

# Resurrecting old antimicrobial agents

## Translational research for old antibiotics: what is lacking?

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## Forgotten antibiotics (Pulcini et al, 2012)

temocillin

pristinamycin

fosfomycin iv/po

quinupristin-dalfopristin

mecillinam/pivmecillinam

aztreonam

chloramphenicol

trimethoprim

fusidic acid

colistin

In addition -

## Revived antibiotics/old antibiotics in ICU

(Cassir et al, 2014; Falagas & Kopterides 2007)

teicoplanin

nitrofurantoin

co-trimoxazole

clindamycin

isepamicin

minocycline iv

## Topics

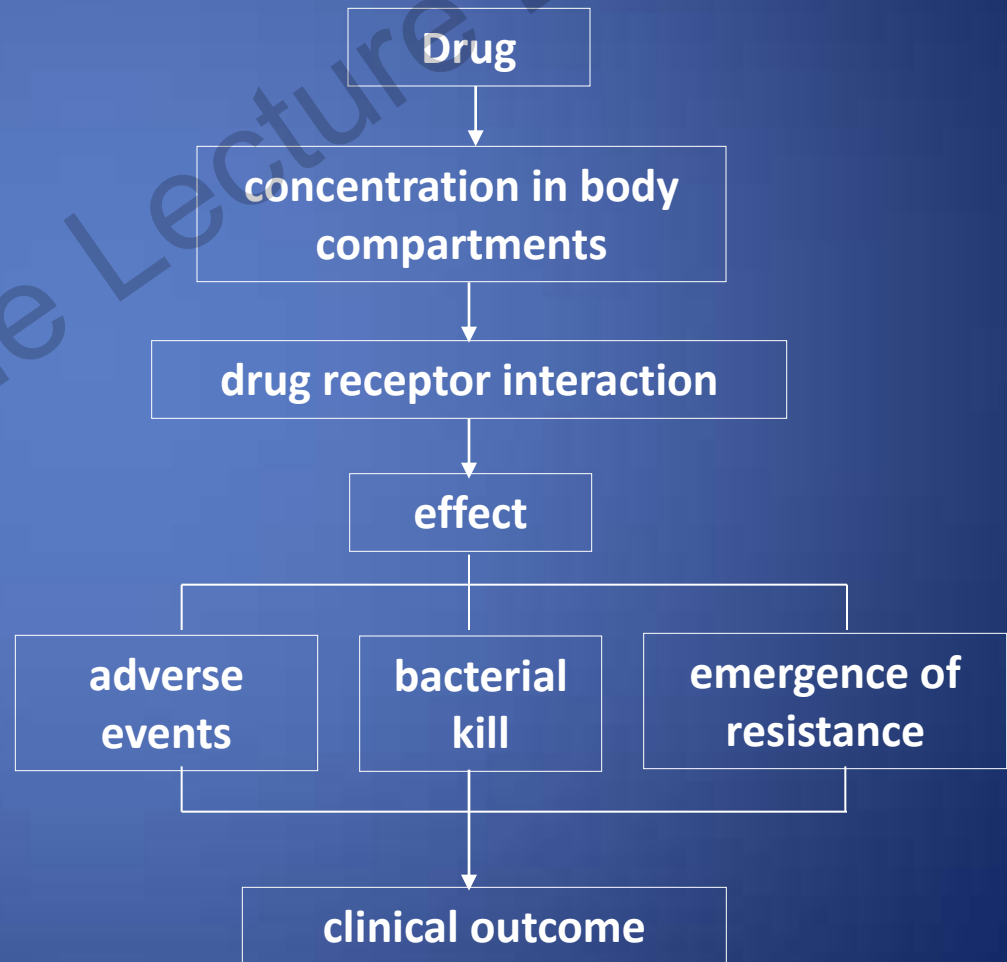
- **what basic science PK-PD do we need for old antibiotics?**
- **how does this contribute to wiser and sustainable use of old antibiotics?**
- **assessment of gaps in the knowledge base**

# Objectives of PK-PD optimisation

- maximise bacterial inhibition/kill for a defined drug dose
- minimise risk of emergence of antibacterial resistance for a defined drug dose

pharmacokinetics  
(PK)

pharmacodynamics  
(PD)



## Basic PK-PD questions in developing anti infective dosing regimen

Which dose (mg)?

Which frequency of dosing (hours)?

Which duration (days)?

Which are the target pathogens ?

What is the clinical breakpoint (mg/L)?

Is combination therapy needed?

## Basic PK-PD tools for translational research (1)

### In vitro experiments

- MICs: wild type and with relevant resistance mechanisms
- Patterns of bacterial killing in fixed concentration kill curves
- [ ➤ persistent antibiotic effects ]
- pharmacokinetic modelling:
  - defining PDI targets
  - defining PDI target size
  - determining risk of emergence of resistance
  - simulation of human dosing
  - combination therapy
  - Other: inoculum, mixed infection, ELF, CSF, urine concentrations
  - Often use wild type strains and those with relevant mechanisms of resistance

## Basic PK-PD tools for translational research (2)

### Animal experiments

neutropaenic murine thigh model

neutropaenic murine pulmonary model

± humanised dosing

peritonitis murine model

septicaemia models

endocarditis models

bone infection models

meningitis models

foreign body infection models

(mice, rats, guinea pigs, rabbits)

# PK-PD pathway

Basic microbiology  
MICs  
patterns of kill  
persistent effects

Basic PK  
➤ ADME  
➤ protein binding  
➤ serum time concentration  
course

## pre clinical PK-PD models

- determine PDI driver
- determine the exposure response relationship
  - PDI driver target  
(dose fractionation/escalation :  
dosing matrix)

use the PDI target with the  
PK to determine likely  
breakpoints and target  
pathogen

confirm targets clinically

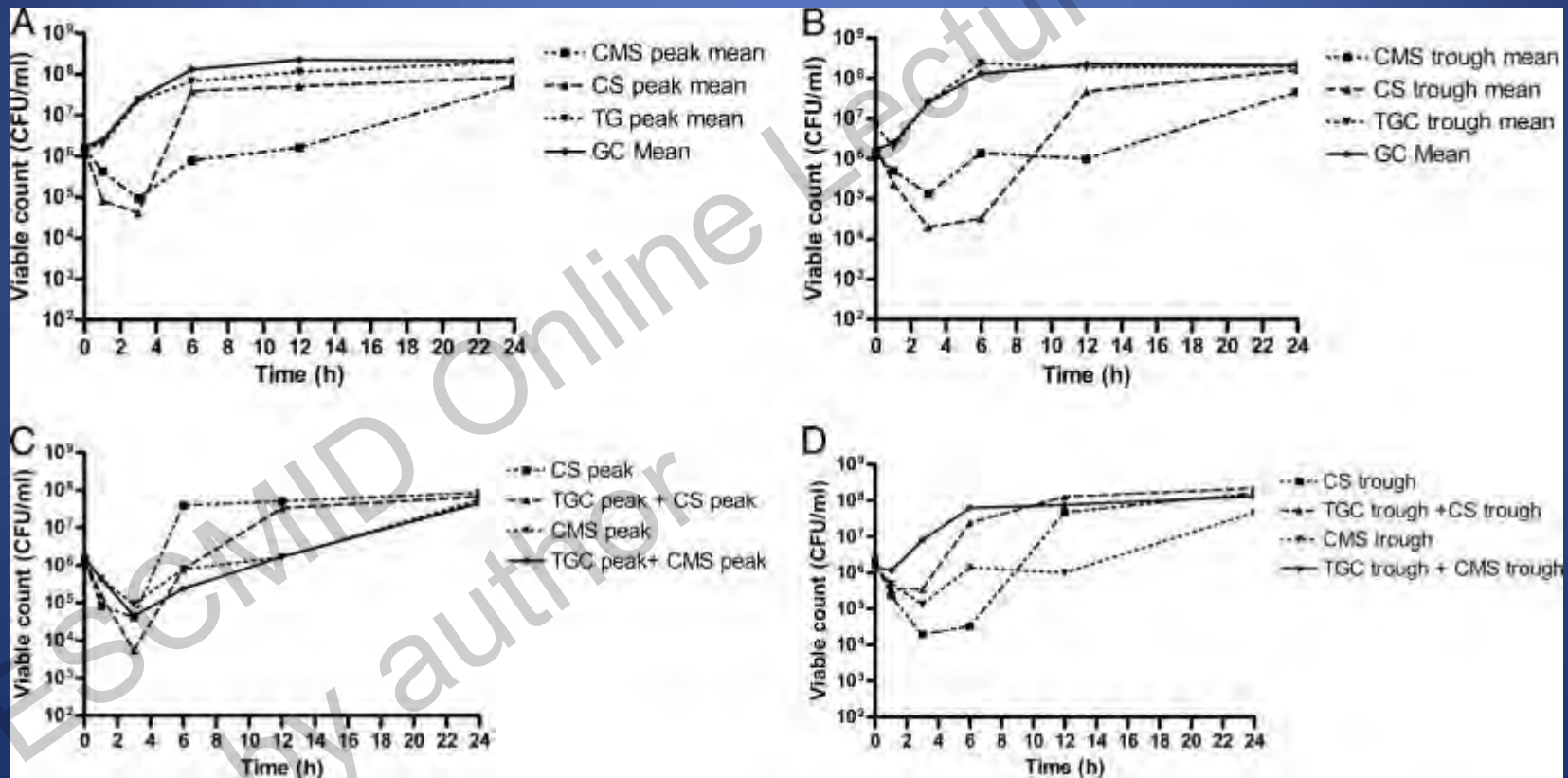


## Some examples

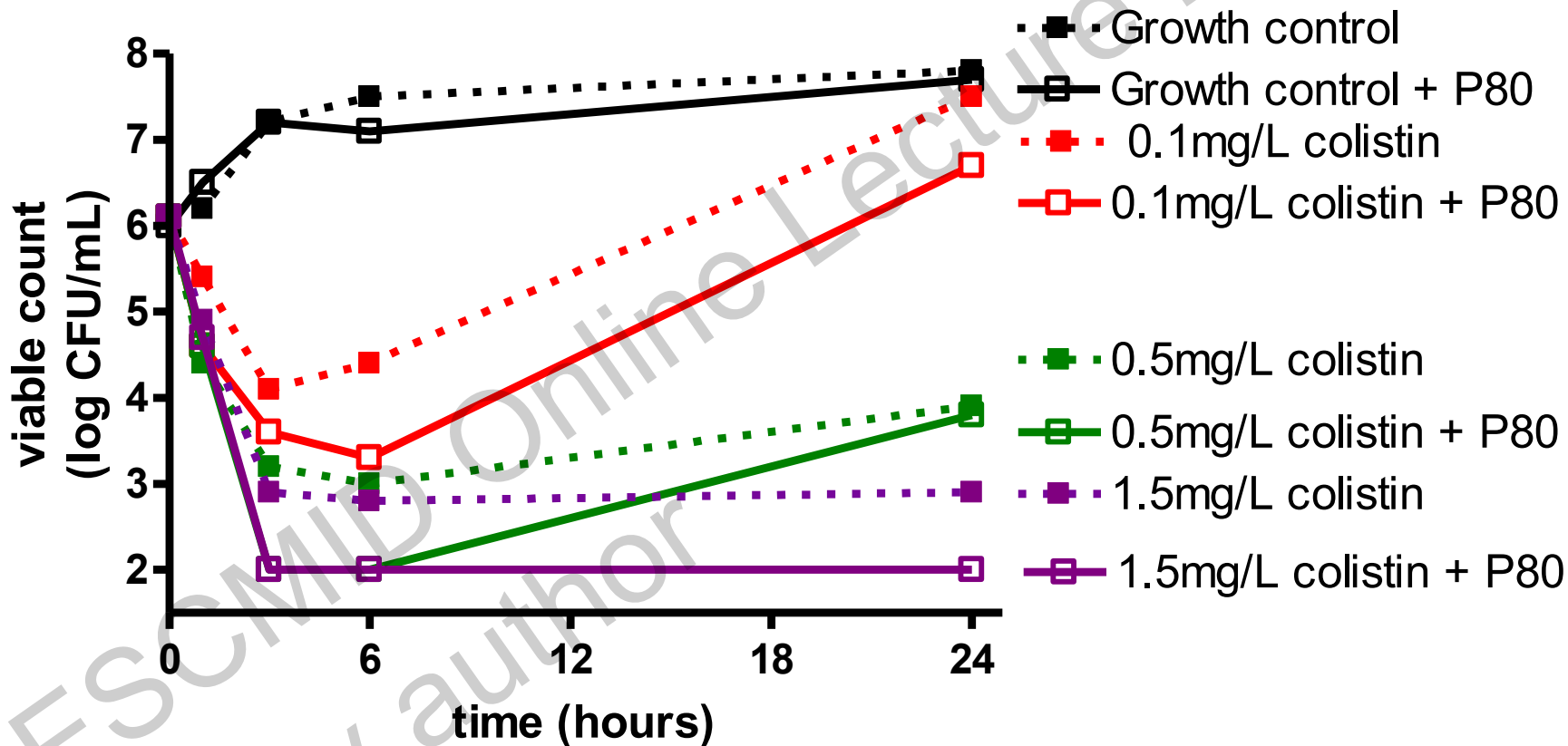
- **static concentration kill curves (colistin)**
- **simulated human doses (temocillin, teicoplanin, minocycline, comparisons and combinations)**
- **determining the pharmacodynamic driver (minocycline)**
- **exposure (using PDI driver) response relationships (minocycline)**
- **emergence of resistance (minocycline)**

# Static concentration time-kill curves

Antibacterial activities of tigecycline, colistin sulfate, and colistin methanesulfonate against NDM-1-producing Enterobacteriaceae at free peak concentrations of individual drugs (A), free trough concentrations of individual drugs (B), combinations of peak concentrations (C), and combinations of trough concentrations (D)

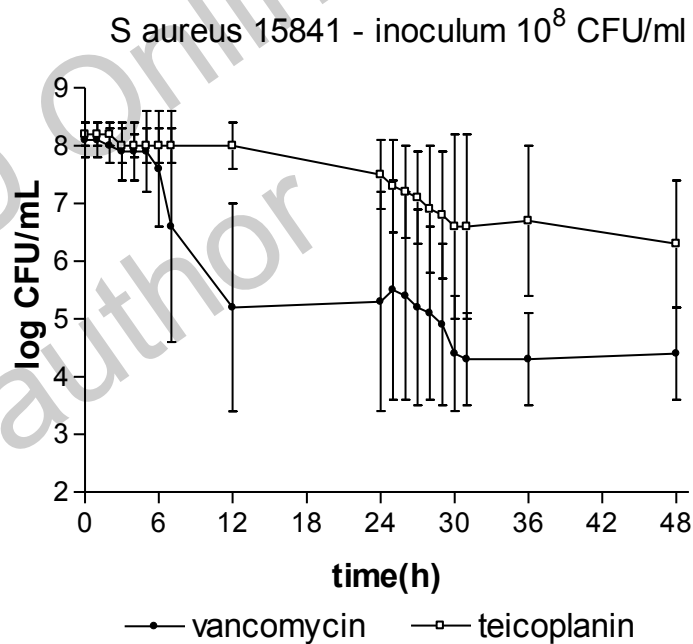
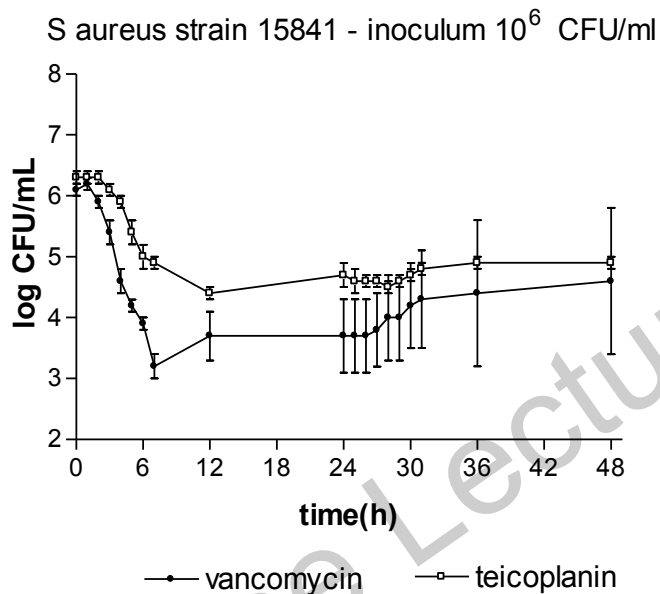


## Antibacterial effect of colistin sulphate against *Acinetobacter* spp

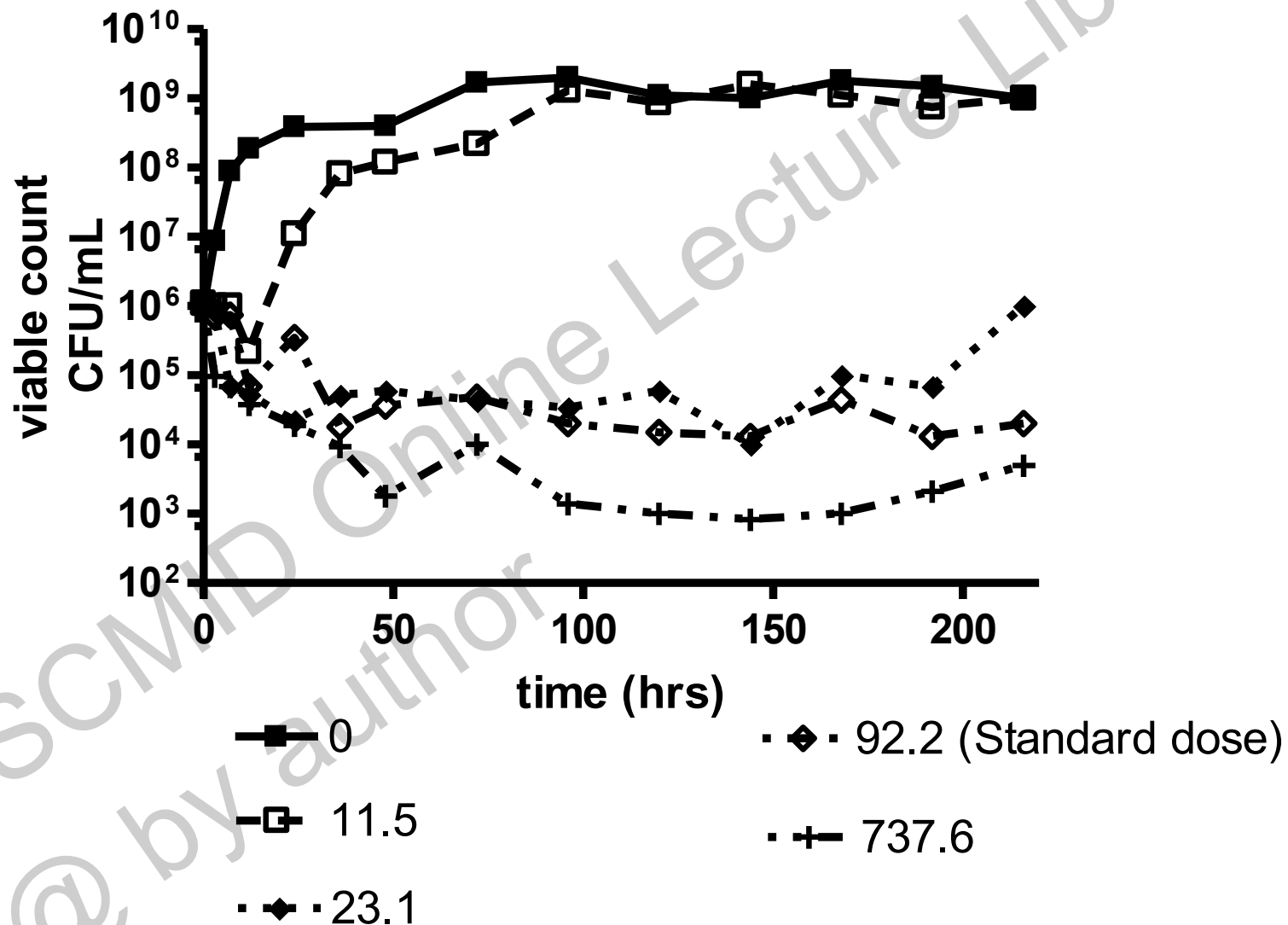


Simulated human doses

Teicoplanin and vancomycin - antibacterial effects: impact of inoculum



# Minocycline antibacterial effect against MRSA Strain 45494 - 10day exposure



*In vitro* activity of 2g 12hr temocillin against  
ESBL producing Enterobacteriaceae

strain	temocillin MIC (mg/L)	log drop at 12hr
31054	1.5	-0.2
35270	2.0	-2.1
36271	3.0	-2.8
ATCC 2922	8.0	+0.8
32427	16.0	+0.7
33212	24.0	+1.4
n=3	MIC <4mg/L	-1.3 ± 1.4
n=3	MIC >4mg/L	+3.3 ± 0.3

Bowker et al, 2006

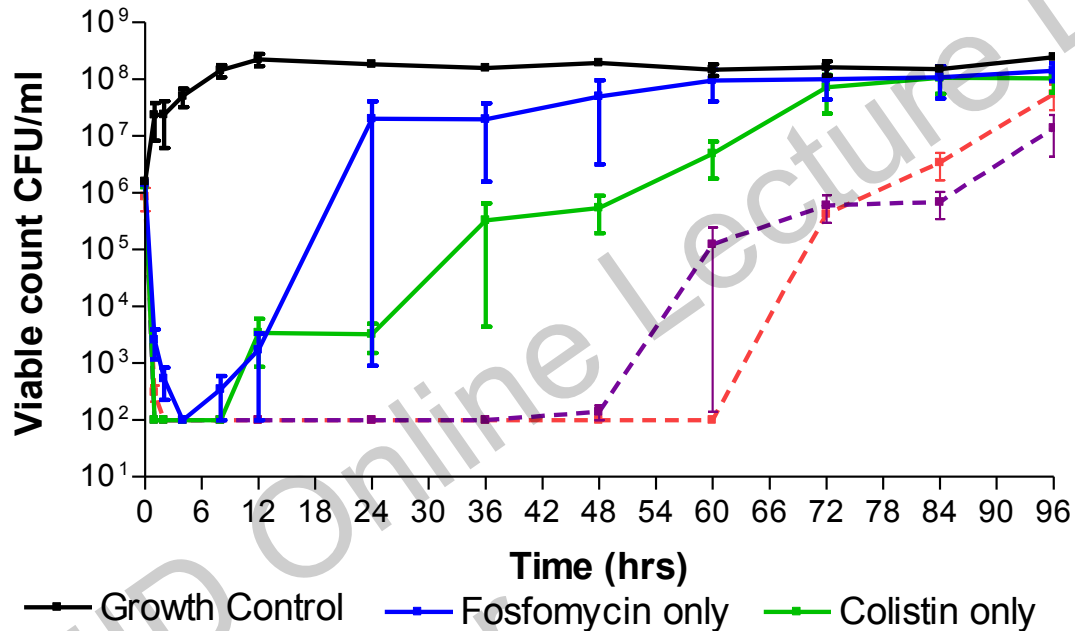
Comparative antibacterial effects of ertapenem, meropenem and temocillin in a hollow fibre *in vitro* model against 4 ESBL producing *Enterobacteriaceae*

agent	log drop in viable count at -	
	12h	24h
Temocillin 2g BD	+0.7 ± 0.8	+2.9 ± 0.7
Ertapenem 1g OD	-4.3 ± 0.4	-4.3 ± 0.4
Meropenem 1g TDS	-4.7 ± 0.3	-4.6 ± 0.1

Bowker et al, 2006

# Combinations: antibacterial clearance

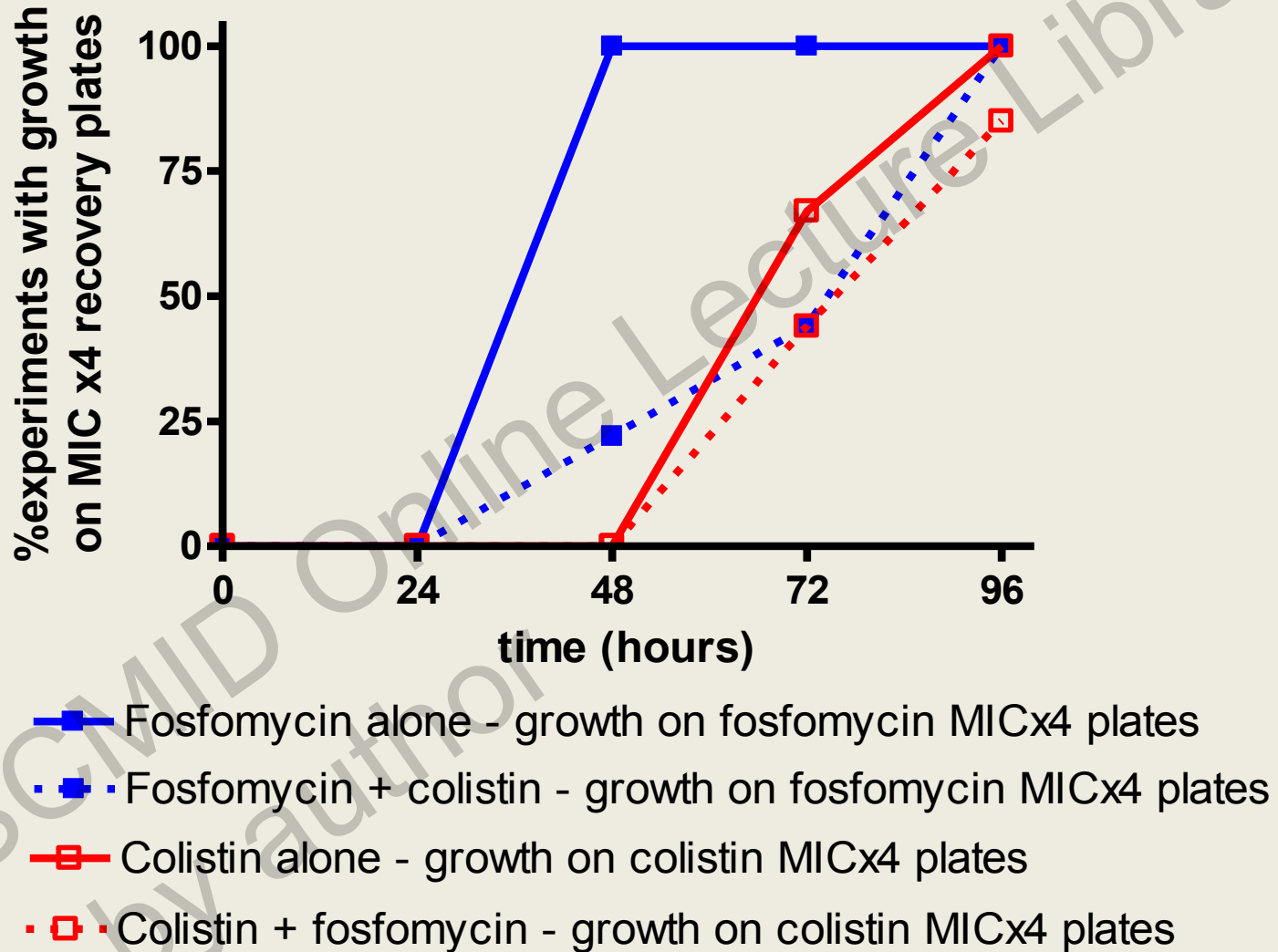
Fosfomycin 4g 8hrly and colistin sulphate 2MU 8hrly against NDM producing E coli and Klebsiella sp



Albur (in press)



## Combination: emergence of resistance



## Determining the pharmacodynamic driver

- hollow fibre system, 1 strain *S.aureus* minocycline  
MIC 0.05mg/L

measure of antibacterial effect	dosing regimen			P value
	67mg TDS	100mg BD	200mg OD	
AUBKC(24)	71 ± 1	80 ± 2	74 ± 3	0.24
log drop at 24h (d24)	-1.7 ± 0.1	-1.5 ± 0.3	-1.6 ± 0.1	0.29
T99.9(h)	>24	>24	>24	>0.05

PD index	R <sup>2</sup> of sigmoid	
	AUBKC	d24
AUC/MIC	0.92	0.87
Cmax/MIC	0.75	0.51
T>MIC	0.63	0.41

**fAUC/MIC ratios required for bacteriostatic and cidal effects for minocycline against MRSA (AIDA Programme data, FP7 EU)**

strain	MIC (mg/L)	fAUC/MIC for 24hr		
		static effect	-1 log drop	-2 log drop
43241	0.25	11.2	20.5	41.5
33827	0.5	3.2	7.3	>200
ATCC 29213	0.19	9.0	17.4	51.2
45494	0.12	19.0	29.3	>200
33922	1.0	19.2	38.2	>200
		12.3 ± 6.8	22.5 ± 11.8	-

fAUC/MIC ratios required for bacteriostatic and cidal effects for minocycline versus Acinetobacter

strain	MIC (mg/L)	fAUC/MIC for			
		24hr		48hr	
		static effect	-1 log drop	static effect	-1 log drop
33980	0.5	14.2	26.1	15.4	24.9
35406	3.0	19.2	24.8	25.2	46.0
34958	4.0	15.8	19.1	18.0	20.3
		16.4±2.6	23.8±3.7	19.5±5.1	30.4±13.7

Noel et al, 2014

## Minocycline *S.aureus* and *Acinetobacter* spp MIC distributions (EUCAST)

MIC (mg/L)	<i>S.aureus</i>		<i>Acinetobacter</i>	
	n	proportion (%)	n	proportion (%)
≤0.03	40	1.7	-	-
0.06	549	22.9	-	-
0.12	1,396	58.4	-	-
0.25	322	13.5	-	-
0.5	32	1.4	30	30
1.0	10	<0.5	7	7
2.0	12	0.5	18	18
4.0	16	0.6	15	15
>4.0	9	<0.5	30	30
PDI target fAUC/MIC		10-15		15-20

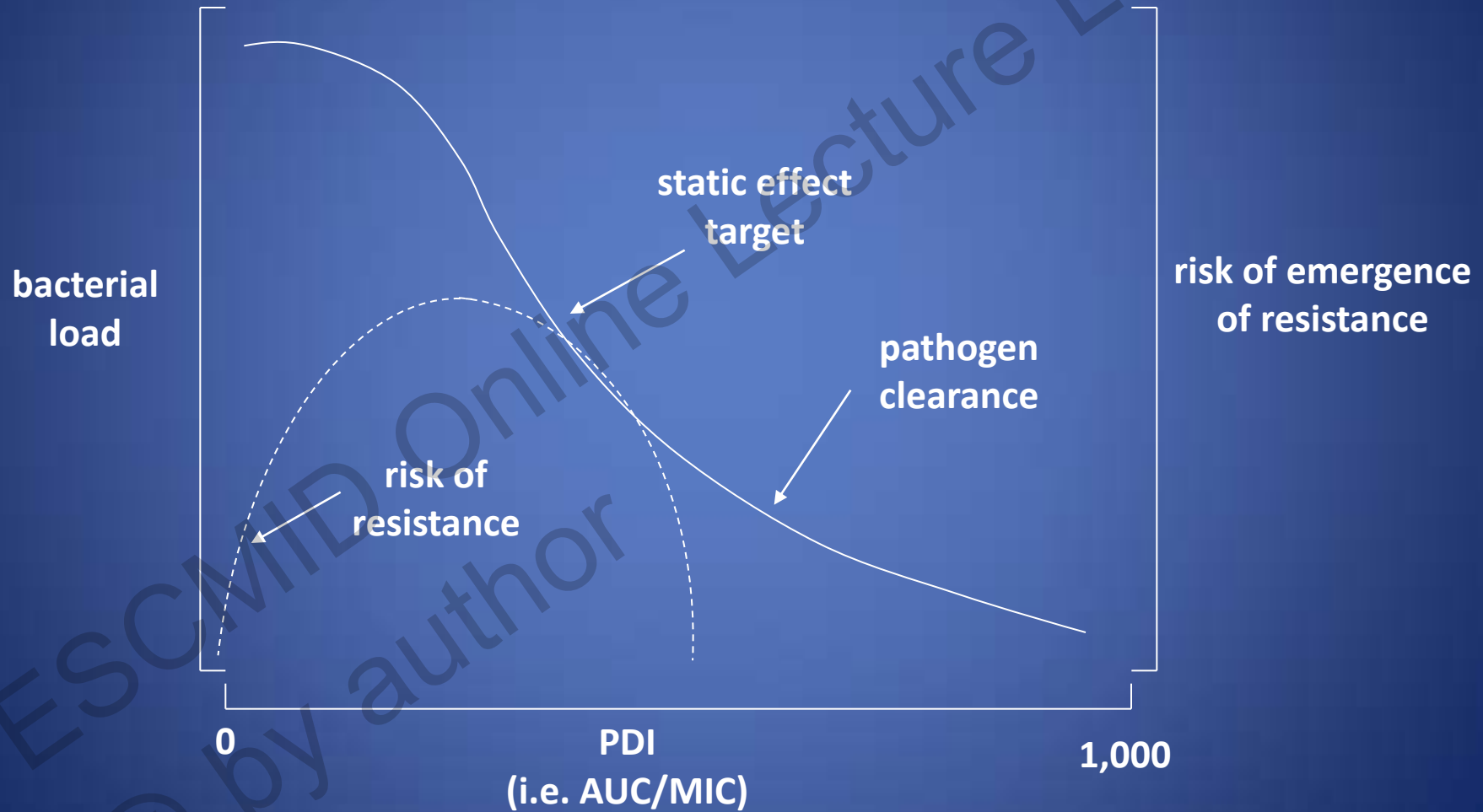
Risk of emergence of resistance – measure by population profiles – at 72h stratified by fAUC/MIC for minocycline versus Acinetobacter spp

fAUC/ MIC	MICx2 media		MICx4 media		MICx8 media	
	number of experiments	bacterial count	number of experiments	bacterial count	number of experiments	bacterial count
1-5	2/3	5.5	1/3	3.6	1/3	3.2
>5-10	2/3	7.8	2/3	7.2	2/3	5.5
>10-15	2/3	8.0	2/3	7.6	0/3	<2
>15-20	0/3	<2	0/3	<2	0/3	<2
>20	0/3	<2	0/3	<2	0/3	<2

➤ inverse “U” relationship of exposure to resistance

Noel et al, 2014

# Exposure response relationships for bacterial clearance and risk of emergence of resistance



## Translational messages – from examples

- concern about teicoplanin dosed at 400mg 24h in high bacterial load infection
- temocillin 2g 12hrly insufficient to treat many ESBL producers (?increase dose by PI/CI, add second agent)
- minocycline 100mg 12hrly po probably okay for MRSA cSSTI
- minocycline 100mg 12hrly probably too low a dose for *Acinetobacter* spp (?increase dose or add second agent)



# Measuring the translational gap – pharmacodynamically based clinical breakpoints – EUCAST

## No Rationale Document

pristinamycin, quinupristin-dalfopristin, aztreonam, chloramphenicol, co-trimoxazole, isepamicin, minocycline iv

## Rationale documents

	pre clinical PDI target	mathematic modelling of PD breakpoint	PK-PD breakpoint
colistin (2010)	Yes	No	No
doxycycline (2009)	No	No	No
fosfomycin iv (2013)	Yes	No	No
fosfomycin- trometamol (2013)	Yes	No	No
fusidic acid (2010)	No	No	No
mecillinam (2010)	Yes	No	No
minocycline (2009)	No	No	No
nitrofurantoin (2010)	No	No	No
trimethoprim (2010)	No	No	No
teicoplanin (2010)	No	No	No

## What gaps do we expect to be filled by 2015-2017?

	<b>PDI target</b>	<b>pop PK and modelling PD breakpoint</b>	<b>Clinical breakpoint</b>
<b>colistin (AIDA and many others)</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes TATFAR</b>
<b>fosfomycin</b>	<b>Yes</b>	<b>No</b>	<b>No</b>
<b>fusidic acid (CEM-102, Cempra)</b>	<b>?</b>	<b>?</b>	<b>?</b>
<b>aztreonam</b>	<b>Yes</b>	<b>?</b>	<b>?</b>
<b>mecillinam</b>	<b>No</b>	<b>No</b>	<b>No</b>
<b>minocycline (AIDA)</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>nitrofurantoin (AIDA)</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>trimethoprim</b>	<b>No</b>	<b>No</b>	<b>No</b>
<b>teicoplanin</b>	<b>No</b>	<b>No</b>	<b>No</b>
<b>pristinamycin</b>	<b>No</b>	<b>No</b>	<b>No</b>
<b>Q-D</b>	<b>No</b>	<b>No</b>	<b>No</b>
<b>chloramphenicol</b>	<b>No</b>	<b>No</b>	<b>No</b>
<b>co-trimoxazole</b>	<b>maybe</b>	<b>No</b>	<b>No</b>
<b>isepamicin</b>	<b>No</b>	<b>No</b>	<b>No</b>

## Conclusions

- **PK-PD development pathway for new agents is well established**
- **the essential pieces of information for old agents can also be easily defined**
- **further public sector funding (in EU and elsewhere) will enable basic science gaps to be filled**
- **more thorough understanding of basic science PK-PD should enhance clinical use of old agents and development of new agents**