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Pk/Pd of antifungal drugs

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Disclosures

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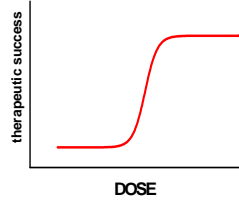


Research grants – advisory boards – speaker

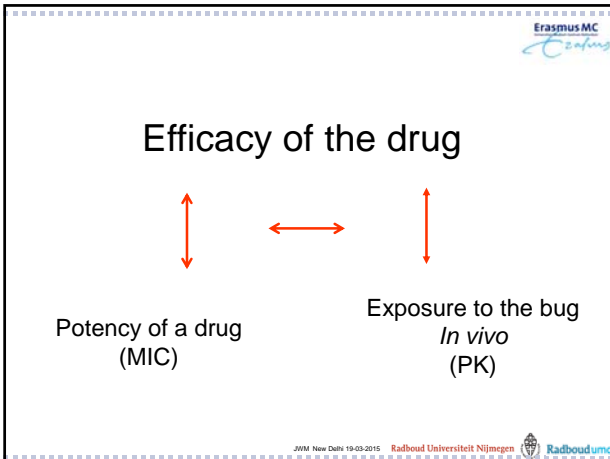
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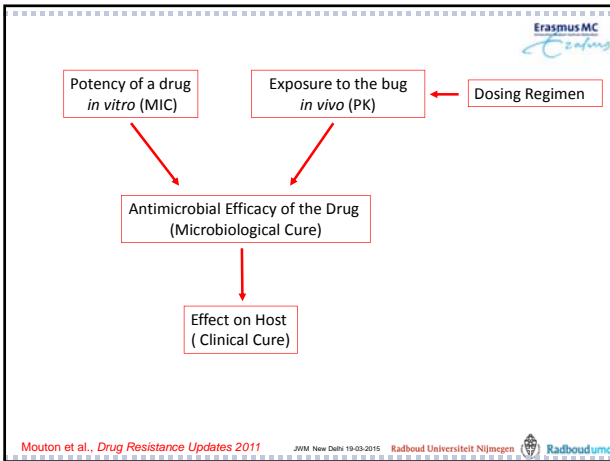
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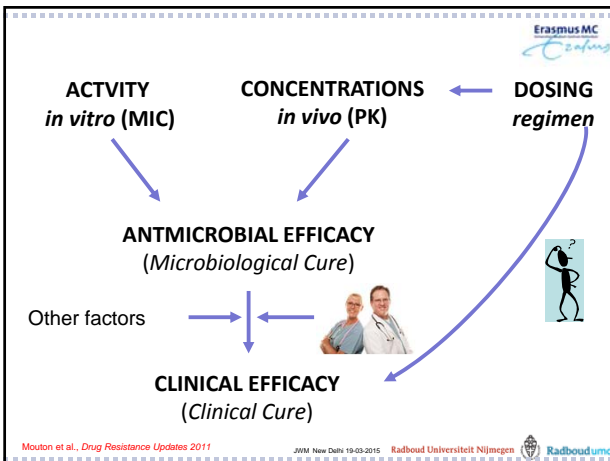
Dosing should be such that the level of antimicrobial activity is associated with a high likelihood of therapeutic success.

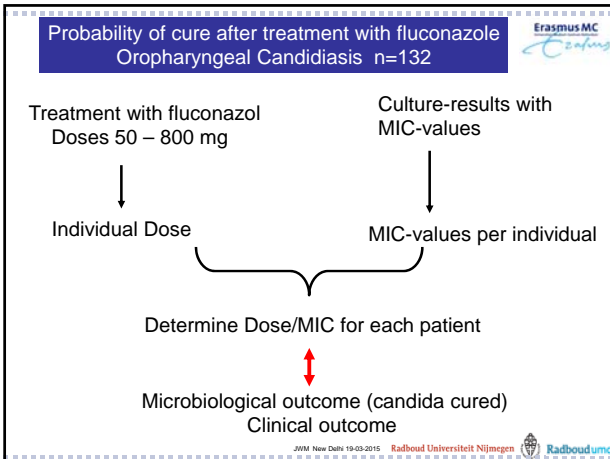


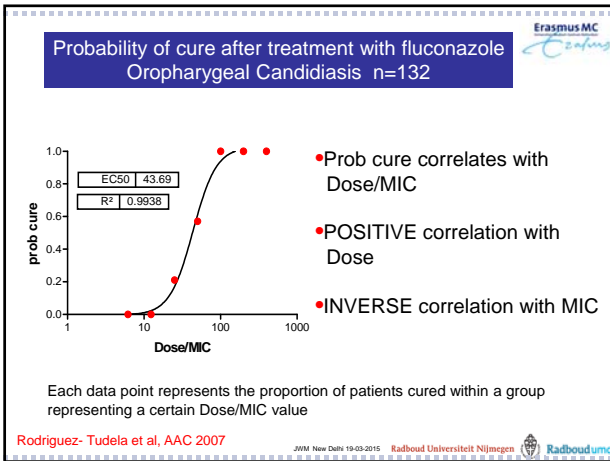
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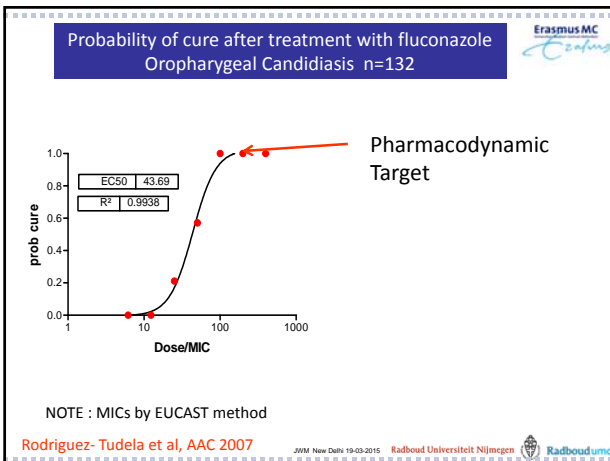


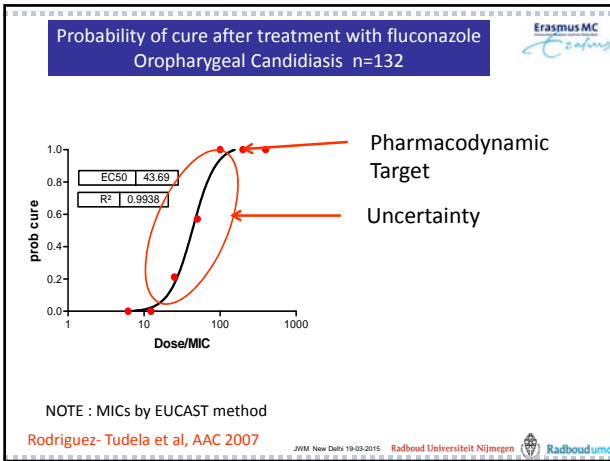


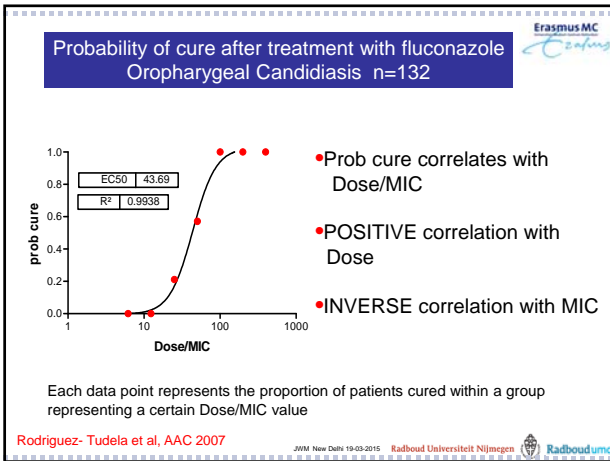


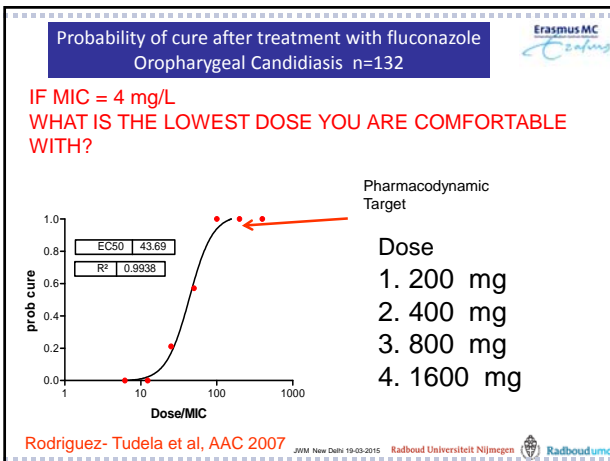


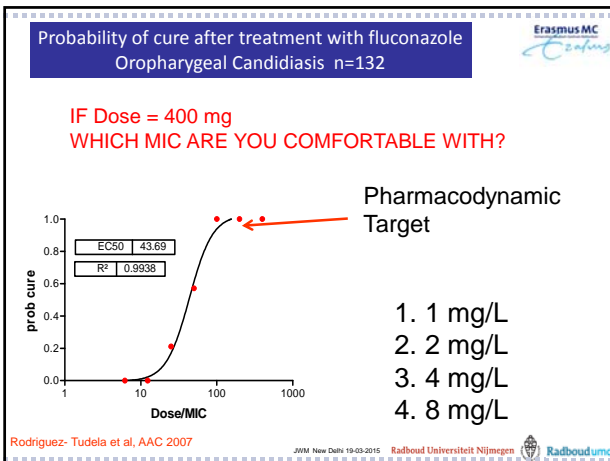


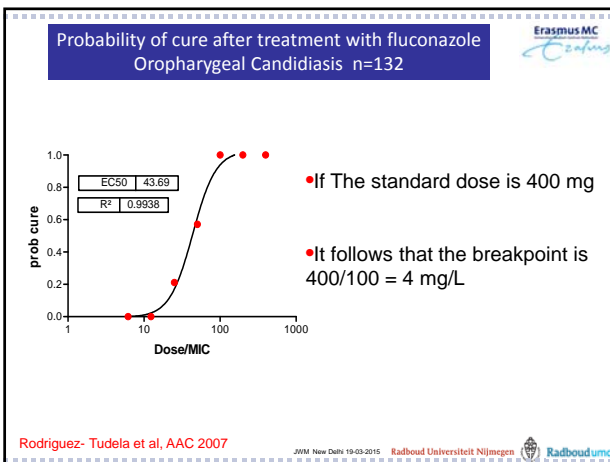












EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Susceptible (S)

A micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

Intermediate (I)

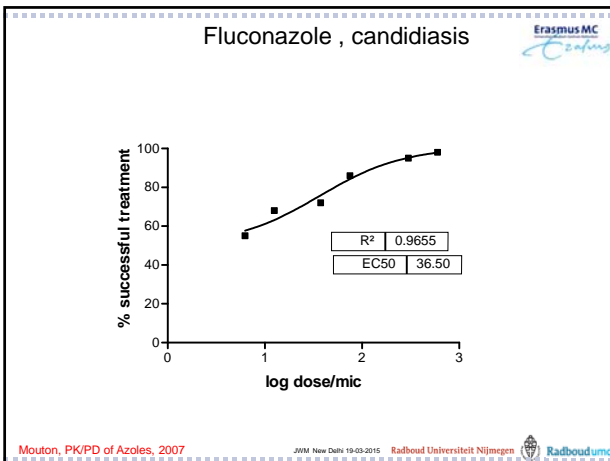
A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

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Resistant (R)

Bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

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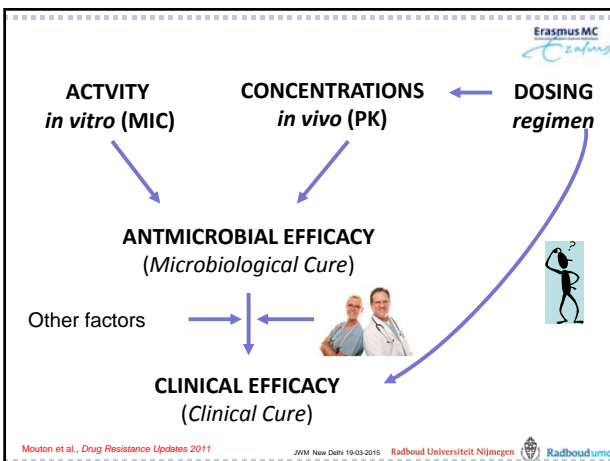


Problem (or is it?):

What if the standard dose is different?

What if the population is different?

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Pharmacokinetic parameters :
Measures of Exposure

AUC is *usually* linearly related to Dose

Dose x 2 = AUC x 2
Dose x 4 = AUC x 4

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So what determines the relationship between dose and exposure?

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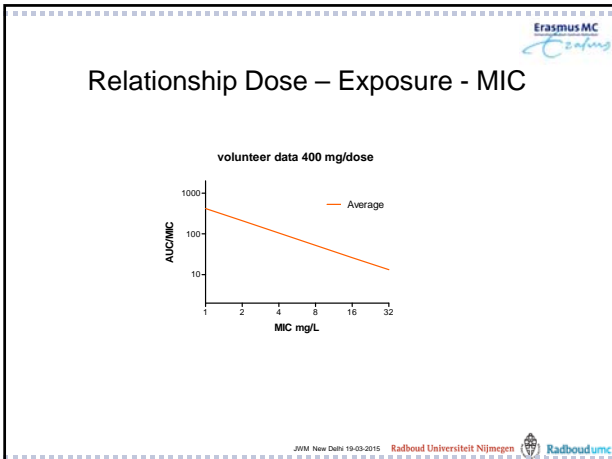
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Fluconazole Dose - AUC Relationship

$r=0.99$

Rodriguez-Tudela et al, AAC 2007

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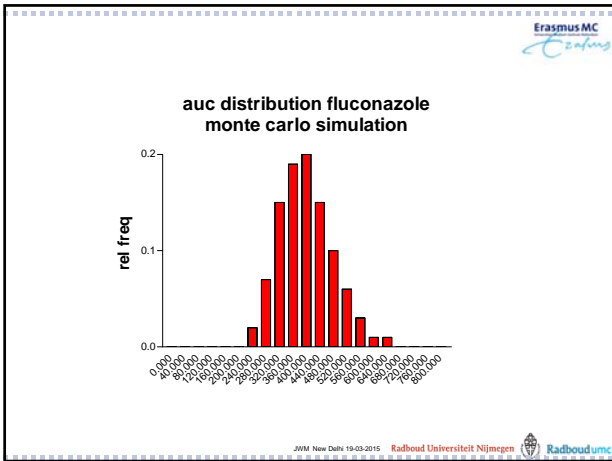


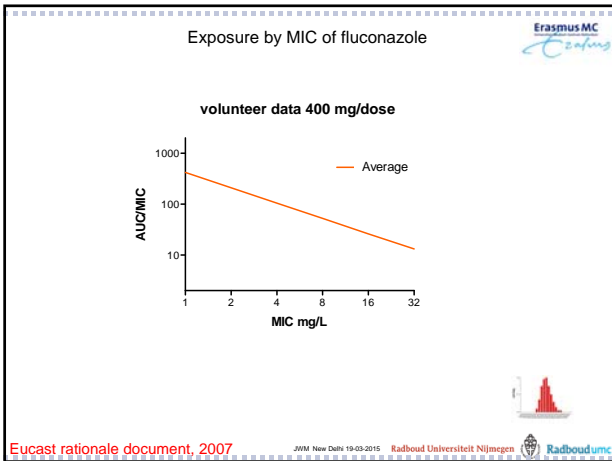
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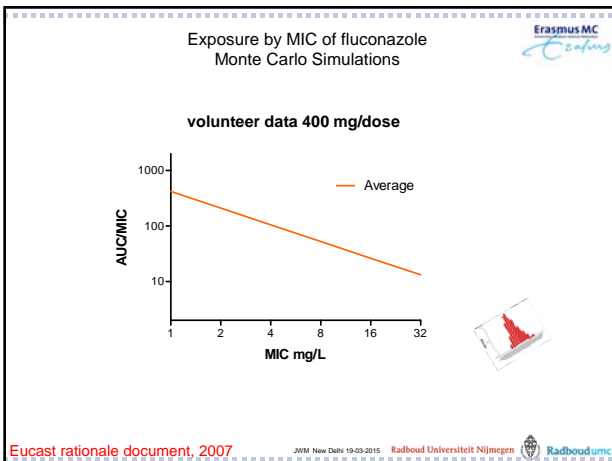
So what more determines the relationship between dose and exposure?

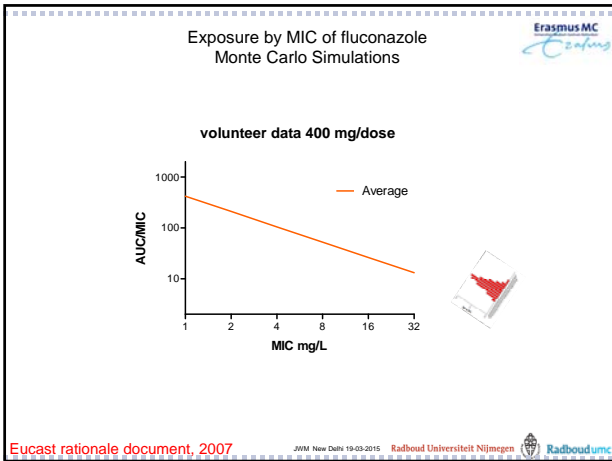
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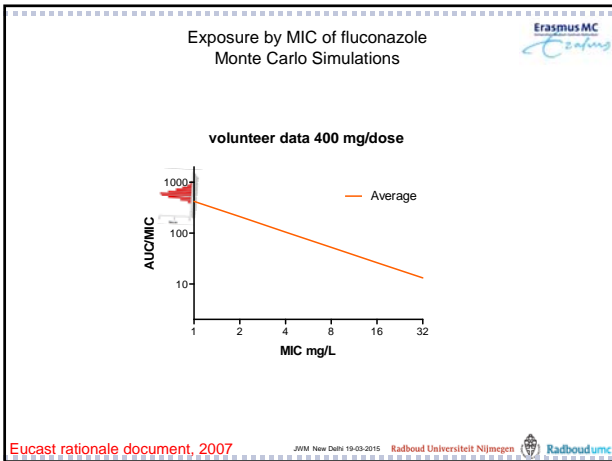


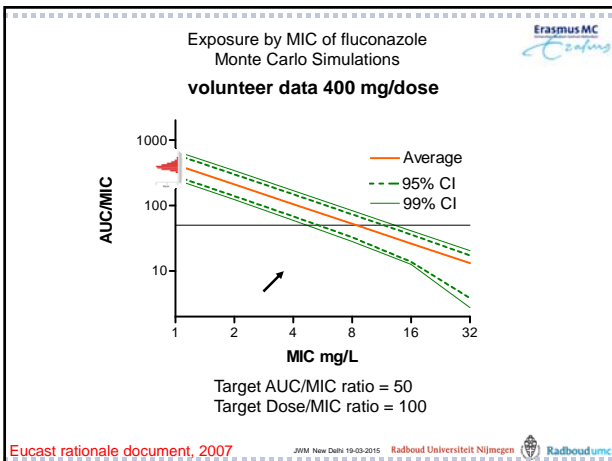












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Resistant (R)
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LAB REPORT

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Sensitivity

Organism 1	Escherichia coli
Hoeveelheid	>=10E5 k.ve/ml
Panel gevoeligheid	5 Urine Coliform
amoxicilline/clavula	Sensitive (0,06 mg/l)
amoxicilline	Sensitive (0,06 mg/l)
cefuroxim	Sensitive (0,06 mg/l)
cefotaxim	Sensitive (0,5 mg/l)
cefazoline	Sensitive (0,25 mg/l)
ciprofloxacine	Sensitive (<=0,06 mg/l)
doxycycline	Sensitive (1 mg/l)
nitrofurantoin	Sensitive (<=32 mg/l)
norfloxacine	Intermediate (1 mg/l)
sulfamethoxazol	Sensitive (<=64 mg/l)
tobramycine	Intermediate (0,25 mg/l)
trimethoprim	Resistant (>64 mg/l)
cotrimoxazole	Sensitive (1 mg/l)
ceftazidim	Sensitive (0,13 mg/l)

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)

BASED ON EXPOSURES OF COMMON DOSES

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cefazoline	Sensitive (0,25 mg/l)
ciprofloxacine	Sensitive (<=0,06 mg/l)
doxycycline	Sensitive (1 mg/l)
nitrofurantoin	Sensitive (<=32 mg/l)
norfloxacine	Intermediate (1 mg/l)
sulfamethoxazol	Sensitive (<=64 mg/l)
tobramycine	Intermediate (0,25 mg/l)
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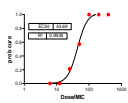
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BASED ON EXPOSURES OF COMMON DOSES IN ADULTS

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Exposures in children : differences

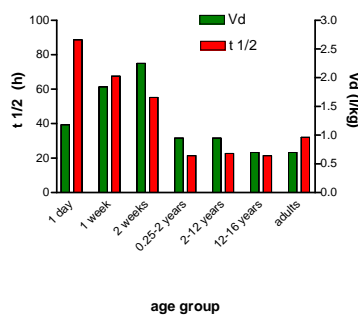


- Lower EXPOSURE then expected
- Clearance in individual

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Pharmacokinetic parameters of Fluconazole by age group

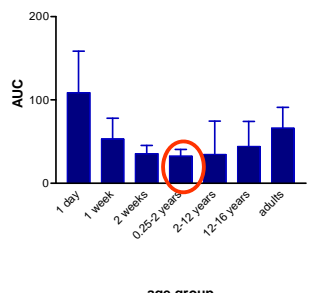


Age Group	t 1/2 (h)	Vd (l/kg)
1 day	~90	~40
1 week	~65	~60
2 weeks	~55	~75
0.25-2 years	~30	~30
2-12 years	~25	~35
12-16 years	~22	~25
adults	~30	~25

Mouton, Antimicrob Pharmacodynamics in Theory and Clin Practice 2007, 357
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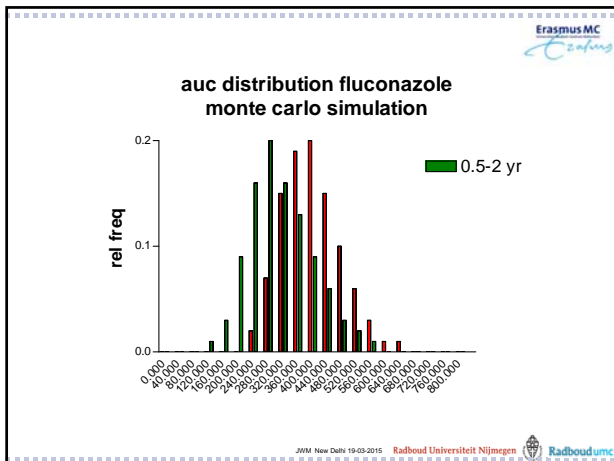
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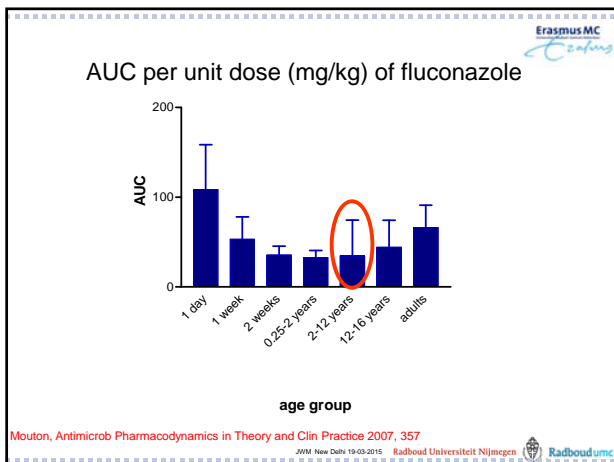
AUC per unit dose (mg/kg) of fluconazole differences by age group

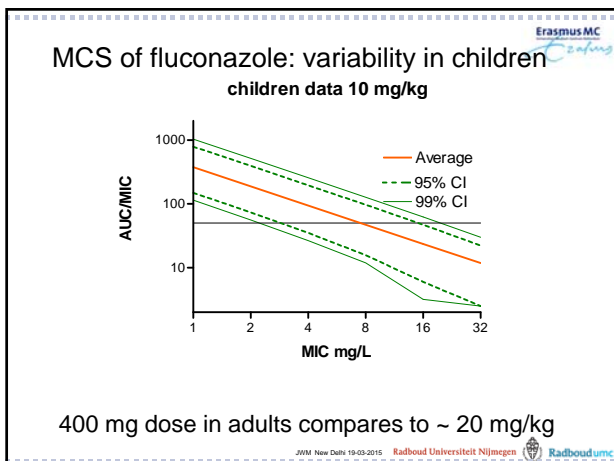



Age Group	AUC (mg/kg)
1 day	~110
1 week	~60
2 weeks	~40
0.25-2 years	~30
2-12 years	~40
12-16 years	~50
adults	~70

Mouton, Antimicrob Pharmacodynamics in Theory and Clin Practice 2007, 357
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Exposures in children:

- Generally lower – increase dose
- Larger variability – be aware, possible increase dose *or monitor or estimate clearance*
- These insights can help to rationalize dosing regimens in children

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To summarize:

- There is a good relationship for exposure and response
- This translates to dosing regimens *for the general population*
- Breakpoints are based on *the most common lowest dose*
- Other populations may require doseadjustments
- For non-predictable concentrations: TDM is a requirement

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