

Kunsten å sette brytningspunkter

Viltypepopulasjon, Mikrobiologiske,
Farmakologiske og kliniske kriterier

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Antibiotikaresistens og resistensbestemmelse

- MIC Minimum inhibitory concentration
- MBC Minimum bactericidal concentration

Resultatet tolkes som **S**, **I** eller **R**

– **Sensitiv**

- Midlet er aktivt ved vanlig dosering (tolkning: det er stor sannsynlighet for at pasienten vil svare på terapi med midlet)

– **Resistent**

- Midlet er ikke aktivt mot mikroben (tolkning: det er liten sannsynlighet for at pasienten vil svare på terapi med midlet)

– **Intermediært følsom** (el. usikkert resultat)

- Midlet er aktivt dersom det kan gis høye doser eller
- midlet konsentreres i infeksjonsfokus
- Usikkert resultat (metodologi eller mangelfull dok. klinisk)

- Agardifusjon (hemningszone i mm)

MIC - Minimum inhibitory concentration

- MIC-bestemmelse
 - Buljong-fortyning (MIC)
 - Agar-fortynning (MIC)
 - Agar-gradientdiffusjon (Etest, MICE, MTS, "IC")
 - Resultatet tolkes som **S**, **I** eller **R**
 - Beregnet "IC – inhibitory concentration" (Regresjonsanalyse, Automatiserte system)

Hvordan bestemmer vi bakteriers følsomhet for antibiotika?

- Resistensmekanismer
- Viltype-populasjoner
- Farmakokinetikk og Farmakodynamikk
- Mikrobiologisk respons
- Klinisk respons
- **Tolkning** baseres på **brytningspunkt (BP)**
 - **S, I eller R**

Wild type MIC distributions of target organisms and epidemiological cut-off values

Wild type (WT)

A micro-organism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.

A micro-organism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.

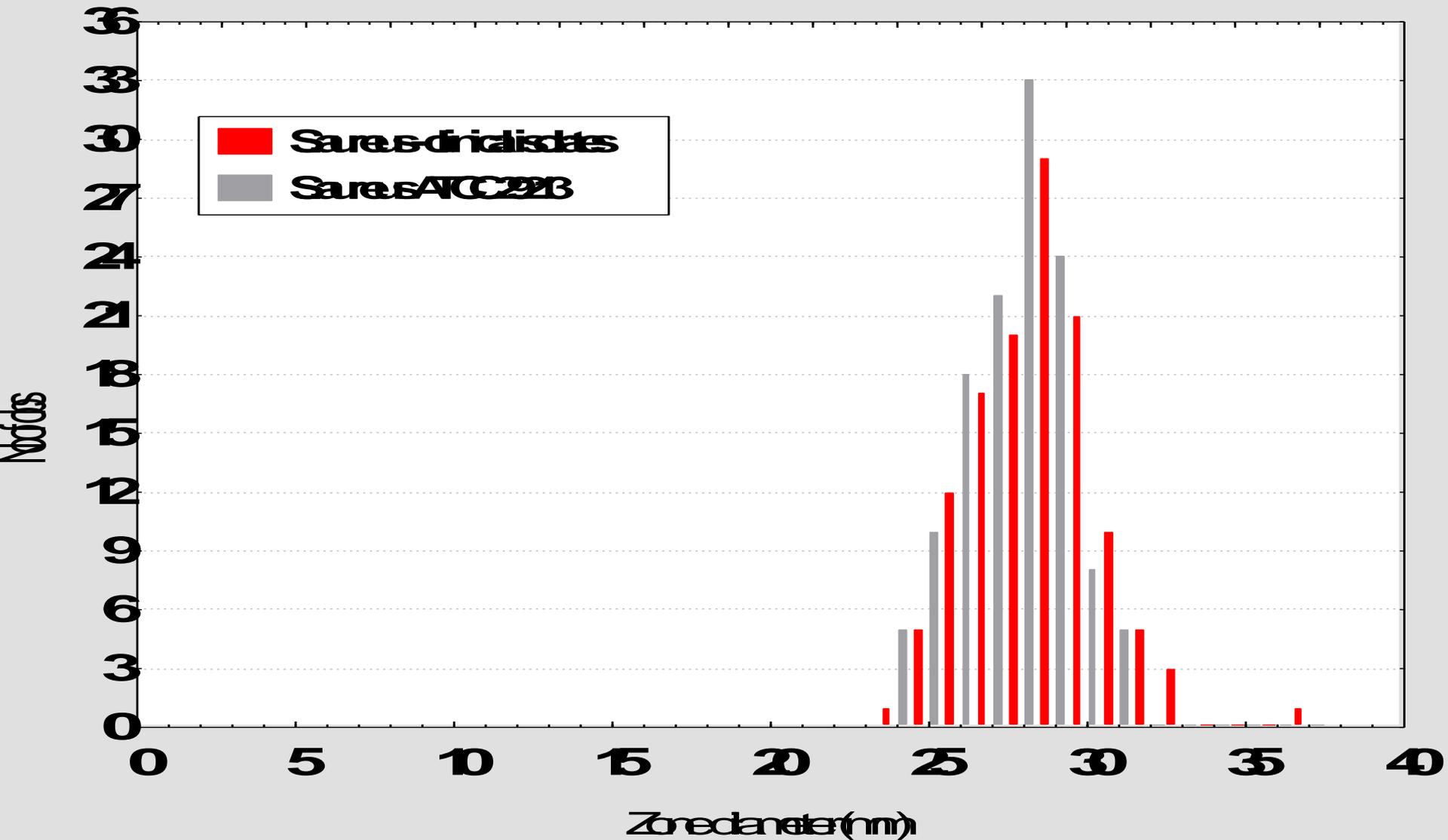
The cut-off value will not be altered by changing circumstances

Wild type micro-organisms may or may not respond clinically to antimicrobial treatment.

EUCAST definition

Sarus-dinical islatas vs Sarus-ATCC29213

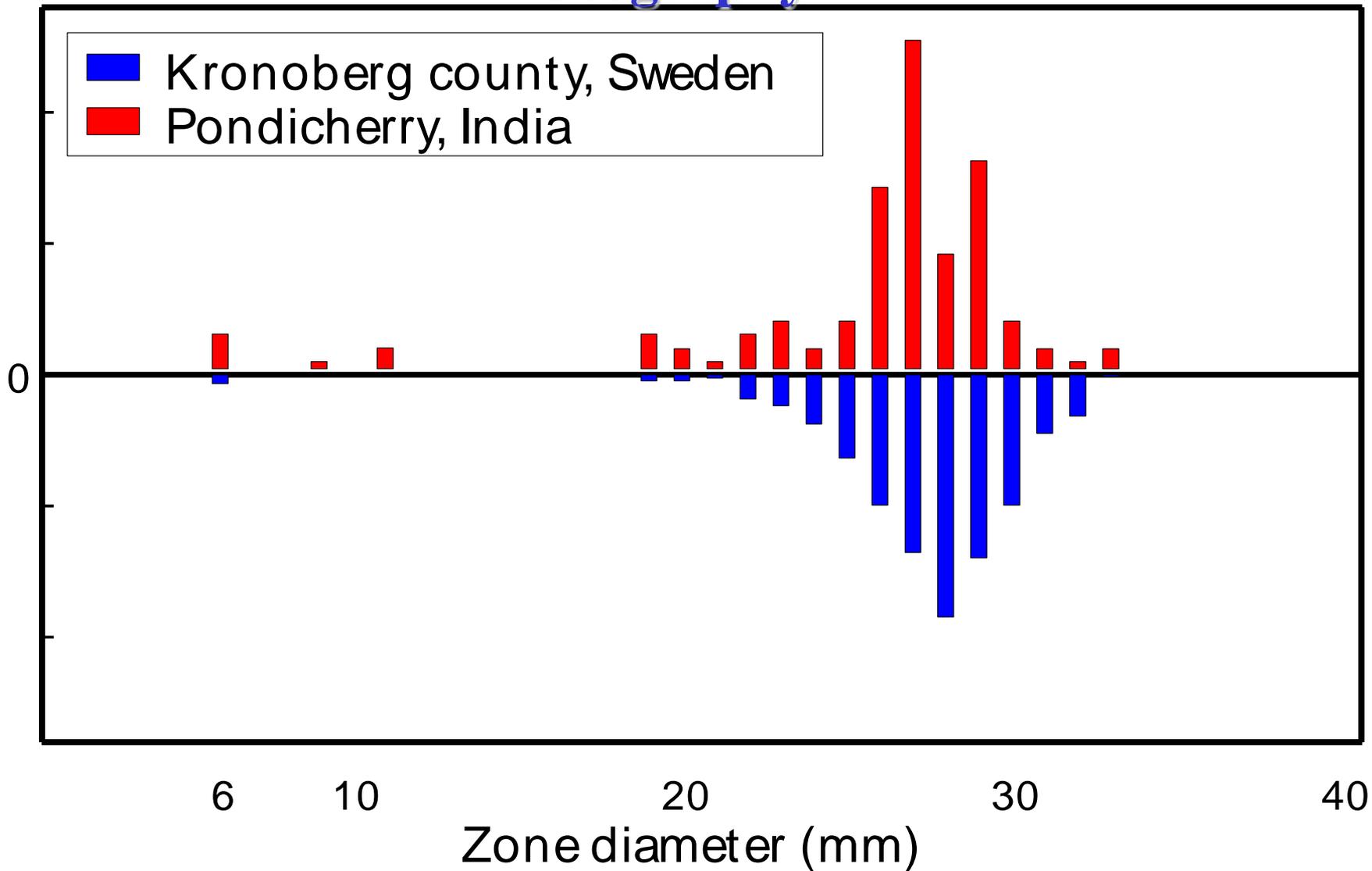
15dinical islatas vs 15deniratosd oetyestrin



S.pneumoniae vs. oxacillin 1 µg

% strains

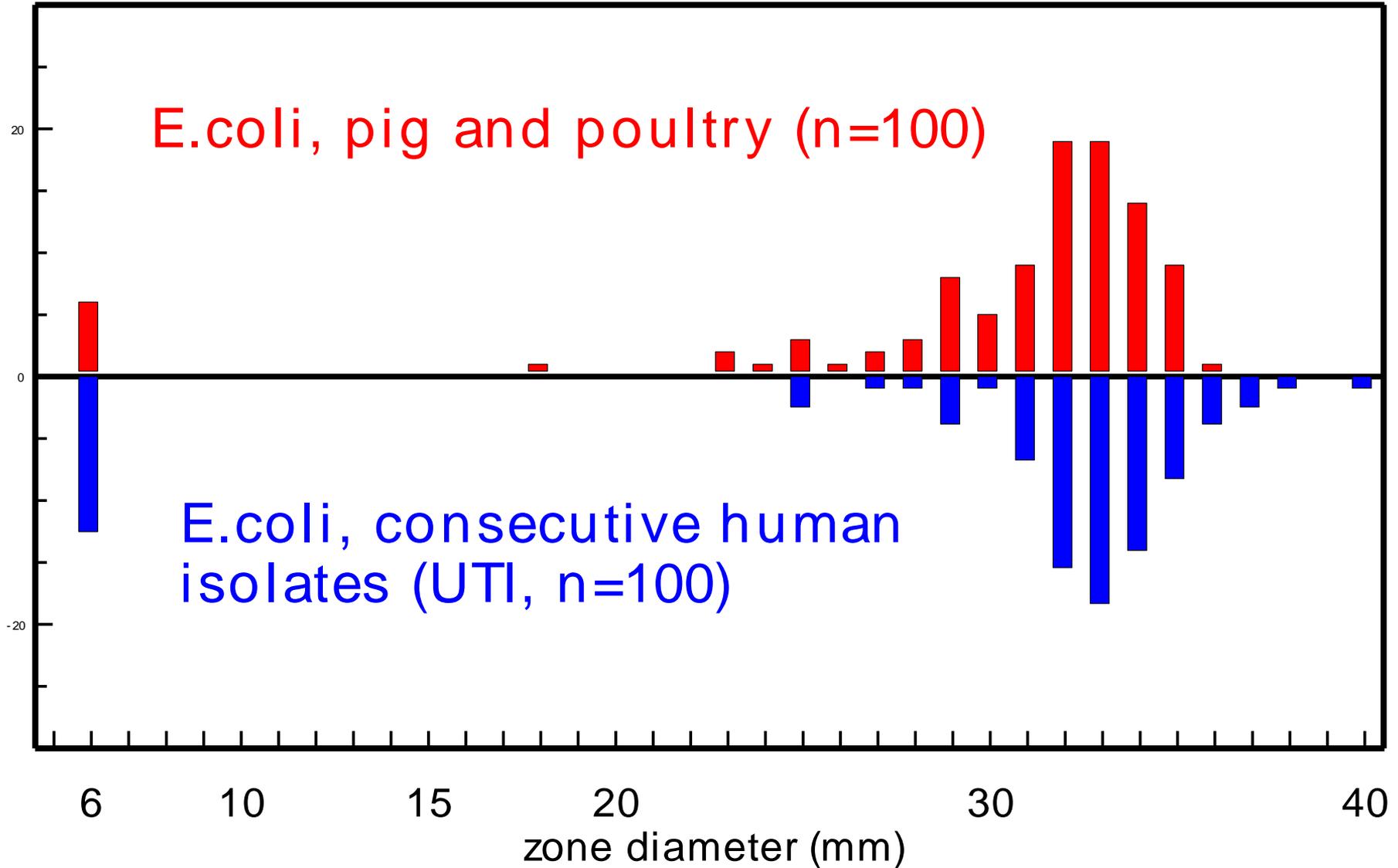
Geography



Origin

E.coli vs. Cotrimoxazole

% strains



MIC distribusjonen til ”villtypen (posisjon/bredde)

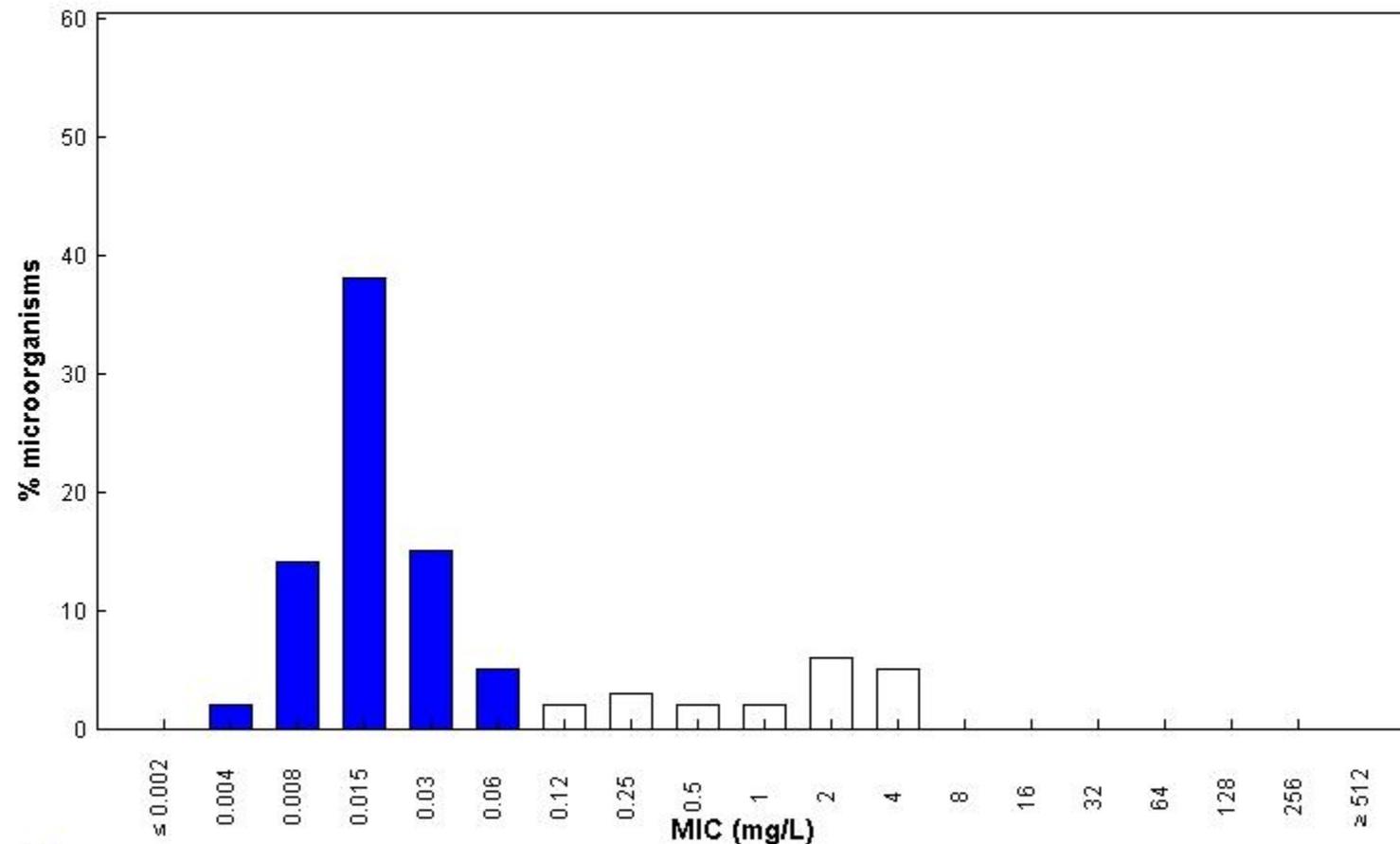
- Endres ikke over **tid**.
- Endres ikke etter **geografisk opprinnelse**
- Endres ikke etter vert – **menneke eller dyr**
- Er så **lite biologisk variabel** at den
 - Ikke kan skille individuelle stammer eller målinger
 - Kan ikke brukes klinisk
- **skal ikke deles av brytningspunktet.**

Brytningspunkt (BP) – basert på MIC-fordeling (populasjonsbasert)

- Godt egnet ved bimodal fordeling med god separasjon av følsom og resistent populasjon (eller unimodal fordeling som for *S. pyogenes* og penicillin)
- **Reduserer metodefeil ved resistensbestemmelse**
- Skiller vill-type populasjonen (WT) fra annen og mer resistent populasjon
- *Bør danne basis for følsomhetskategorisering ved diffusjonsmetode*

Benzylpenicillin / *Streptococcus pneumoniae*
International MIC Distribution - Reference Database 2016-05-03

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



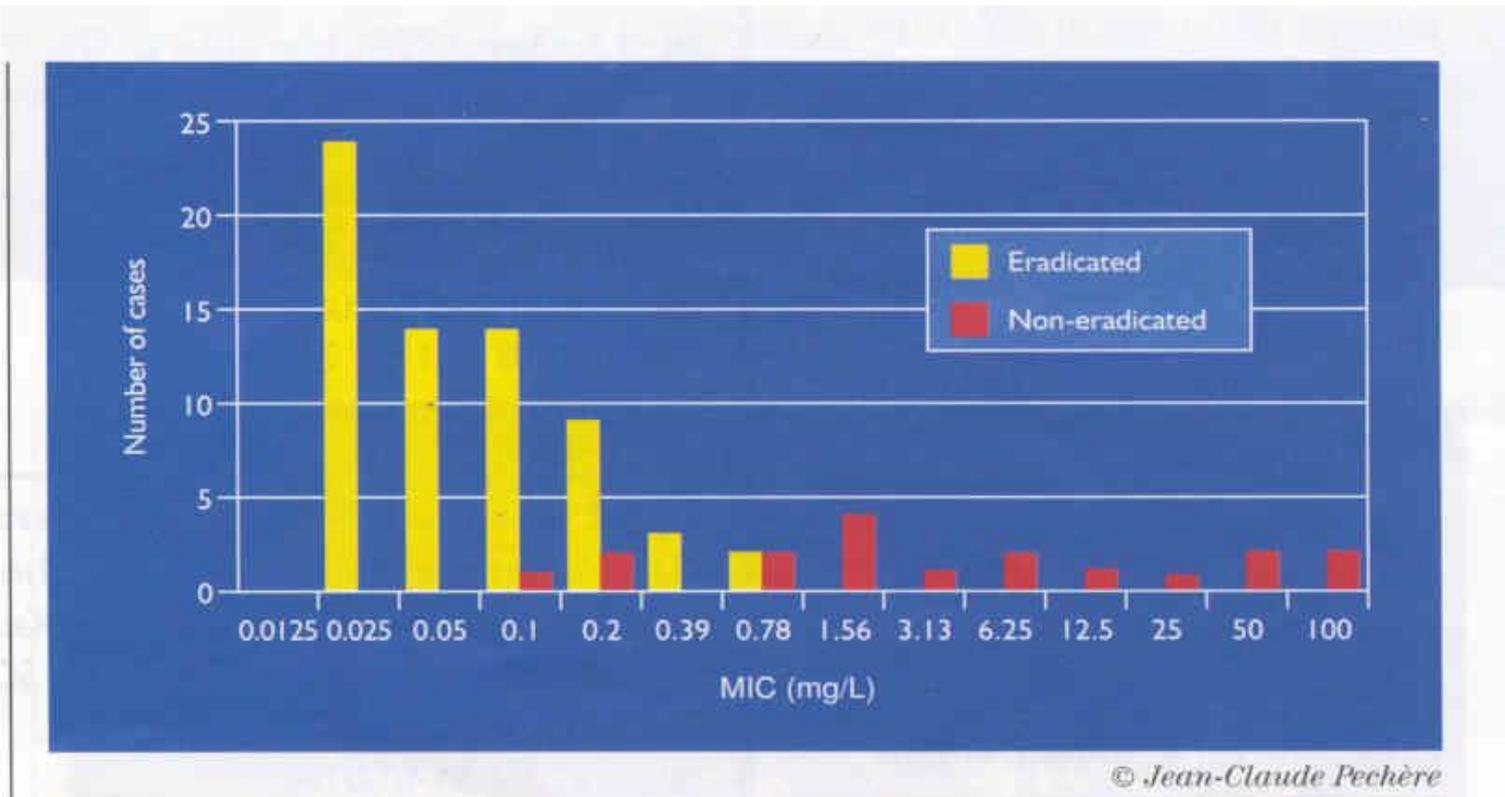
MIC
 Epidemiological cut-off (ECOFF): 0.064 mg/L
 Wildtype (WT) organisms: ≤ 0.064 mg/L

37742 observations (33 data sources)

Hvordan karakterisere mikrobers antibiotika-følsomhet?

- Påvise resistensmekanisme
 - ”Enkel” resistensfaktor
 - beta-laktamase
 - mecA-protein (el. mecC) hos *S. aureus*
 - rpoB-gen hos *M. tuberculosis*
- Populasjonsstudier (histogram) kan skille følsom og resistent bakteriepopulasjon
- Helbredelse versus MIC
 - Mikrobiologisk effekt (mikroben blir borte)
 - Klinisk effekt (pasienten blir bra)

Sammenheng mellom mikrobiologisk respons og MIC ved nosokomial pneumoni – et eksempel



Forskjell på mikrobiologisk og klinisk (farmakologisk) resistens

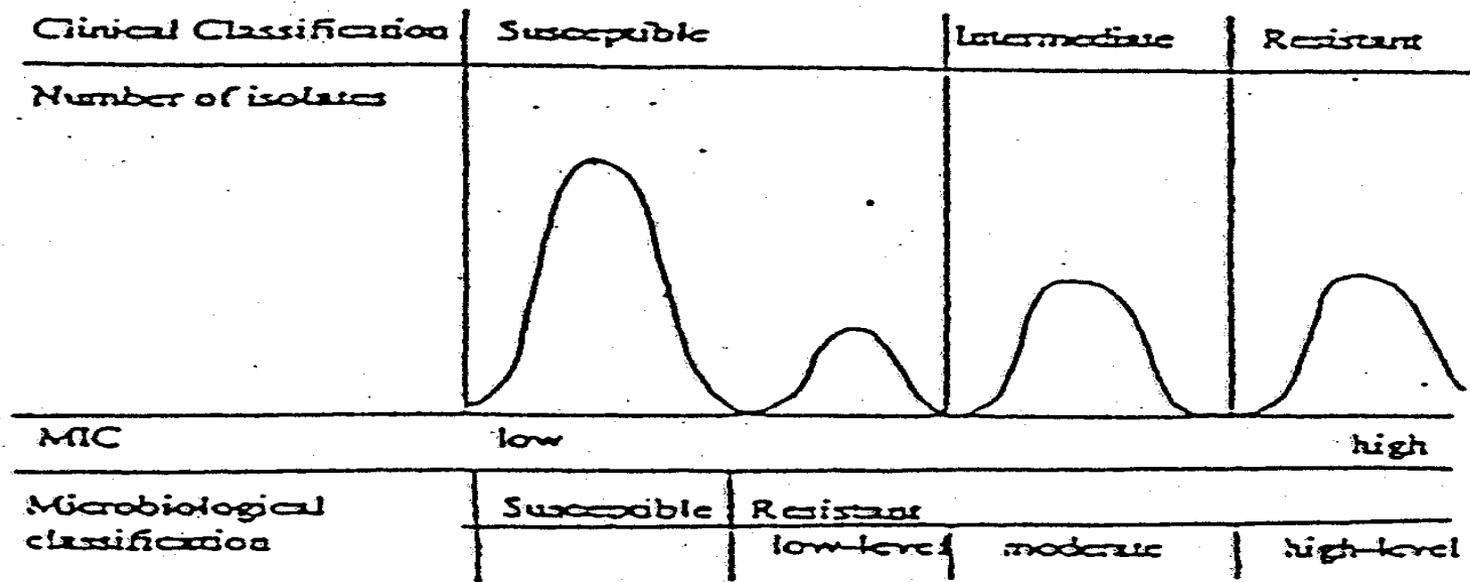


Figure 1 Hypothetical distribution of MICs among strains of bacteria isolated from infected patients, classified as Clinically Susceptible, Intermediate or Resistant, and microbiologically Susceptible or Low-level, Moderately or High-level Resistant.

BP– basert på bakteriologisk respons

- Proof of the pudding?
 - Mikroben forsvinner
 - hvordan har pasienten det?
 - Oppfølgende (ny) prøve er ofte vanskelig etisk å få tatt
 - Hvilken mikrobe er årsak til infeksjonen?
 - Vanskelig ved luftveisinfeksjoner
 - Må baseres på gode kvantitative data (MIC eller mm hemningssone) – SIR-kategori ikke godt nok for evaluering

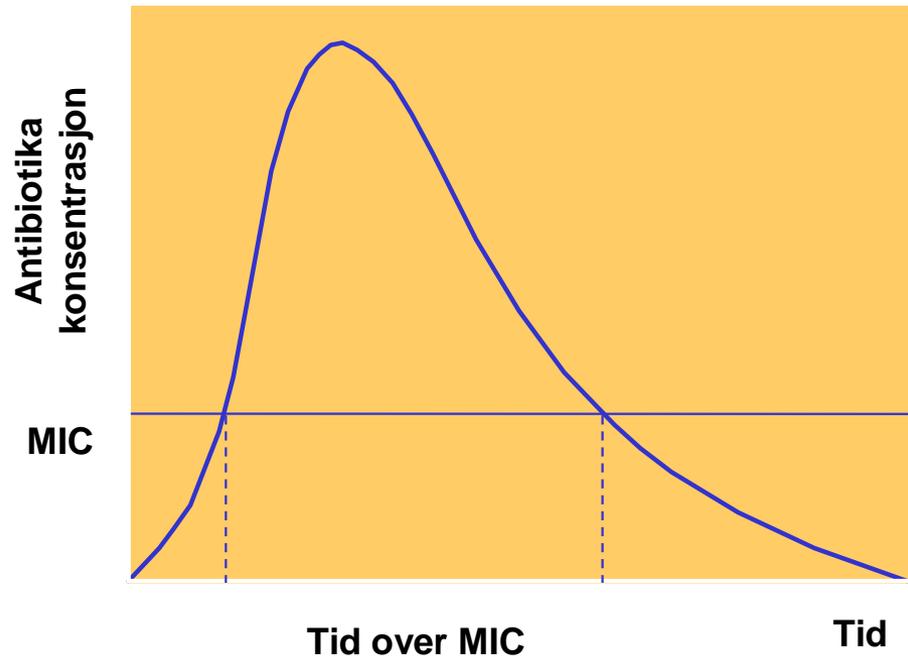
Hva betyr kategoriene SIR?

- S
 - Sensitiv - stor sannsynlighet for terapeutisk suksess
- R
 - Resistent – liten sannsynlighet for terapeutisk suksess
- I
 - Intermediær følsom
 - Terapeutisk suksess kan forventes ved økt dose el. midlet konsentreres i infeksjonsfokus
 - Usikkert resultat
- Alle tolkningskriterier er knyttet til dosering

BP- basert på farmakokinetikk og farmakodynamikk

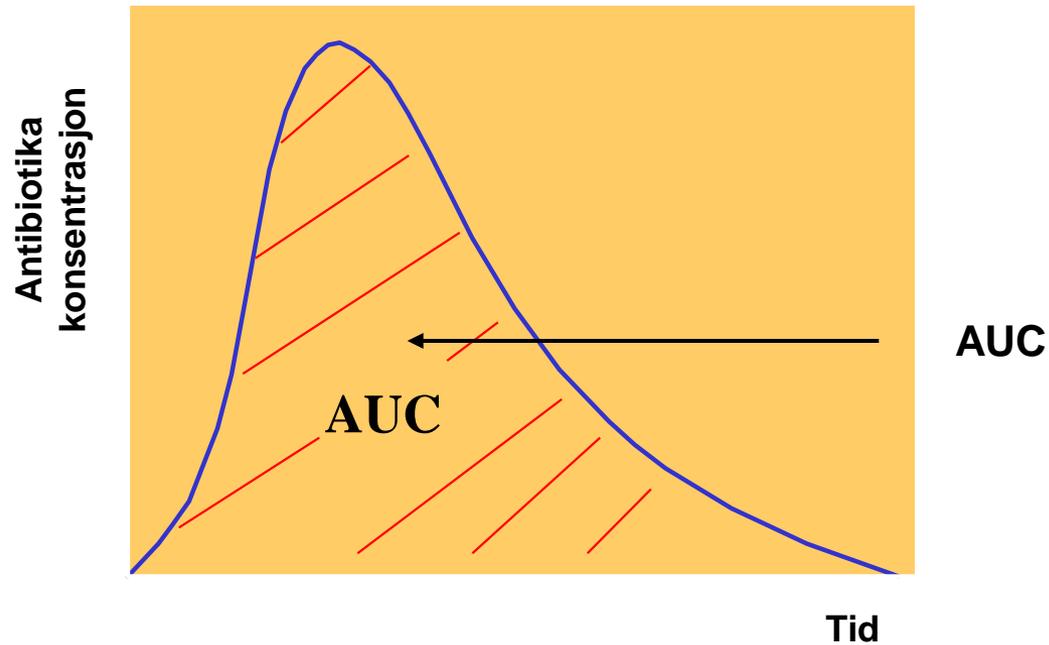
- Farmakokinetikk og dyreeksperimentelle studier viser antibiotikas (og bakterienes) skjebne i vev (oftest hos mus)
- Tar også i betraktning ulike vertsfaktorer for å bestemme brytningspunkt (f. eks. må serumkonsentrasjonen av beta-laktamantibiotika overstige MIC i 40-50% av doseintervallet)
- Tar ikke hensyn til fordeling av bakterie-populasjonen og kan introdusere metodefeil («BP» deler normalpopulasjonen)

'Tid over MIC'



Tid over MIC = tiden serumkonsentrasjonen av fritt antibiotikum er over MIC, uttrykt som en prosentandel av doseringsintervallet

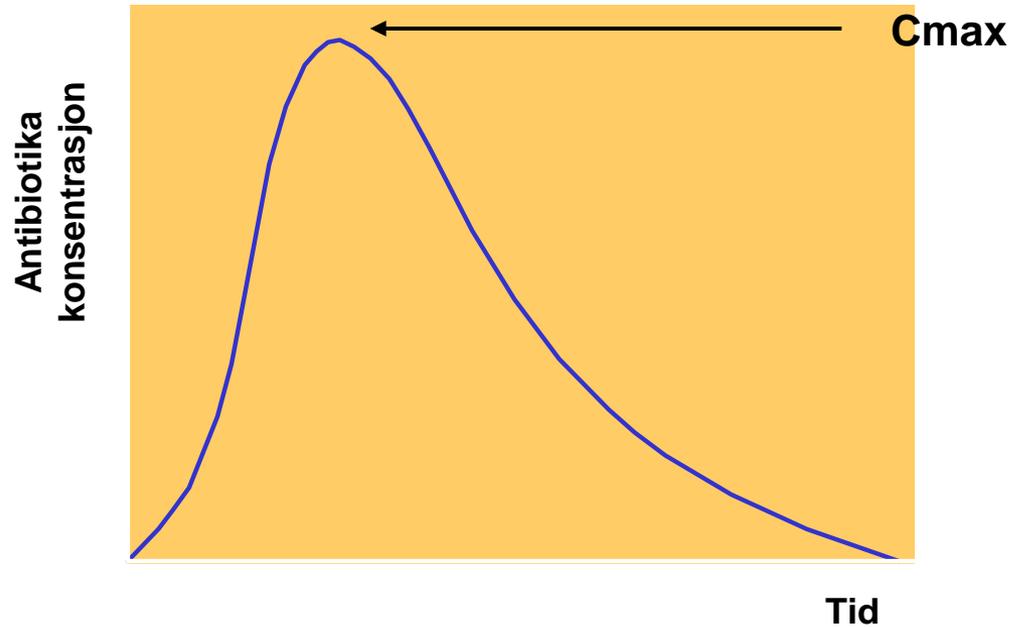
AUC/MIC



AUC / MIC =

24 timers arealet av fritt serumkonsentrasjon delt på MIC.

C_{max}/MIC



$C_{max} / MIC =$

den maksimale frie serumkonsentrasjonen
delt på MIC

Monte Carlo simulations Ciprofloxacin and *S. pneumoniae*

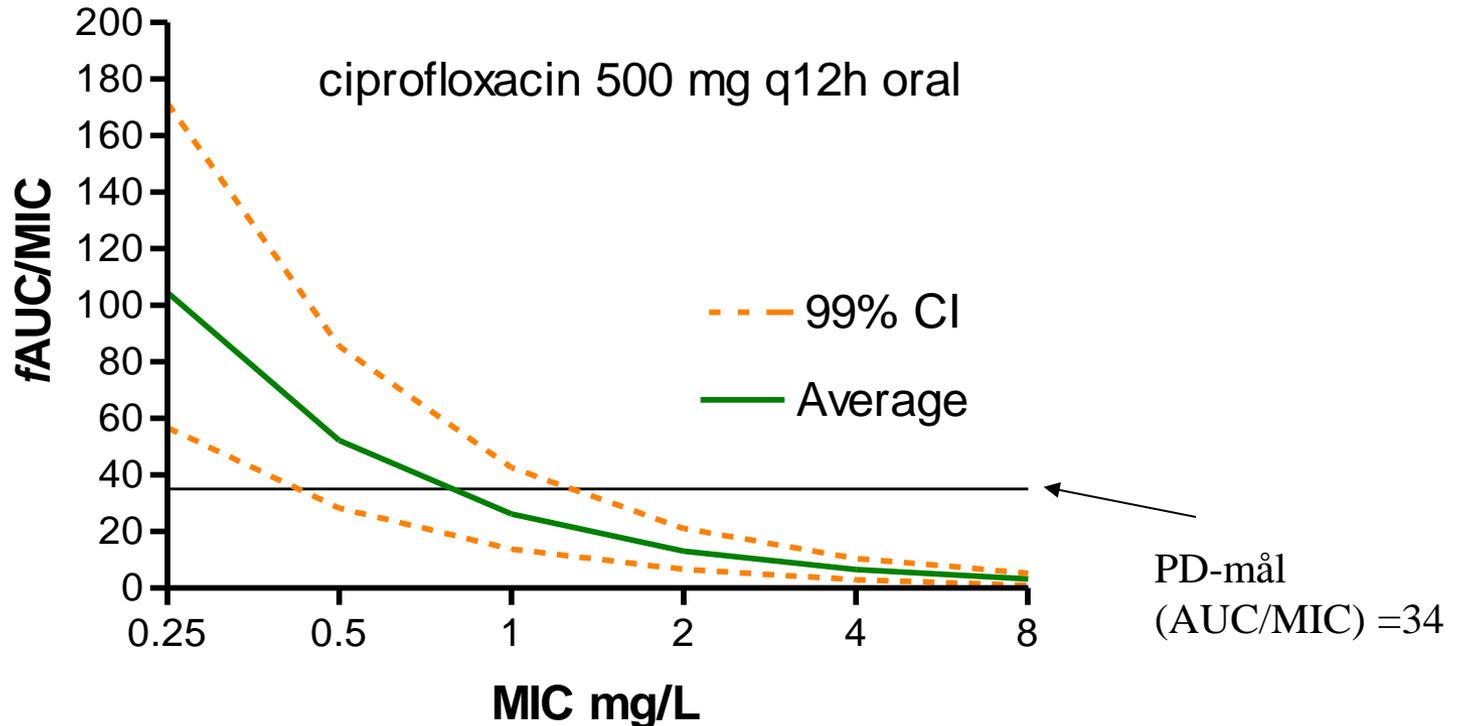


Figure 1. Probabilities of Target Attainment for Ciprofloxacin orally for 500 mg q12h. The horizontal line indicates the Pk/Pd target for *S. pneumoniae*. The following pharmacokinetic parameters were used to obtain the PTA: V_d 180L, CV 17%; Cl 31 L/h, CV 17%; F_u 70%; K_a 2h⁻¹; F 0.8, CV 12%. Results of simulations for the 400 mg IV dose do not markedly influence conclusions.

5. Pharmacodynamics

	Enterobacteriaceae	<i>Pseudomonas aeruginosa</i>	<i>Streptococcus pneumoniae</i>	<i>Staphylococcus aureus</i>
fAUC/MIC for bacteriostasis	30-40		30 - 40	25-30
fAUC/MIC for 2 log reduction	80-100			60
fAUC/MIC from clinical data	80 – 100	100	30 - 40	
Comments	<ul style="list-style-type: none"> Data are from non-neutropenic subjects, unless specified otherwise. Two values are given where references differ. Cells are left empty when data are not readily available. 			

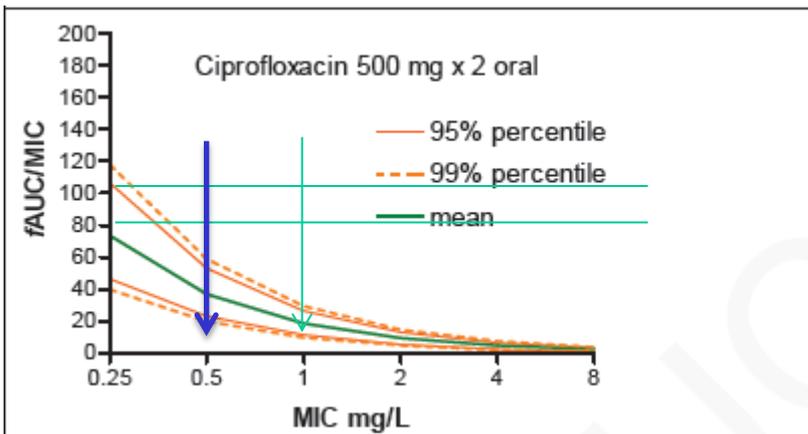


Figure 1. Probabilities of Target Attainment for Ciprofloxacin 500 mg x 2 oral.

The following pharmacokinetic parameters were used to obtain the PTA:
 Volume of Distribution (Vd): 180L, CV 17%
 Clearance (Cl): 31 L/h, CV 17%
 Fraction unbound (Fu): 70%
 Absorption rate coefficient (Ka): 2h⁻¹
 Bioavailability (F): 0.8, CV 12 %

Results of simulations for the 400 mg x 2 iv dose do not markedly influence conclusions.

The wild type MIC distributions of most Enterobacteriaceae, including *Salmonella* spp, exhibit MIC values ≤ 0.125 mg/L. A breakpoint of ≤ 0.5 mg/L allows low-level quinolone resistant Enterobacteriaceae to be categorised as susceptible to ciprofloxacin.

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Ciprofloxacin_rationale_1.9.pdf

BP – basert på klinisk respons

- Proof of the pudding?
 - Pasienten blir bra av infeksjonen, men hva skjedde med mikroben og hadde antibiotika noe med resultatet å gjøre
 - F. eks LVI, *H. influenzae* og makrolider
 - Det er jo bakterien vi måler (resistens-bestemmer) og ikke egenskaper ved pasienten
 - Vanskelig å skaffe gode data
 - Krever gode kvantitative resistensdata
 - Slike data er avgjørende for evaluering av behandlingseffekt (og indirekte resultat av resistensbestemmelse)

Dicloxacillin dose vs. Time > MIC of free (non-proteinbound) concentration

Dose

Time > MIC

in h

in % of dosing interval

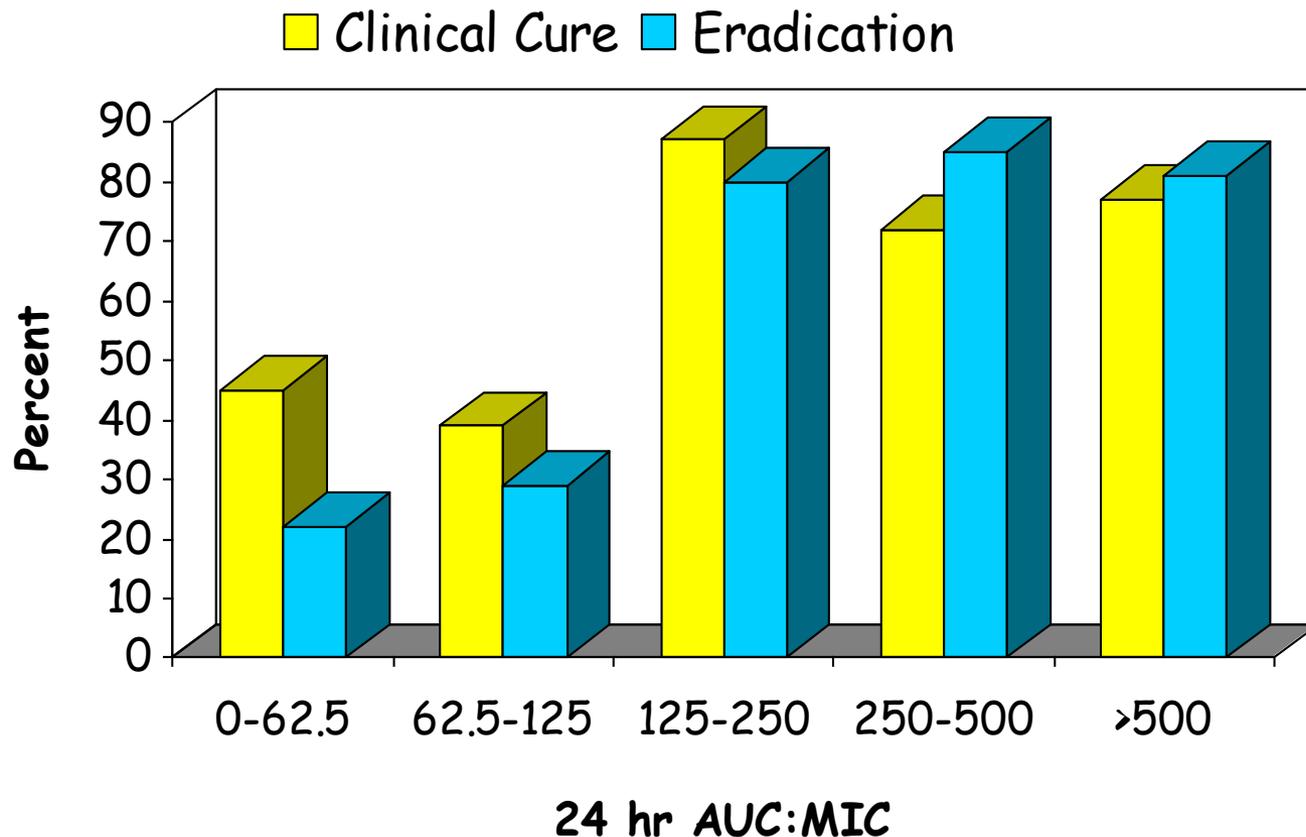
1 g x 3	1.8 – 2.8	23 - 35 %
1 g x 4	-	30 - 47 %
2 g x 3	2.4 – 3.6	30 - 45 %
2 g x 4	-	40 - 60 %

$T_{1/2} = 0.6-0.8$ h; $V_d = 0,13- 0,19$ l/kg; Prot.bind.= 91-98 %; MIC-s.a.= 0,4

Treatment and outcome of *S. aureus* bacteremia: A prospective study of 278 cases. Jensen AG et al. Arch Intern Med, 2002, 162: 25-32

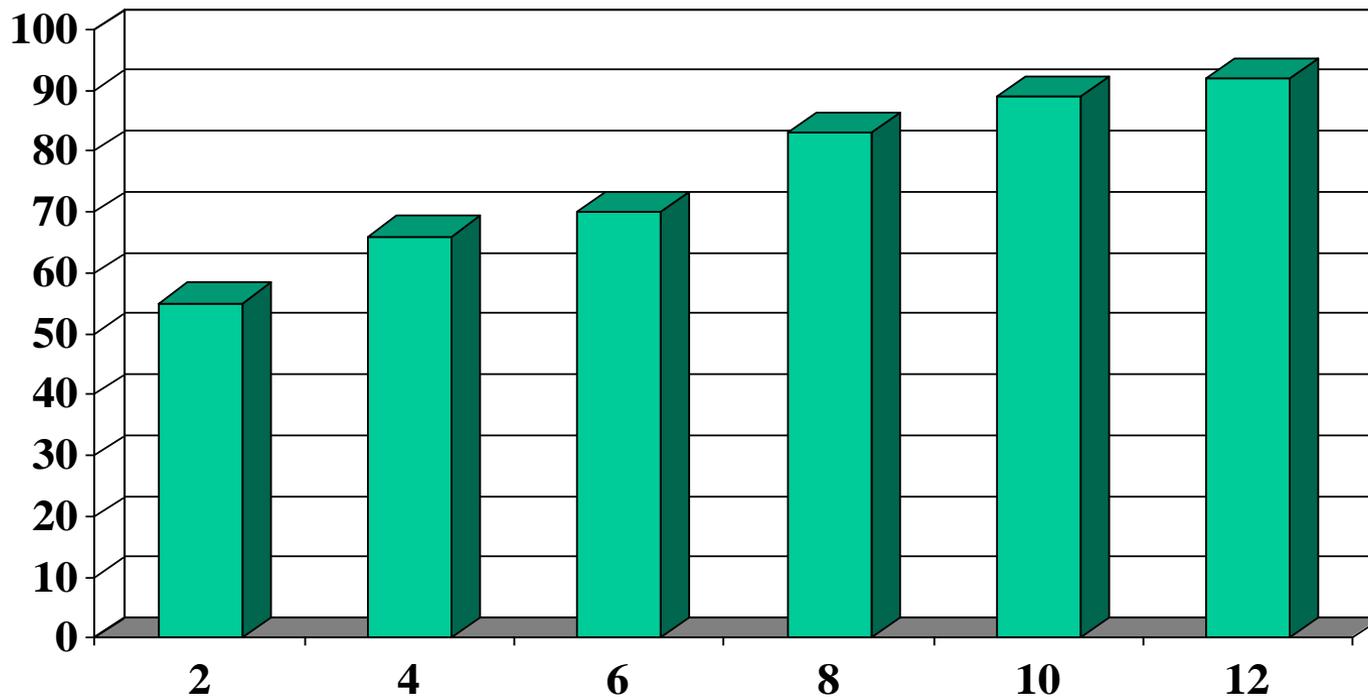
	+ Risk factor Died/total,%	-Risk factor Died/total,%	Univariate	P
Focus not eradicated	42/125 34%	4/61 7%	7.2	<0.001
Septic shock	18/38 47%	28/148 19%	3.9	0.001
Diclox daily dose < 4g	40/142 28%	6/44 14%	2.5	0.02
Age > 60 y	32/96 33%	14/90 16%	2.7	0.006

Relationship Between Ciprofloxacin AUC:MIC and Efficacy in Treating Bacterial Pneumonia. Forrest, AAC 37:1073.



Relationship between max. Peak/MIC ratio and the rate of clinical response for aminoglycosides. Moore et.al. J Infect Dis, 1987, 155: 93

**Response
rate, %**



Maximum Peak/MIC ratio

Hvordan bestemmer vi bakteriers følsomhet for antibiotika?

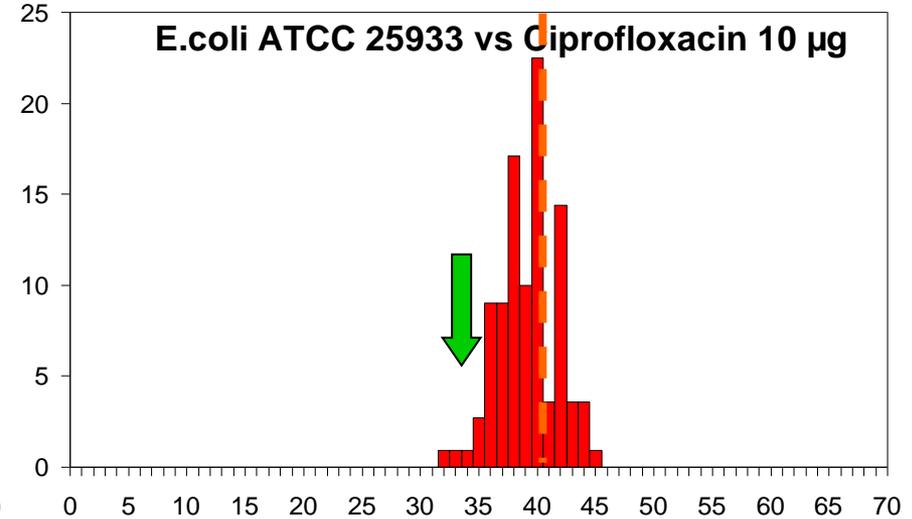
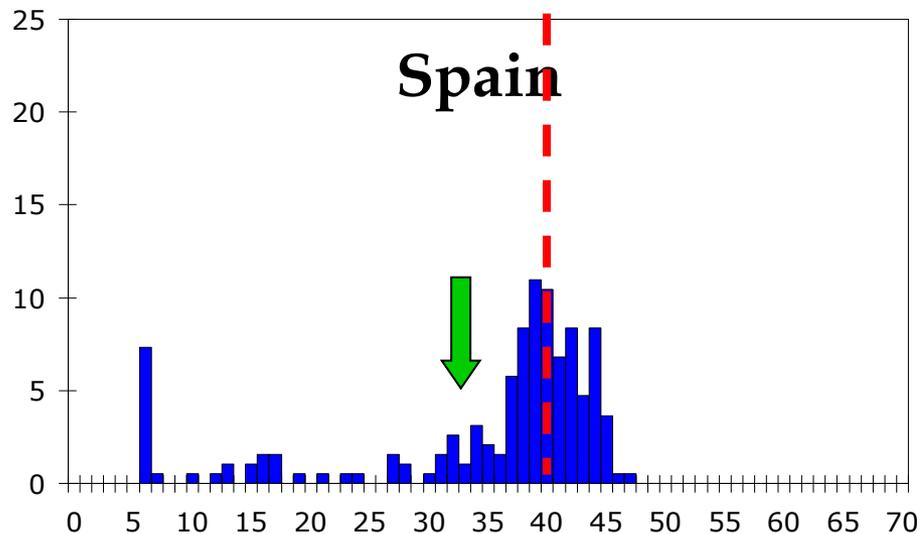
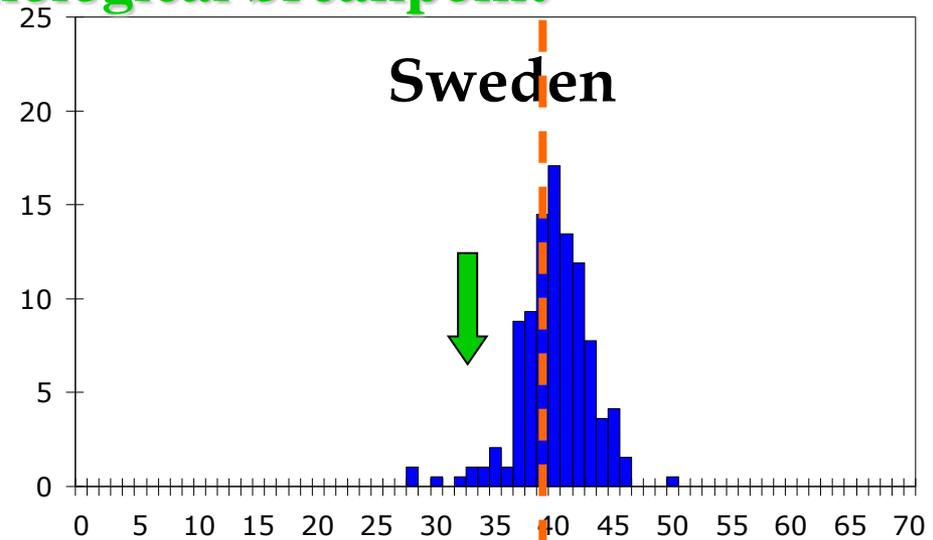
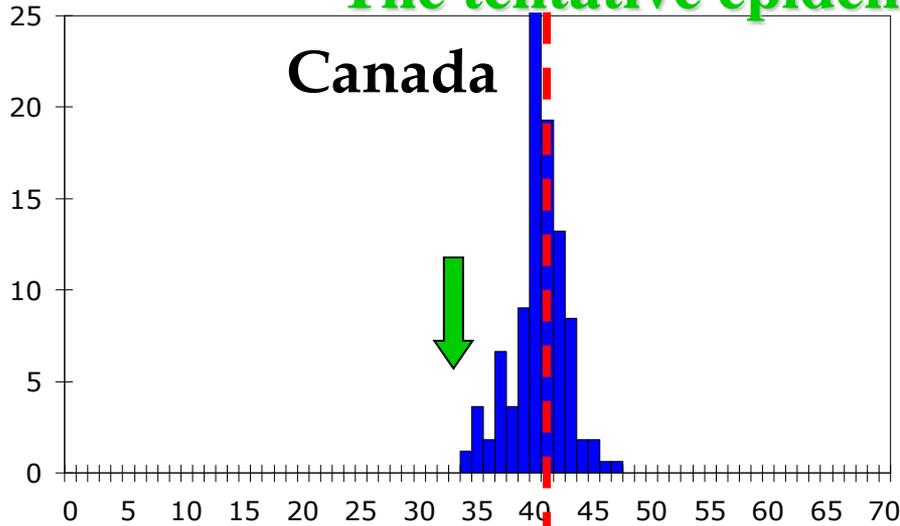
- Resistensmekanismer
- Viltype-populasjoner
- Farmakokinetikk og Farmakodynamikk
- Mikrobiologisk respons
- Klinisk respons
- **Tolkning** baseres på **brytningspunkt (BP)**
 - **S, I eller R**

Takk for oppmerksomheten!

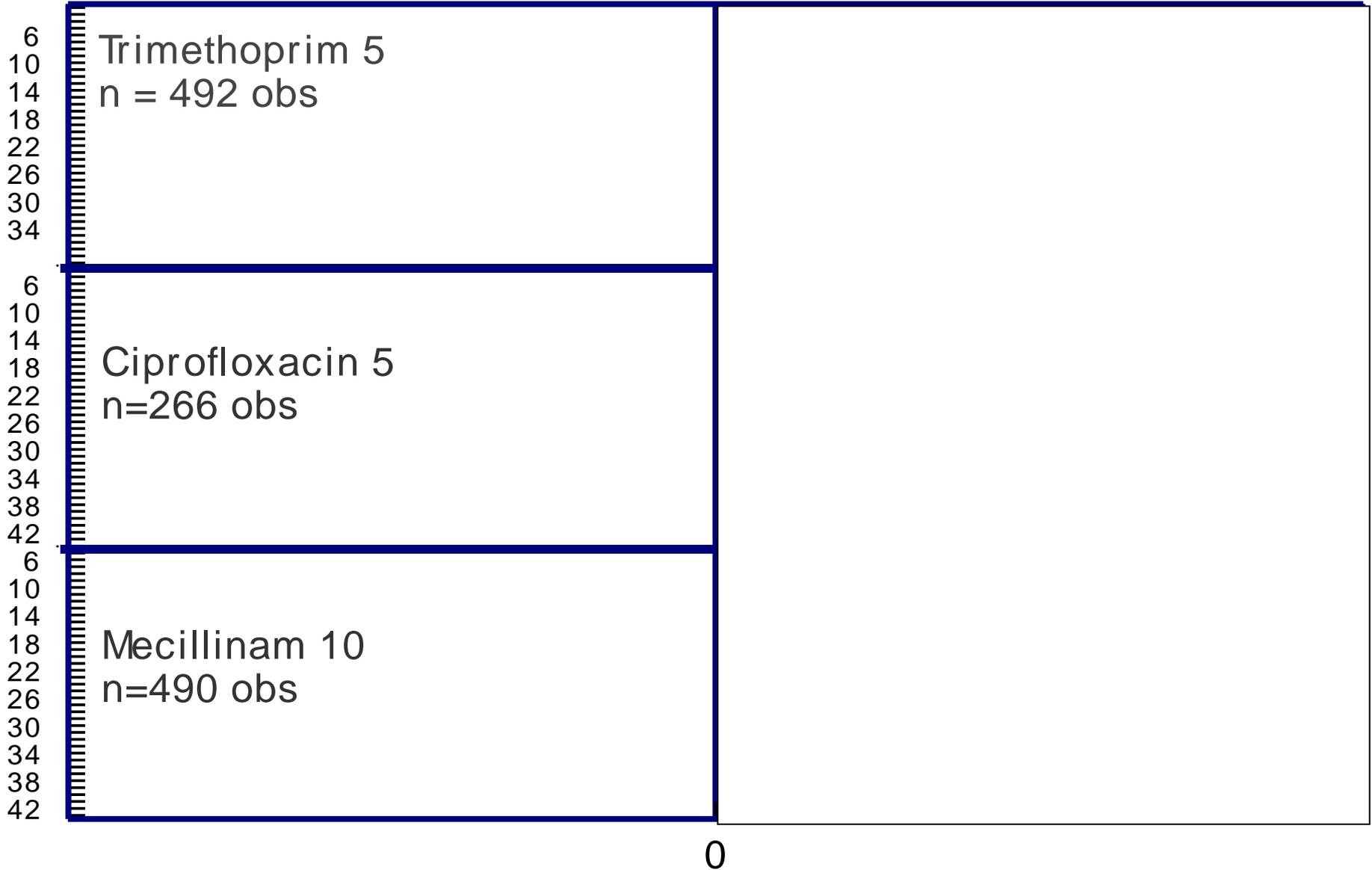


E.coli and ciprofloxacin in ECO•SENS

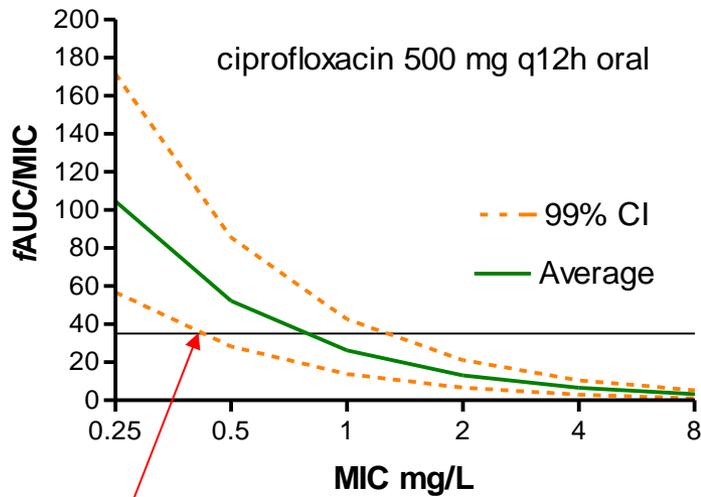
The tentative epidemiological breakpoint



E.coli - clinical isolates vs E.coli ATCC 25922

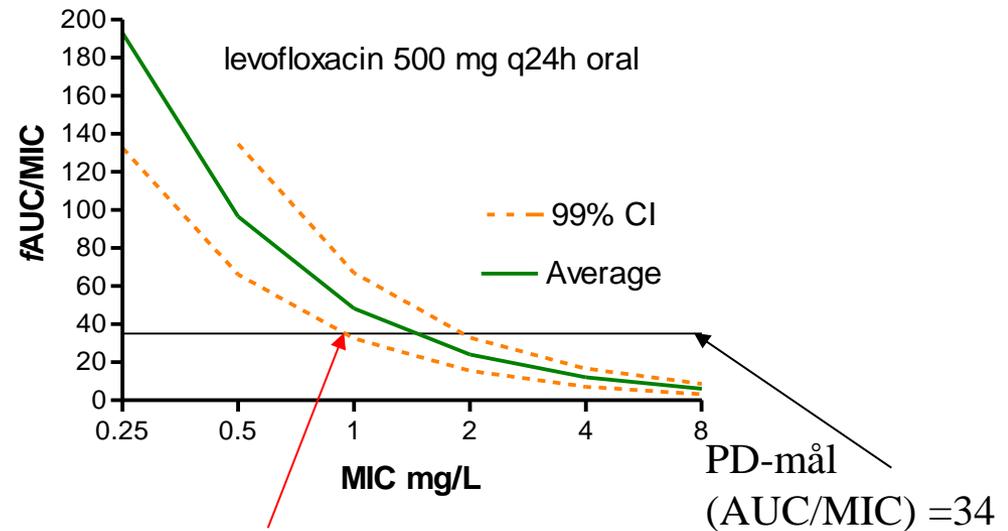


4. Using available Pk/Pd data, Monte Carlo simulations are performed and a Pk/Pd breakpoint calculated based on conventional dosing regimens



S = 0.5 mg/L

Pk/Pd



S = 1 mg/L

Ciprofloxacin vs. Pivampicillin for epididymitis in men > 40 years
(prosp,rand,d-b): N=55 E. coli. Eickhoff et.al. Brit J Urol 1999, 84: 827-834

Total N = 158	Pivampicillin 700 mg x 2 N = 25	Ciprofloxacin 500 mg x 2 N = 30
Cured	8 (32%)	27 (90%)
No effect: Persisting fever, septicaemia or constant local symptoms, shift of treatm	17 (68%)	3 (10%)

P = 0.001

NF-M 2001

**Ciprofloxacin vs. Pivampicillin for epididymitis in men > 40 years
(prosp,rand,d-b): N=55 E. coli. Eickhoff et.al. Brit J Urol 1999, 84: 827-834**

Total N = 158	Pivampicillin 700mg x 2 N = 25	Ciprofloxacin 500mg x 2 N = 30
Cured	8 (32%)	27 (90%)
No effect:	17 (68%)	3 (10%)

P = 0.001

Amox/Pivampicillin dose	Time > MIC, h (%) (MIC = 8 mg/l)
250 mg	1,3 (11%)
375 mg	1,9 (16%)
500/700 mg	2,3 (19%)
1000 mg	3,2 (27%)
3000 mg	4,9 (41%)

Aminoglycosides: Pharmacodynamics in vivo Gram-negative bacteraemia. Moore et al. J Infect Dis 149: 443, 1984

Initial serum peak level	Died	Survived
< 5 mcg/ml	9 (21%)	34 (79%)
≥ 5 mcg/ml	1 (2%)	40 (98%)

P < .01

Optimizing aminoglycoside therapy for nosocomial pneumonia (NP) caused by Gram-neg. Bacteria. Kashuba et.al. AAC, 1999, 43: 623-29

- 78 patients with NP caused by Gram-neg. bacteria treated with gentamicin or tobramycin:
- Cox hazard model of C_{\max} , AUC, total dose, duration of therapy, MIC, age, ICU adm., nutritional status, Pseudomonas infection, concurrent therapy with beta-lactam:
- Targeting an MIC of 1 $\mu\text{g}/\text{ml}$, empirical aminoglycoside loading doses of 348 (25th- to 75th-percentile range, 275 to 432) mg were calculated to obtain a C_{\max}/MIC of 10 in our patient population
- 90% probability of temperature - and leucocyte count resolution by 7 days:
- ***If $C_{\max}/\text{MIC} \geq 10 \text{ mg/l}$ within first 48 h***

Farmakodynamikk: Dosering

- Tid > MIC:

konstant infusion

lang halveringstid

hyppig dosering

Pen: 1-2 MIO x 4-6

Ampi: 1g x 4

Cefur: 0.75-1.5g x 3

Ceftriaxon: 1-2g x 1

Diclosil: 1g x 4 el. 2g x 3

- AUC/Peak:

Høy dosering

dosering 1 x dgl

gentamicin:

peak > 10 x MIC

dosis: 5-7 mg/kg x 1

ciprofloxacin:

AUC > 125 mcg/ml/h

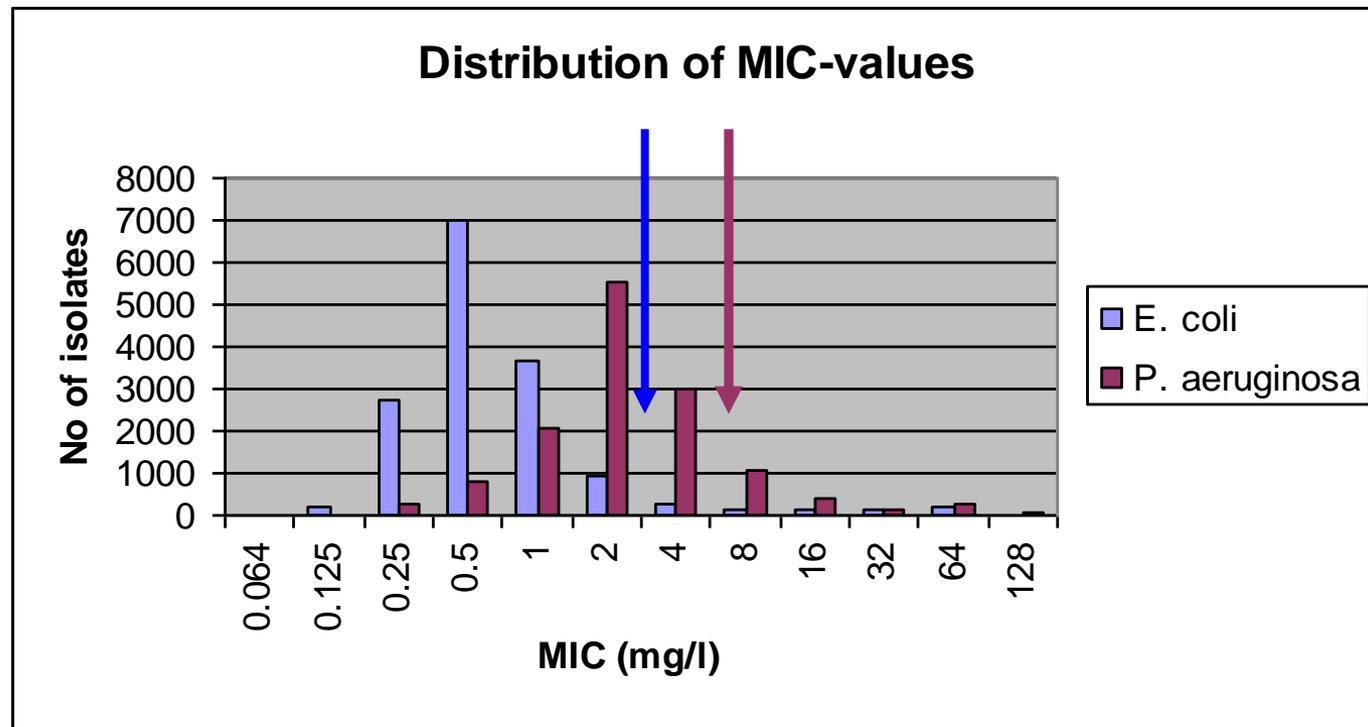
dose: 4-600 mg x 2

Momenter ved valg av metode for resistensbestemmelse

- **Biologisk variasjon**
 - innen en gruppe, slekt eller art
 - mellom bakterieslekter
- **Metodens egnethet**
 - Valgt metode må kunne skille mellom følsomme og resistente stammer
 - Enkelte midler er bedre egnet til å påvise følsomhet enn andre innen samme legemiddelgruppe

Måleunøyaktighet og biologisk variasjon

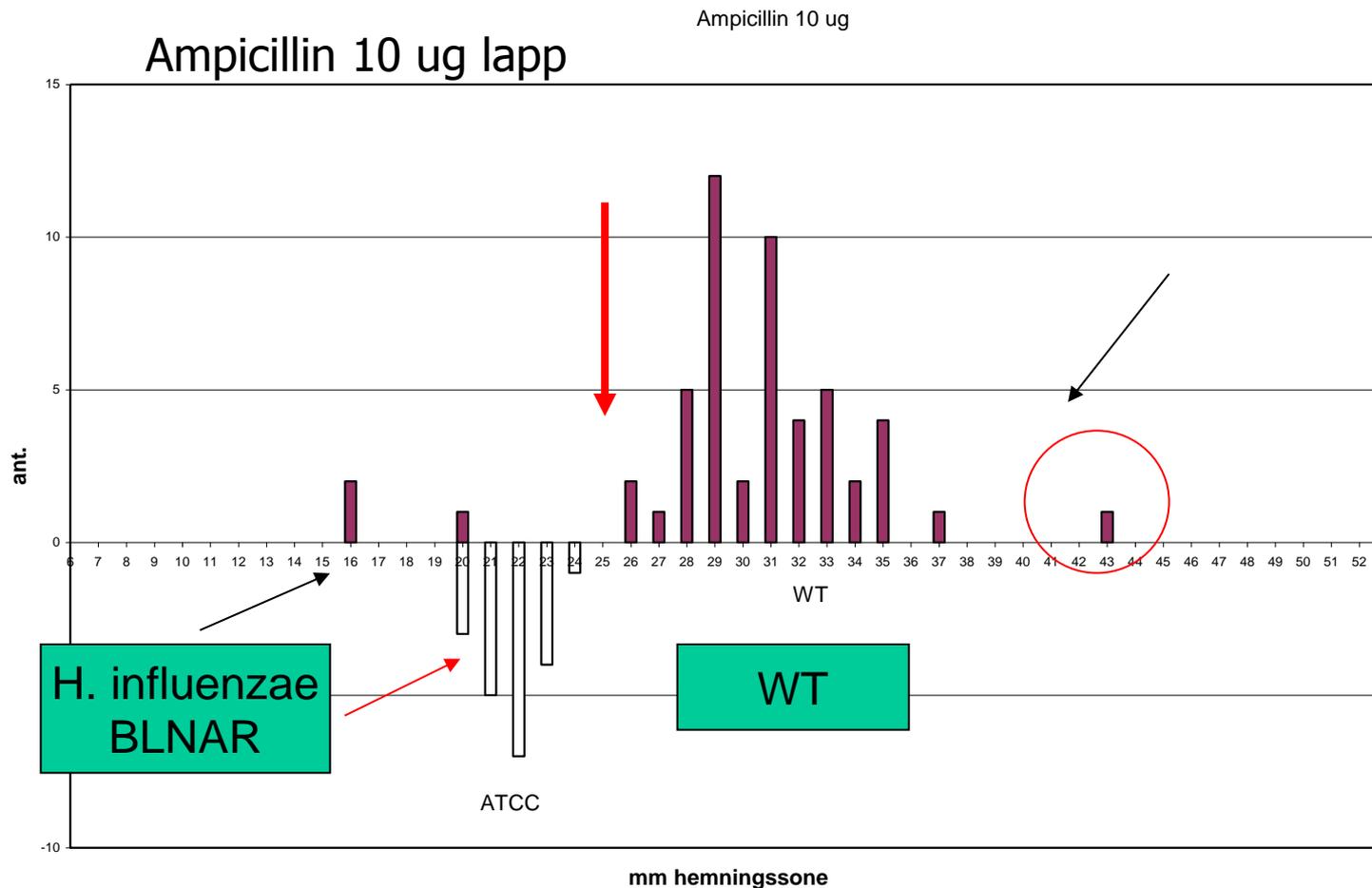
- MIC for WT viser genusspesifikk variasjon



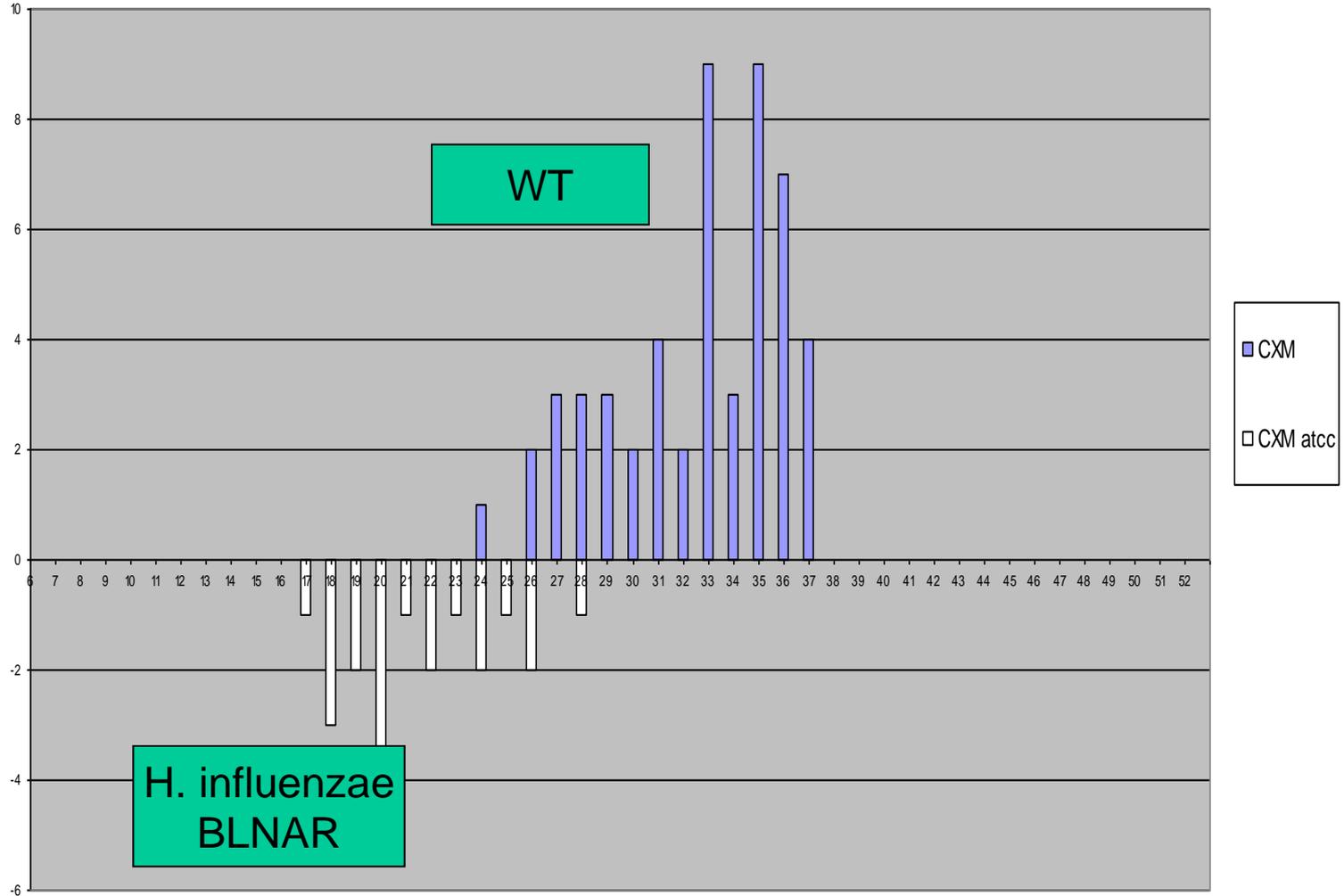
Gentamicin

Måleunøyaktighet og biologisk variasjon

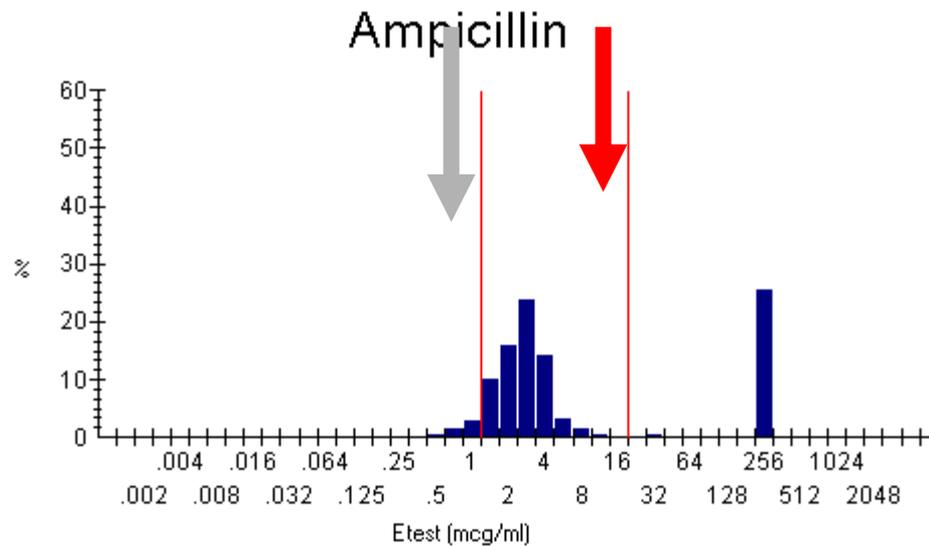
- gjentatte analyser gir ulike svar, WT (Wild type)



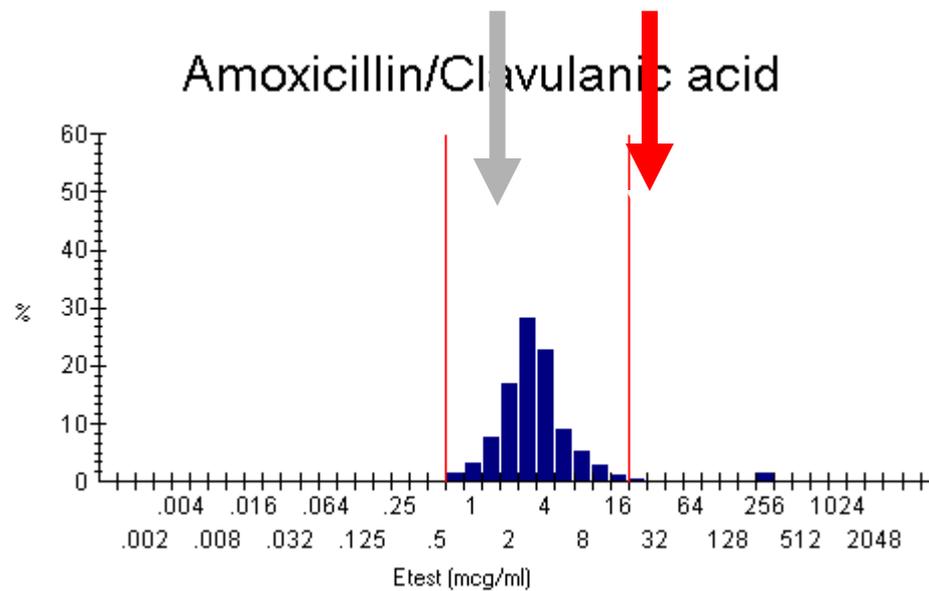
Cefuroxim 30 μ g fapp



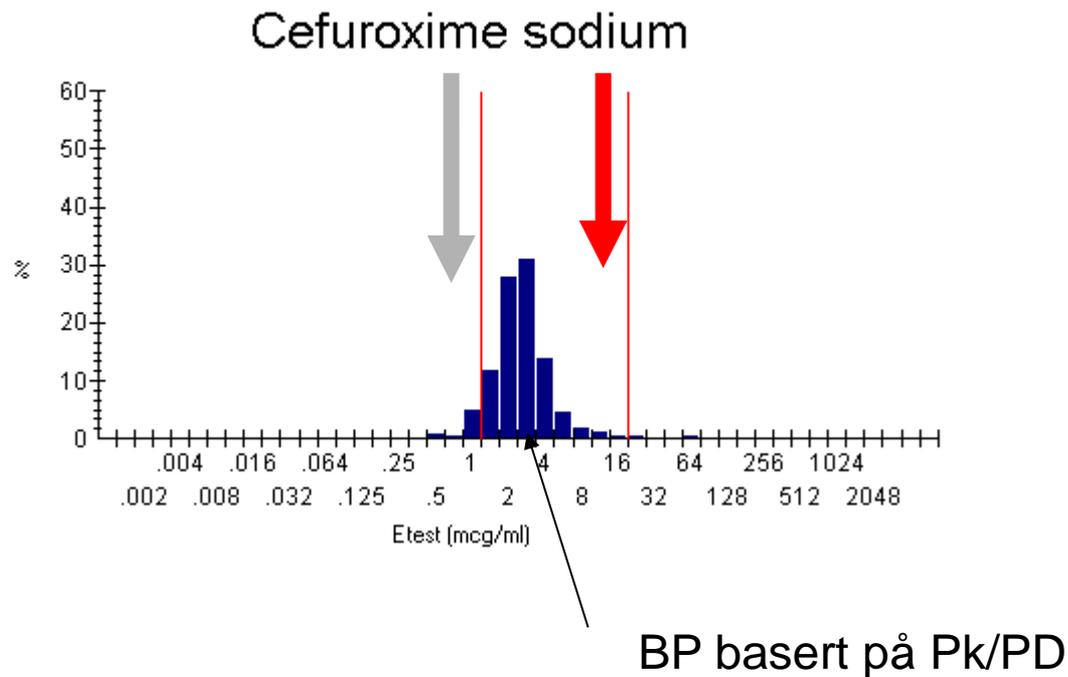
Blood cultures E. coli 2002 (n=959)



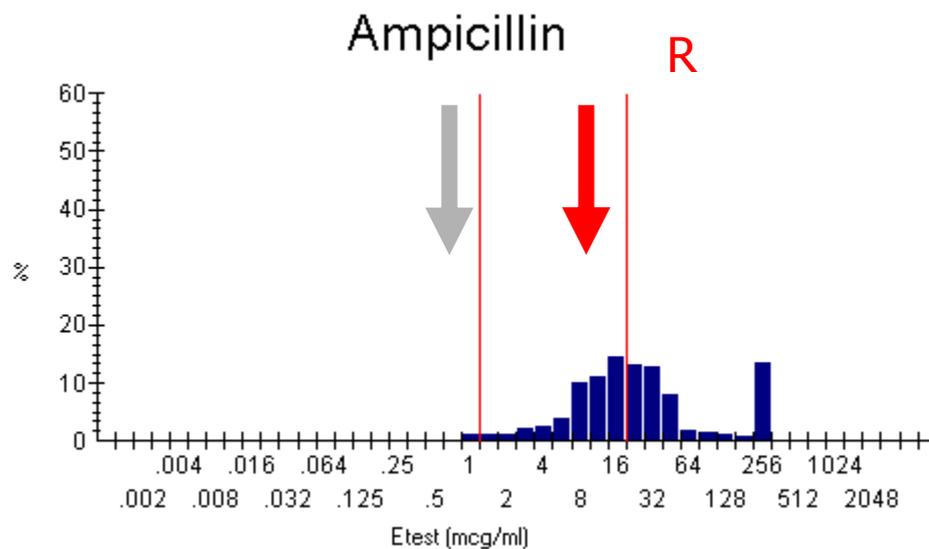
Blood cultures *E. coli* 2002 (n=959)



Blood cultures E. coli 2002 (n=959)



Blood cultures *Klebsiella* spp 2002 (n=352)



Alle *Klebsiella* har kromosomal klasse A bla og er resistente for Ampicillin

EUCAST definitions of epidemiological cut off values

Wild type (WT)

- a microorganism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a microorganism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild type microorganisms may or may not respond clinically to antimicrobial treatment.

Microbiological resistance - non-wild type (NWT)

- a microorganism is defined as non-wild type (NWT) for a species by the presence of an acquired or mutational resistance mechanism to the drug in question.
- a microorganism is categorized as non-wild type (NWT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- non-wild type microorganisms may or may not respond clinically to antimicrobial treatment.

Epidemiological cut-off values will not be altered by changing circumstances.

The wild type is presented as $WT \leq z \text{ mg/L}$ and non-wild type as $NWT > z \text{ mg/L}$

EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)

- a microorganism is defined as susceptible if inhibited in-vitro by a concentration of an antimicrobial agent that is associated with a high likelihood of therapeutic success
- a microorganism is **categorized** as susceptible (S) by applying the appropriate breakpoint in a defined phenotypic test system.

Clinically Intermediate (I)

- a microorganism is defined as intermediate by a level of antimicrobial agent activity associated with uncertain therapeutic effect.
 - It implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physically concentrated or when a high dosage of drug can be used; it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.
- a microorganism is **categorized** as intermediate (I) by applying the appropriate breakpoints in a defined phenotypic test system

Clinically Resistant (R)

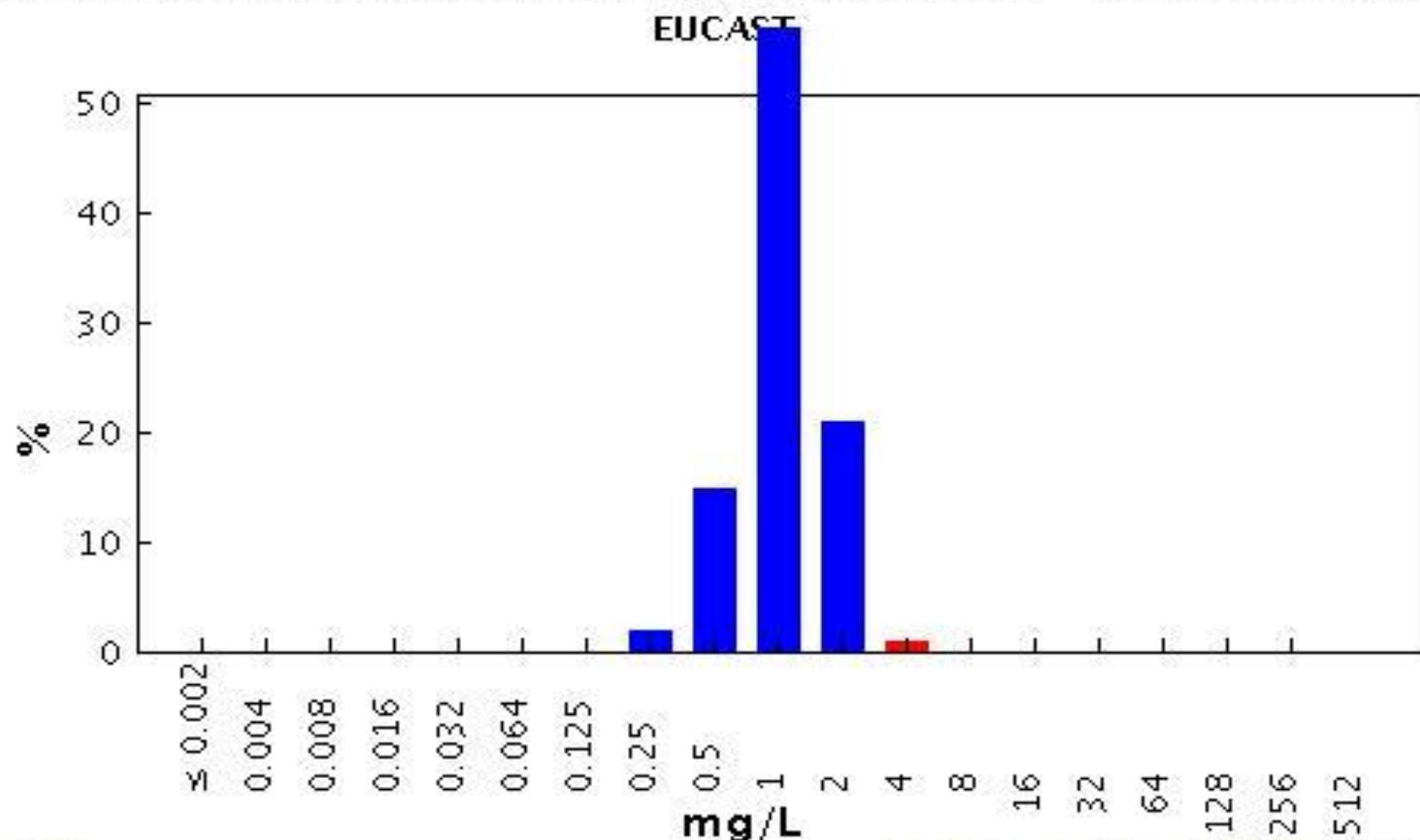
- a microorganism is defined as resistant if inhibited in-vitro by a concentration of an antimicrobial agent that is associated with a high likelihood of therapeutic failure
- a microorganism is **categorized** as resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system.

Clinical breakpoints may be altered with legitimate changes in circumstances

Clinical breakpoints are presented as $S \leq x$ mg/L; $I > x, \leq y$ mg/L; $R > y$ mg/L

Ciprofloxacin / *Streptococcus pneumoniae*

Antimicrobial wild type distributions of microorganisms - reference database



MIC

Epidemiological cut-off: WT ≤ 2 mg/L

63516 observations (38 data sources)

Clinical breakpoints: S ≤ 0.125 mg/L, R > 2 mg/L

EUCAST wild type MIC distributions and epidemiological cut-off values – the concept

EUCAST developed the concept of antimicrobial wild type MIC distributions and epidemiological cut-off values (JAC 52:145-148, 2003). Software was created to receive and display large volumes of MIC data for bacteria and fungi over the internet. It is freely available at <http://www.eucast.org>.

Distributions are displayed in an aggregated format. Tables and graphs show the part of the MIC distribution which, when EUCAST has defined the "epidemiological cut-off value", is considered the "wild type distribution".

The **epidemiological cut-off value** separating microorganisms without (wild type) and with acquired or mutational resistance (non-wild type) and **clinical breakpoints** are shown on the bottom line of the graph.

The epidemiological cut-off value (left lower corner) is shown as $WT \leq X$ mg/L.

The clinical breakpoints (right lower corner) are shown as $S \leq Y$ mg/L and $R > Z$ mg/L.

EUCAST agreed breakpoints

- **Cephalosporins**
 - Cefazolin
 - Cefepime
 - Cefotaxime
 - Ceftazidime
 - Ceftriaxone
 - Cefuroxime
- **Carbapenems**
 - Ertapenem
 - Imipenem
 - Meropenem
- **Fluoroquinolones**
 - Ciprofloxacin
 - Levofloxacin
 - Moxifloxacin
 - Norfloxacin
 - Ofloxacin
- **Aminoglycosides**
 - Amikacin
 - Gentamicin
 - Netilmicin
 - Tobramycin
- **Glycopeptides**
 - Vancomycin
 - Teicoplanin
- **Linezolid**
- **Tigecycline**
- **Aztreonam**
- **Daptomycin**

- **Penicillins**
- **Macrolides**
- **Miscellaneous drugs**

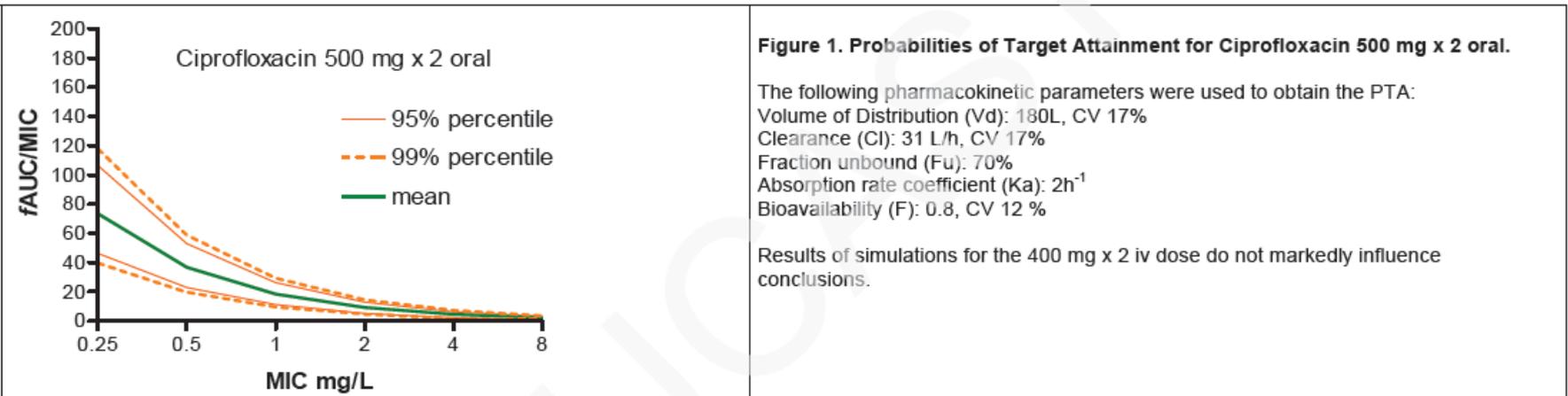
EUCAST Rationale documents

- Dosages (national)
- MIC-distributions
- National BP prior to harmonization
- PK data
- PD data
- Monte Carlo simulation
- Clinical data
- Clinical breakpoints
- Exceptions (if any)

4. Pharmacokinetics				
Dosage (mg)	400 x 2 iv	500 x 2 oral	750 x 2 oral	
C _{max} (mg/L)	3.2	2.3 - 2.8	3.2 - 3.9	
C _{min} (mg/L)				
Total body clearance (L/h)	26.8			
T _{1/2} (h), mean (range)	(4.2 - 4.3)	(2.5 - 3.9)	4.0	
AUC _{24h} (mg.h/L)	21 - 29	19.2 - 19.8	39	
Fraction unbound (%)	70 - 80	70 - 80	70 - 80	
Volume of distribution (L)	100 - 180			
Comments	<ul style="list-style-type: none"> Pharmacokinetic parameters from references Drusano and Dudley were obtained after a 200 mg iv dose; linearity was assumed. AUCs reported for single doses were converted to 24h AUCs assuming linearity. Two values are given where references differ. Cells are left empty when data are not readily available. 			
References	<ul style="list-style-type: none"> Drusano et al., <i>Antimicrob Agents Chemother</i> 1987; 31:860 Dudley et al., <i>Antimicrob Agents Chemother</i> 1987; 31:1782 Crump et al., <i>Antimicrob Agents Chemother</i> 1983; 24:784 Bergan et al., <i>Antimicrob Agents Chemother</i> 1986; 29:298 Zlotos et al., <i>J Pharm Sci</i> 1998; 87:215 Catchpole et al., <i>J Antimicrob Chemother</i> 1994; 33:103 de Marie et al., <i>Int Care Med</i> 1998; 24:343 			

6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of Target Attainment (PTA) for 500 mg x 2 oral are shown in Figure 1.



8. Clinical breakpoints

Non-species-related breakpoints	<p>Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.</p> <p>Breakpoints are $S \leq 0.5$ mg/L, $R > 1$ mg/L. These render wild type Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Staphylococcus</i> spp., <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i> and <i>Neisseria</i> spp. susceptible.</p>
Species-related breakpoints	<p>The wild type MIC distributions of most Enterobacteriaceae, including <i>Salmonella</i> spp, exhibit MIC values < 0.125 mg/L. A breakpoint of ≤ 0.5 mg/L allows low-level quinolone resistant Enterobacteriaceae to be categorised as susceptible to ciprofloxacin.</p> <p>For <i>Acinetobacter</i> spp. and <i>Staphylococcus</i> spp. the S/I breakpoint was increased to 1 mg/L to avoid dividing wild type MIC distributions. Therefore these breakpoints relate to the higher dosages of ciprofloxacin.</p> <p>For <i>S. pneumoniae</i>, more than 95% of wild type strains have MICs of 0.25, 0.5 or 1 mg/L, which means that neither of the non-species-related values can be used as a breakpoint without causing major splitting of the wild type distribution and thus problems with the reproducibility of S, I and R categorisation. A breakpoint of $S \leq 0.125$ mg/L categorises wild type <i>S. pneumoniae</i> as intermediate to ciprofloxacin and a breakpoint of $R > 2$ mg/L categorises non-wild type <i>S. pneumoniae</i> as resistant to ciprofloxacin. Both consequences were intended.</p> <p>The breakpoints allow <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i> with low-level fluoroquinolone resistance to be categorized as susceptible to ciprofloxacin.</p> <p>Many laboratories screen for fluoroquinolone resistance with a nalidixic acid 30 µg disc; but note that <i>Neisseria gonorrhoeae</i> and <i>Salmonella typhi</i> that are ciprofloxacin resistant but not clearly nalidixic acid resistant have been reported.</p>
Species without breakpoints	<p><i>Streptococcus</i> spp., <i>Enterococcus</i> spp. and anaerobic bacteria were considered poor targets for ciprofloxacin therapy and for that reason did not receive breakpoints.</p>
Clinical qualifications	<p>There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by <i>Salmonella</i> spp with low-level fluoroquinolone resistance ($MIC > 0.064$ mg/L). EUCAST has suggested that the epidemiological cut off value ($S \leq 0.064/R > 0.064$ mg/L) be used in <i>Salmonella</i> spp. systemic infections.</p>
Dosage	<p>Breakpoints apply to an oral dose of 500 mg x 2 (or as low as 250 mg x 2 for uncomplicated urinary tract infections) to 750 mg x 2 and an intravenous dose of 400 mg x 2 to 400 mg x 3.</p>
Additional comment	

EUCAST websites are found at

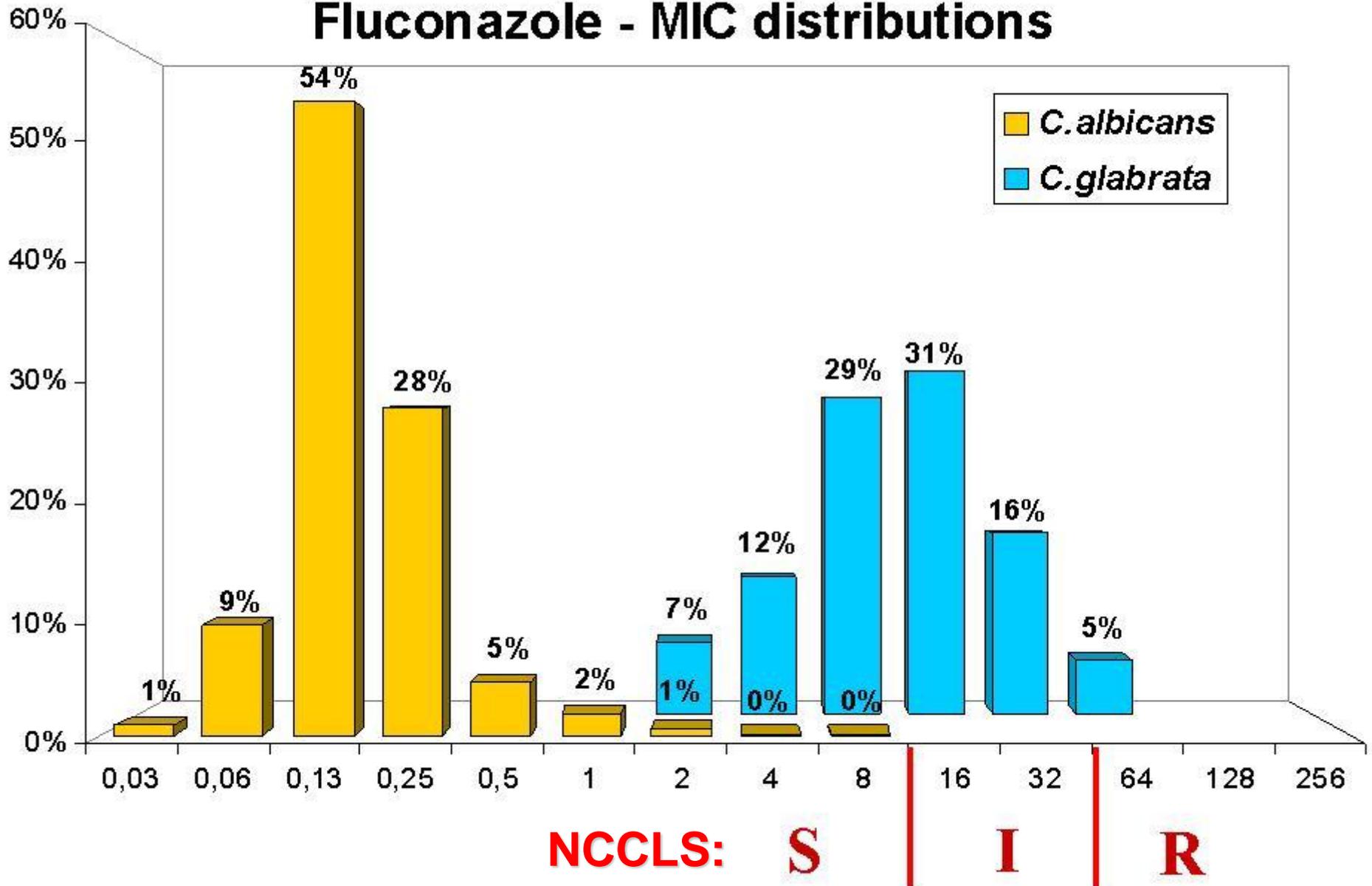
www.eucast.org

The EUCAST websites are accessed via **www.eucast.org**

This is a section of the official ESCMID website giving details of all EUCAST activities including

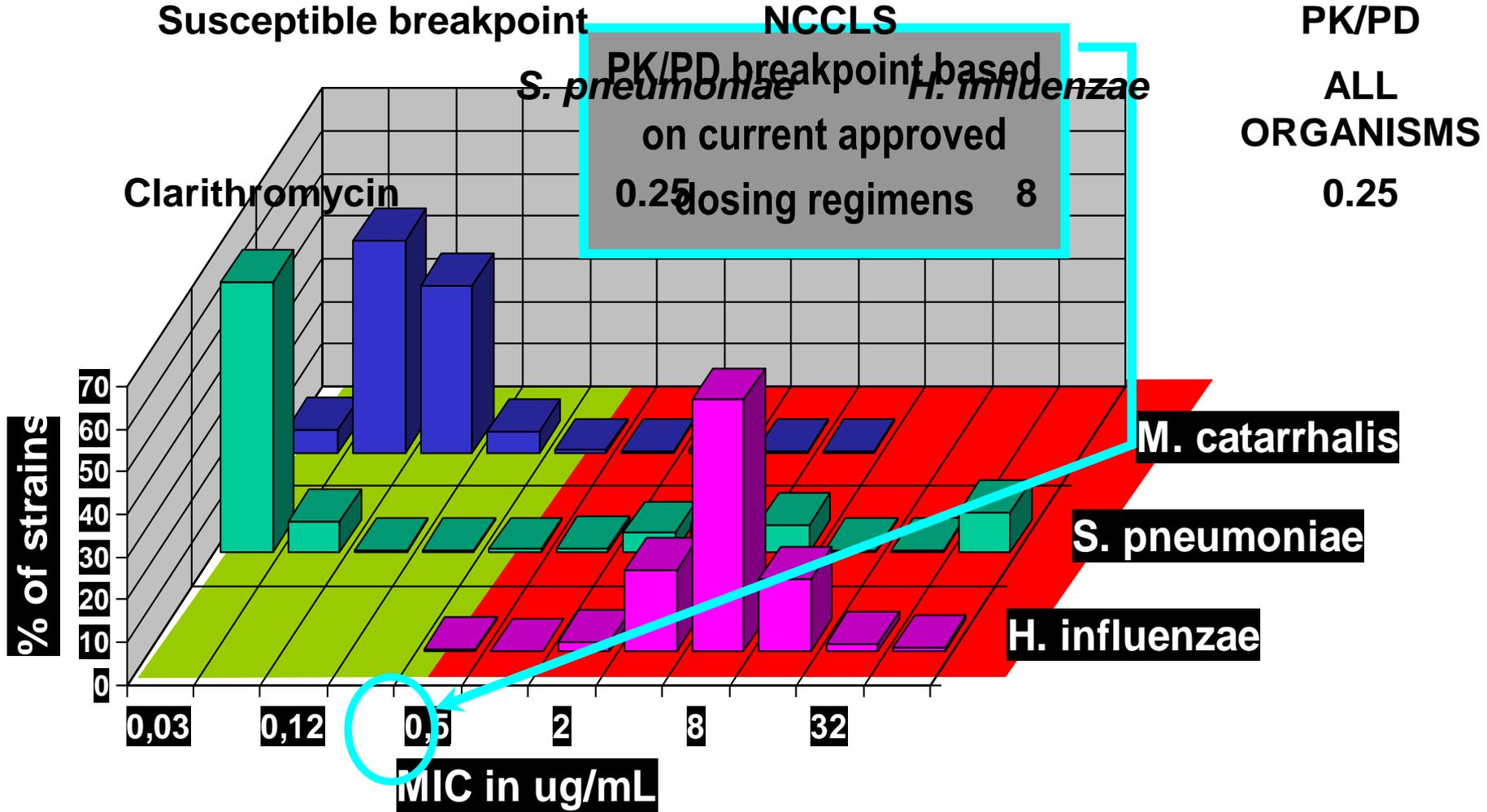
- constitution
- organisation
- committee member lists
- meetings
- EUCAST documents
- clinical MIC breakpoint tables
- MIC distributions for wild type bacteria and fungi
- epidemiological MIC cut-off values

Fluconazole - MIC distributions





Clarithromycin

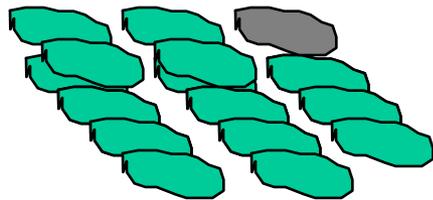


Antibiotikaresistens - Hvorfor?

- Genetisk evolusjon
 - mutasjon, genoverføring
- Seleksjon
 - Bruk av antibiotika selekterer de bakteriene som har resistens mot det antibiotikum som brukes
- Overføring av mikrober mellom individer (smittespredning)

Antibiotkaresistens - Seleksjon

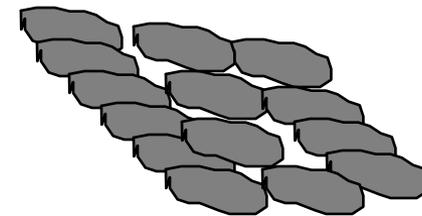
Opprinnelig
bakterie-
populasjon



Bakterie med
mutasjon
overlever



Resistente
bakterier er
selektert



Antibiotikabehandling

Sammenhengen mellom mm og MIC

- Fick's diffusjonslov
 - Diffusjonskonstanten
 - for et middel bestemmes av molekylstørrelse og mediets viskositet
 - Temperatur
- Dannelse av hemningssone
 - IC (inhibitory concentration)
 - Kritisk tid (avhengig av inokulat og veksthastighet)
- Antibiotikakonsentrasjonen i agaren er omvendt proporsjonal med kvadratet av avstand fra diffusjonsentrum.
- For de fleste mikrober og antibiotika finnes det en IC som akkurat hemmer veksten og her vil hemningssonen dannes.

