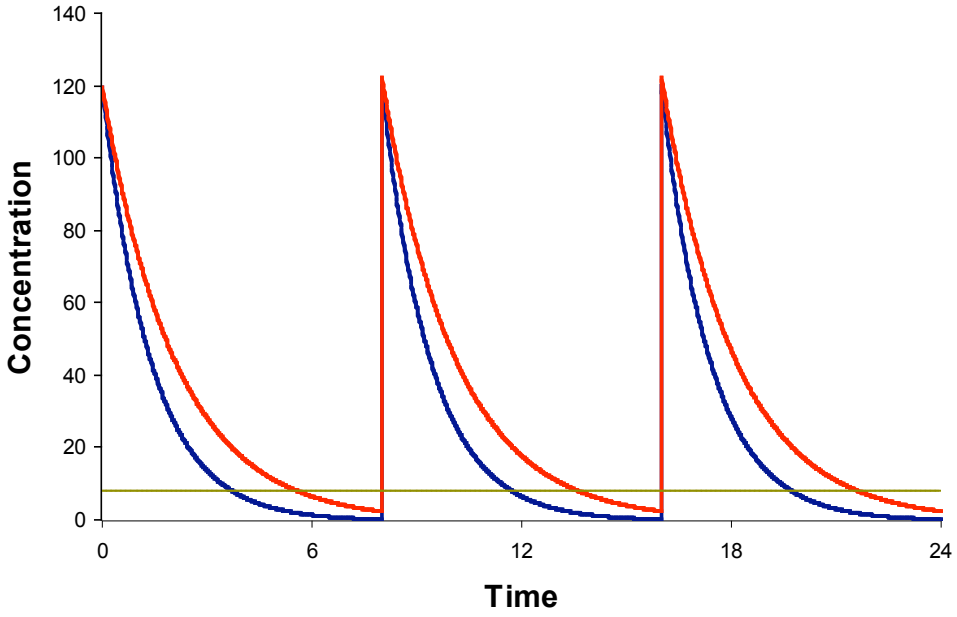
Drug treatment risk function for cefuroxime





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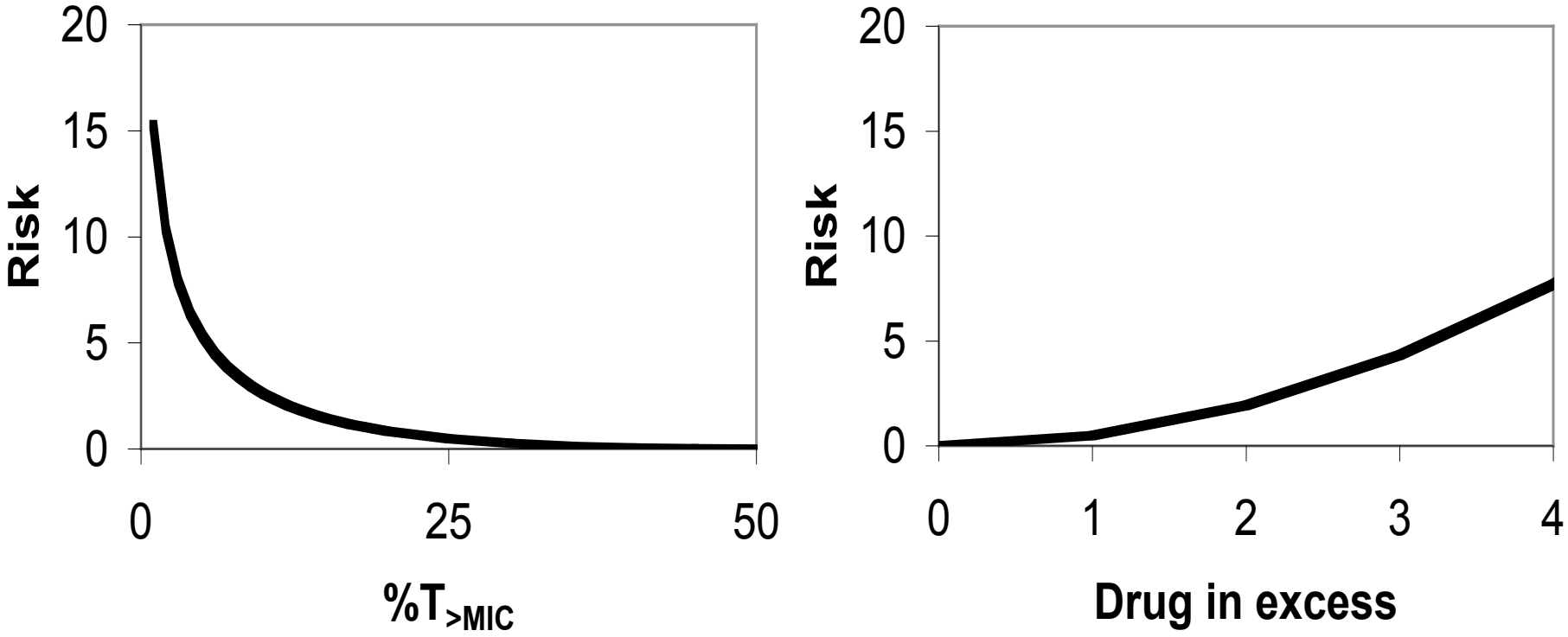
Risk function minimized during dosing estimation



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Establishing dosing strategies

- Target population
- Estimate the dosing
- Evaluate the dosing

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Target population characteristics

- Cefuroxime population PK model to simulate a large population
- Empirical distribution of covariates reflecting target population
  - CLcr covariate for clearance
  - WT covariate for V1

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Estimation of dosing

Clcr (mL/min)	Dose (mg)	Dosing interval (h)
< 20	750	24
20-40	750	12
40-80	750	8
> 80	1500	8

In this example

- Fixed dose sizes
- Estimating dosing intervals and CLcr cut-offs
- Varying number of dosing categories

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Estimated dosing

2 dosing categories 3 dosing categories 4 dosing categories

Clcr (mL/min)	Dosing interval (h)	Clcr (mL/min)	Dosing interval (h)	Clcr (mL/min)	Dosing interval (h)
≤ 50	12.04	≤ 30	17.61	≤ 30	17.61
> 50	5.28	30-80	9.51	30-50	9.50
		> 80	5.29	50-70	6.23
				> 70	4.19

Which is the best???

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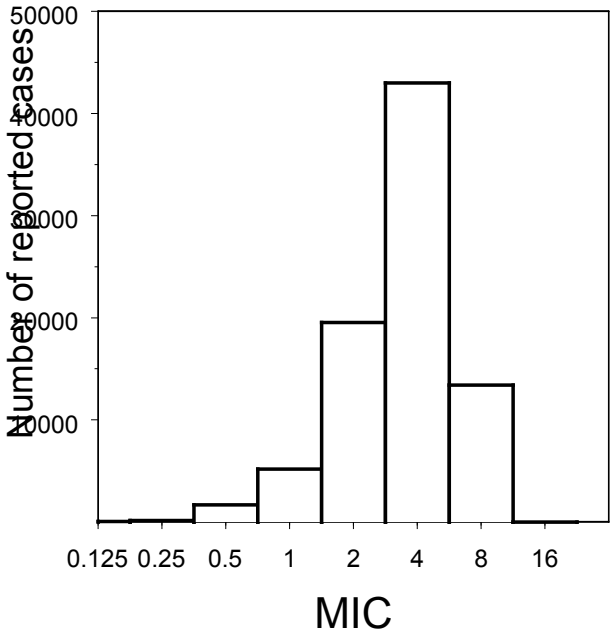
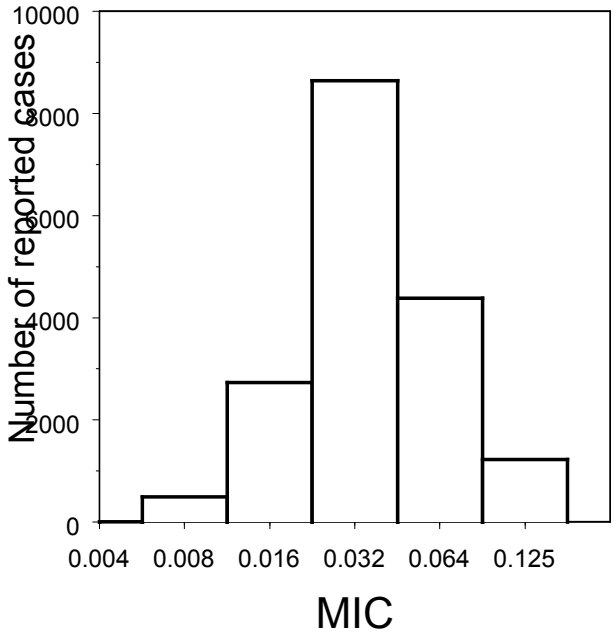
Evaluating the estimated dosing

- Each individual was assigned one MIC value from each MIC distribution
- Deviations from from the target using the MIC distributions was graphically analyzed



Escherichia coli



Streptococcus pneumoniae

www.eucast.org

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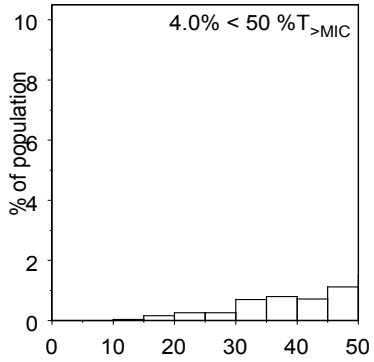
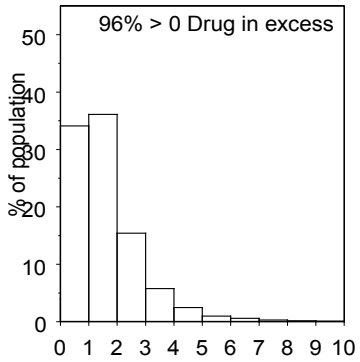
Evaluating with respect to *E.coli*

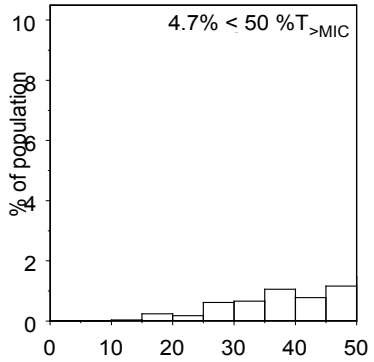
4 dosing categories

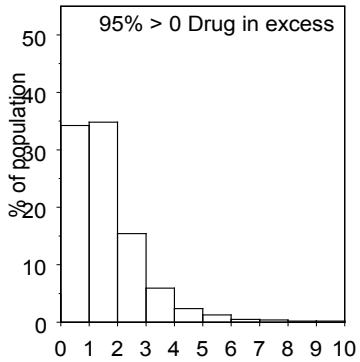
3 dosing categories

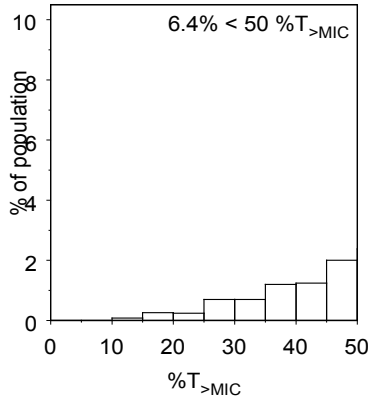
2 dosing categories

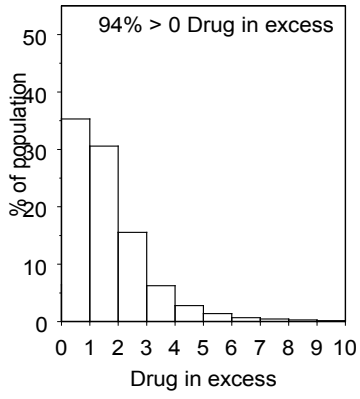












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Estimated dosing with respect to *S.pneumoniae*

Clcr (mL/min)	**Dosing interval (h)**
≤ 40	43.3
> 40	19.9

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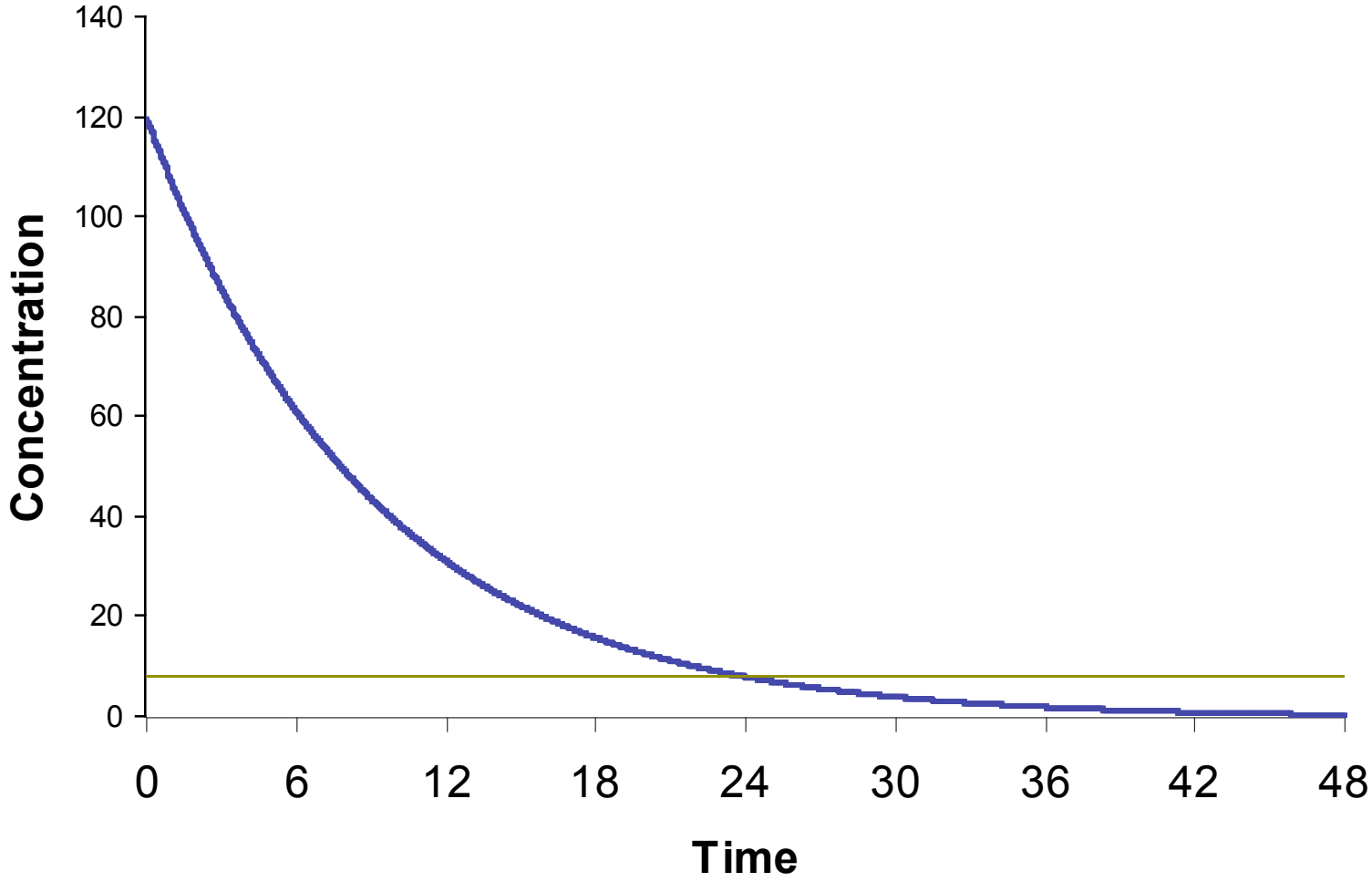
48 hour dosing interval



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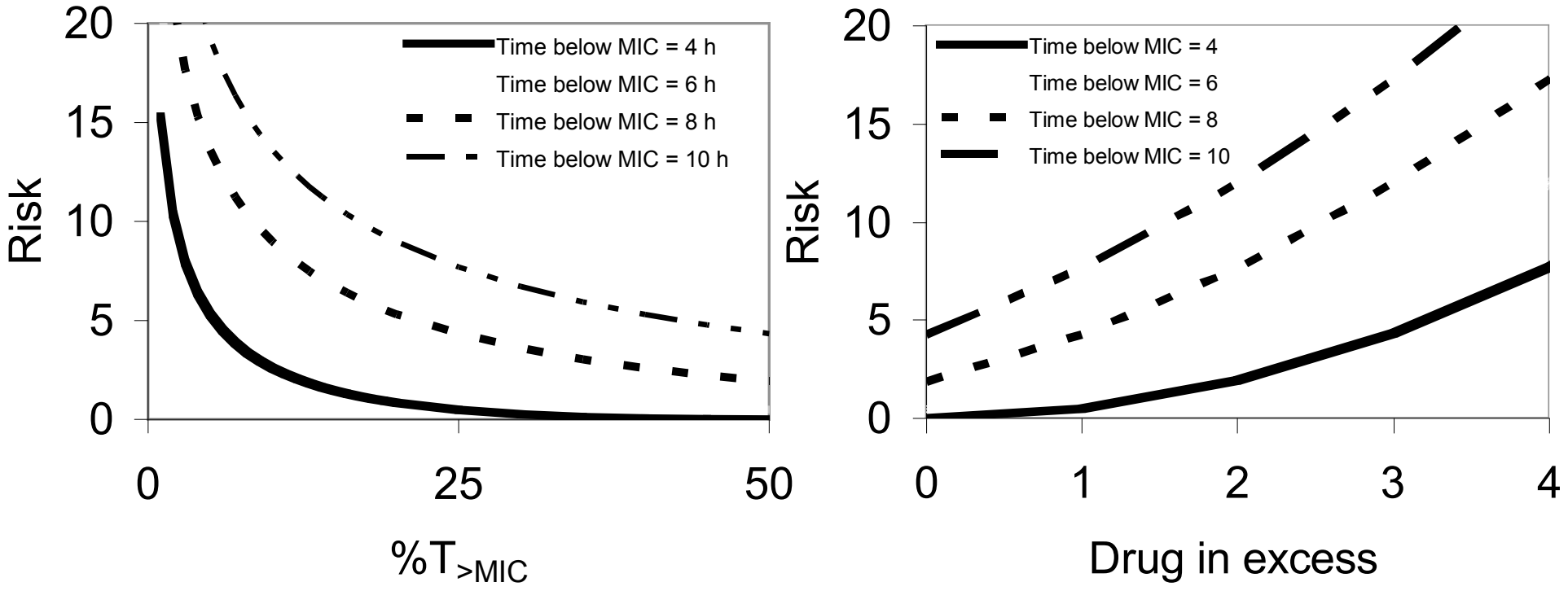
Expanded risk function



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Estimated dosing with respect to *S.pneumoniae*

Original risk function Expanded risk function

Clcr (mL/min)	**Dosing interval (h)**	**Clcr (mL/min)**	**Dosing interval (h)**
≤ 40	43.3	≤ 40	19.35
> 40	19.9	> 40	11.6

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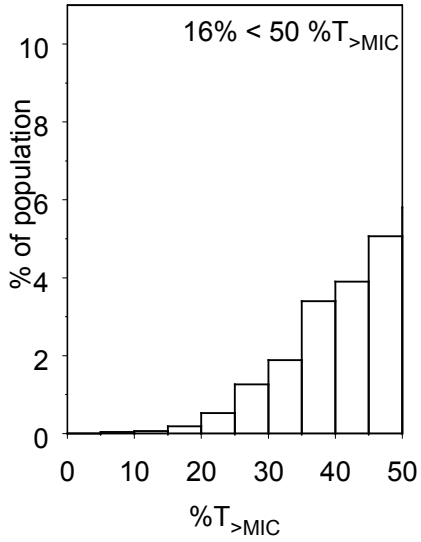
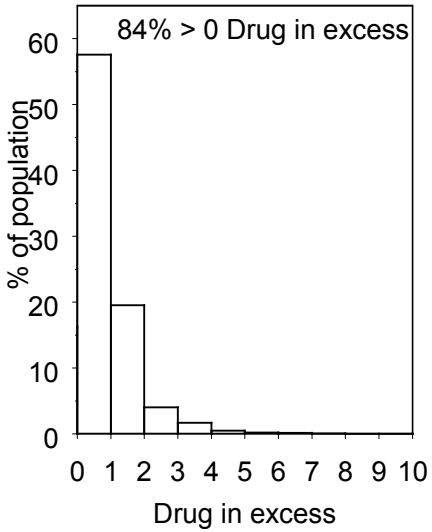
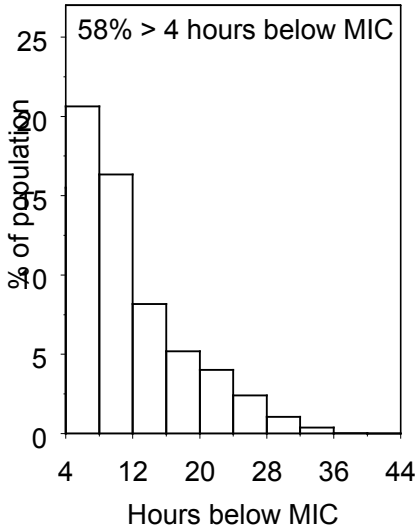
Evaluating with respect to *S.pneumoniae*

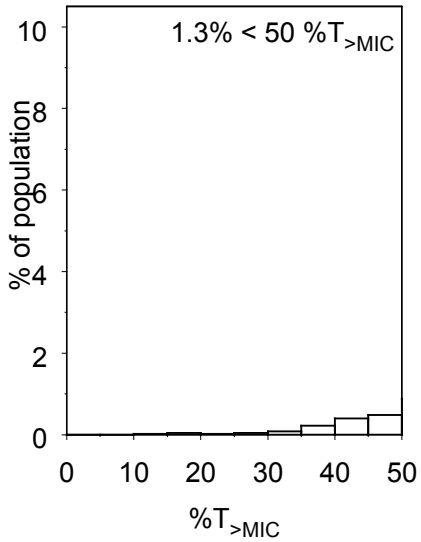
Original risk function

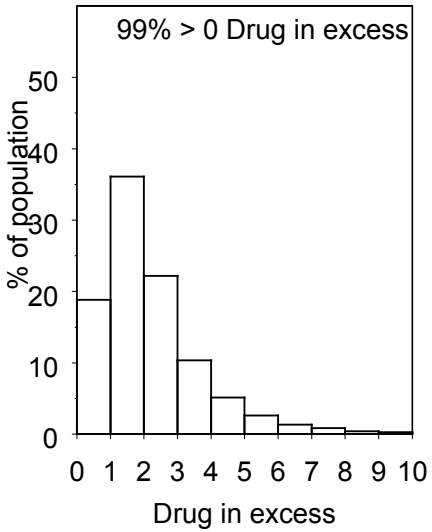


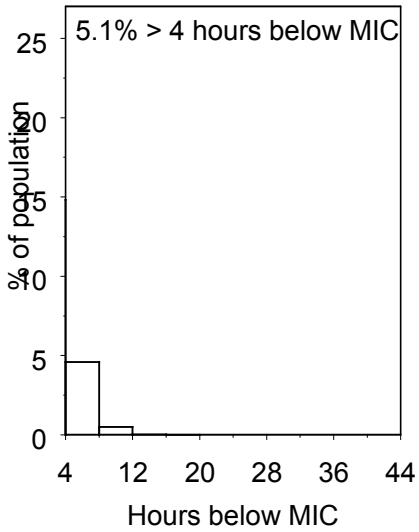




Expanded risk function







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Dosing strategies

E.coli

Clcr (mL/min)	Dose (mg)	Dosing interval (h)
≤ 50	1500	12
> 50	1500	6

S.pneumoniae

Clcr (mL/min)	Dose (mg)	Dosing interval (h)
≤ 40	250	24
> 40	250	12

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Summary

- Illustration of how individualized dosing strategies can be estimated using a combined risk function
- Different dosing strategies for cefuroxime might be used for different infecting species
- An example of how MIC distributions can be used in drug development