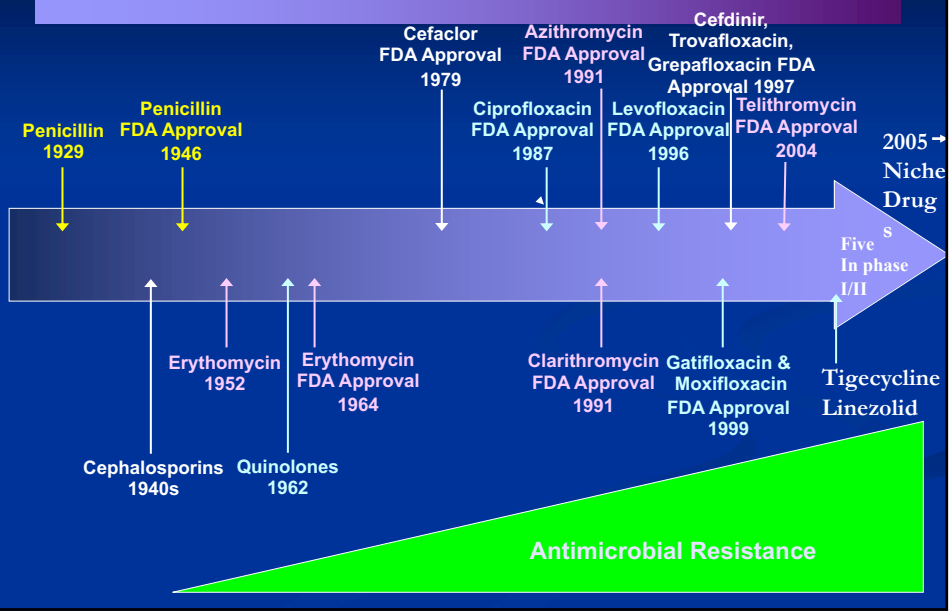
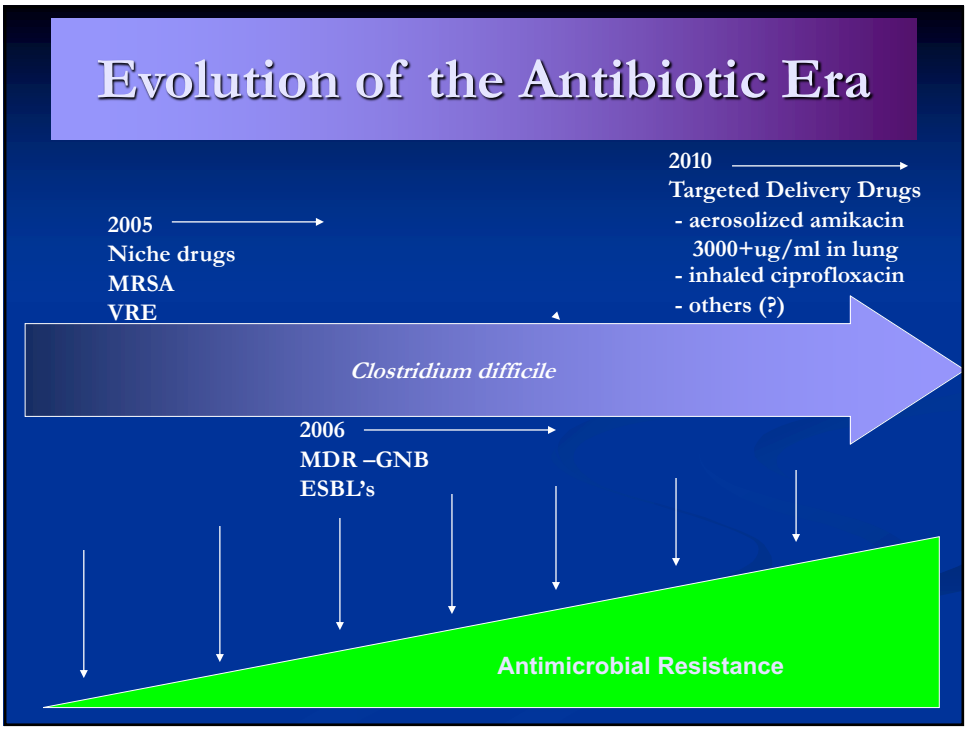
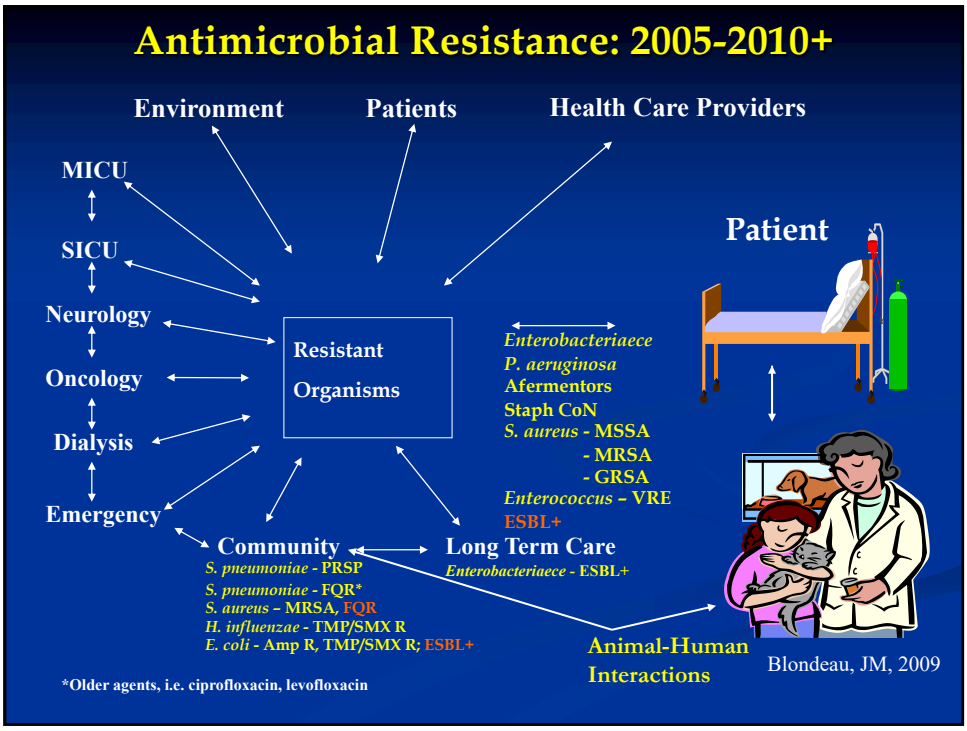
Antimicrobial Susceptibility, Resistance, Length of Therapy and Clinical Outcome: What Have We Learned From In Vitro Measurements

J. M. Blondeau, M.Sc., Ph.D., RSM(CCM), SM(AAM), SM(ASCP), FCCP
Head, Clinical Microbiology
Provincial Lead, Clinical Microbiology
Royal University Hospital & Saskatoon Health Region
Adjunct Professor of Microbiology and Immunology
Clinical Associate Professor of Pathology
Clinical Associate Professor of Ophthalmology
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Evolution of the Antibiotic Era




Evolution of the Antibiotic Era
2005
Niche drugs
MRSA
VRE
2010
Targeted Delivery Drugs
- aerosolized amikacin
3000+ug/ml in lung
- inhaled ciprofloxacin
- others (?)
Clostridium difficile
2006
MDR –GNB
ESBL's
Antimicrobial Resistance


Antimicrobial Resistance: 2005-2010+
Environment
Patients
Health Care Providers
MICU
SICU
Neurology
Oncology
Dialysis
Emergency
Resistant
Organisms
Patient
Enterobacteriaece
P. aeruginosa
Afermentors
Staph CoN
S. aureus - MSSA
- MRSA
- GRSA
Enterococcus – VRE
ESBL+
Community
S. pneumoniae - PRSP
S. pneumoniae - FQR*
S. aureus – MRSA, FQR
H. influenzae - TMP/SMX R
E. coli - Amp R, TMP/SMX R; ESBL+
Long Term Care
Enterobacteriaece - ESBL+
Animal-Human
Interactions
*Older agents, i.e. ciprofloxacin, levofloxacin
Blondeau, JM, 2009

Antimicrobial Resistance: 2005-2010+

Environment
Patients
Health Care Providers
Patient

MICU
SICU
Neurology
Oncology
Dialysis
Emergency

Resistant Organisms

Enterobacteriaece
P. aeruginosa
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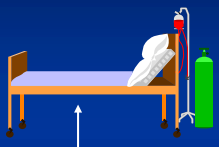
S. aureus - MSSA
- MRSA
- GRSA
Enterococcus – VRE
ESBL+




Community
S. pneumoniae - PRSP
S. pneumoniae - FQR*
S. aureus – MRSA, FQR
H. influenzae - TMP/SMX R
E. coli - Amp R, TMP/SMX R; ESBL+

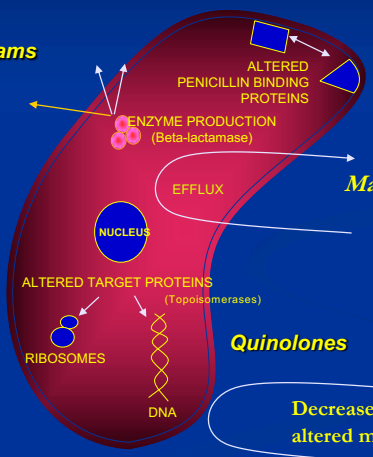
Long Term Care
Enterobacteriaece - ESBL+

Animal-Human Interactions

*Older agents, i.e. ciprofloxacin, levofloxacin

Blondeau, JM, 2017

ANTIMICROBIAL MECHANISMS OF RESISTANCE



Beta-lactams

Beta – lactams:
penicillins,
cephalosporins,
carbapenems,
monobactams

Enzamatic inactivation
-Chloramphenicol
-aminoglycosides

Macrolides, quinolones

Macrolides
-azalides
-triamilides

Quinolones

Decreased uptake/
altered membrane permeability

BACTERIAL CELL

Blondeau, 1998; updated 2009

The Superbug Challenge

Acronym	Definition	Screening	Bacteria	Significance
CRE	Carbapenemase resistant Entero	Carb resistant	Kleb, Pseud, Entero	R to carbapenems
ESBL	Extended spectrum beta-lactamase	R to 3rd gen cephalosporins*	*E. coli*, *Kleb.* Spp. *Enterobacteriaceae*	R to most cephalosporins
MRSA	methicillin R *S. aureus*	R to oxacillin PCR – *mec* A Chromo agar Cefoxitin R	*S. aureus*	R to all beta-lactams**
VRE	vancomycin R *Enterococcus*	Van screen plate PCR-van genes chromo agar	*Enterococcus* spp.	R to vancomycin
VISA	Vancomycin inter *S. aureus*	reduced S to Van	*S. aureus*	reduced S to van
VRSA	Vancomycin R	resistance to Van	*S. aureus*	R to vancomycin

*cefotaxime, cefpodixime, ceftriaxone, ceftazidime
** penicillins, cephalosporins, carbapenems, monobactams

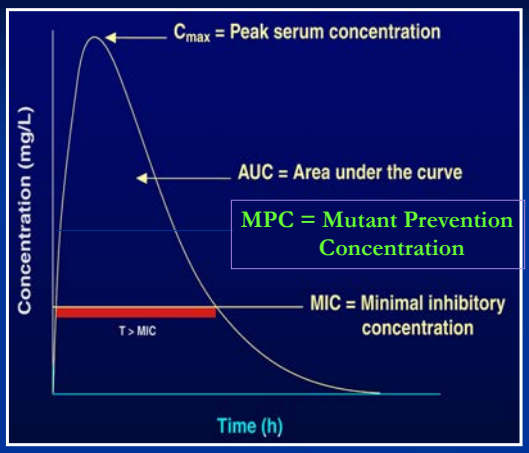
Blondeau, JM, 2013, STAT – Steps to Antimicrobial Therapy, Companion Animals, 2nd Edition: North American Compendium

Contributors to resistance

- Overuse
- Non-clinical use
- Under dosing
- Prolonged therapy
- Incorrect therapy
- Ease of use (minimal side effects)
- Patient expectations
- Susceptibility testing – underestimates
- Breakpoints ?
  - Laboratory
  - clinical
- Prophylactic use without clear benefits
- Empiric use in non-critically ill patients

PK/PD Relationships: Surrogate markers

- Concentration-dependent
  - Peak/MIC >8 - 12
  - AUC/MIC = AUIC
    - >125 Gram –
    - ~30-50 Gram + (??)*
    - >100 Gram +**
  - AUC/MPC = 22***
    - AUIC-PMA
- Time-dependent
  - T > MIC; 40-50%



*Schentag *et al*, (2001), CID; 32 (Suppl. 1):S39-46. Drusano *et al* (2001), CID; 32:2091-2092. Schentag *et al* (2001), CID (Response); 33: 2092-2096.

**File *et al* (2009), for human pathogen *S. pneumoniae*, reported that patients with an acute exacerbation of chronic bronchitis were statistically less likely to progress to pneumonia if the AUIC was >100. Int J Antimicrob Agents 33, 58-64 (2009).

***Oloffson *et al* (2006), J Antimicrob Chemother; 57(6):1116-1121.

Blondeau, updated, 2009

Bacterial Burdens during Infection

CFUs/ml

10^2 10^5 $\geq 10^9$

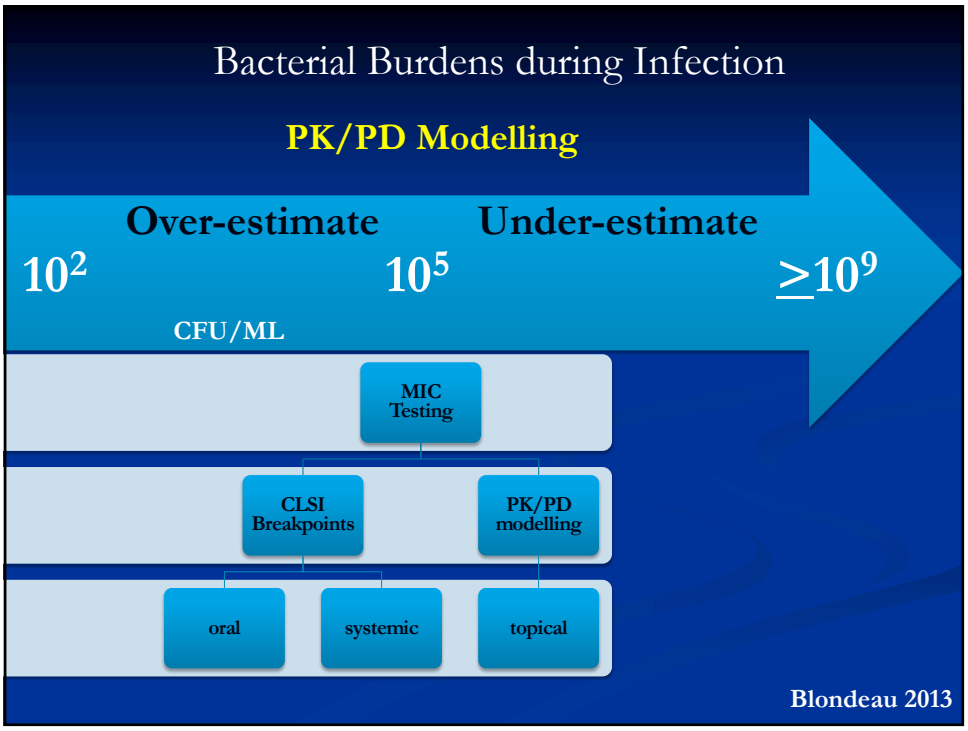
In pneumococcal pneumonia, the total number of bacteria may be as high as 10^{10} to 10^{12}.
Frisch *et al*. J. Exp. Med. 1942; 76:505-510.

Bingen *et al*., Eur J Clin Microbiol Infect Dis 1990;9:278-281
- -2x10 to 4x10^9 CFU/ml in CSF
- -*H. influenzae* type B, *N. meningitidis* , *S. pneumoniae*, *E. coli* K1, *S. agalactiae* had bacterial counts $\geq 10^7$CFU/ml

Fagon *et al*., Am Rev Resp Infect 1990;142:1004-1008
- -10^2 to 10^7 CFU/ml in PBS from patients with ABECB
- -*Haemophilus influenzae* at $\leq 10^7$ CFU/ml
- -*Streptococcus pneumoniae* at $\leq 10^7$ CFU/ml

Feldman, J of Pediatr 1976;88:549-552
- -4.5x10^3 to 3x10^8 CFU/ml in CSF
- -"persistence of + culture may be related to large initial concentrations of bacteria"
- -"relative resistance *in vitro* … large initial concentrations of bacteria"

Blondeau 2013



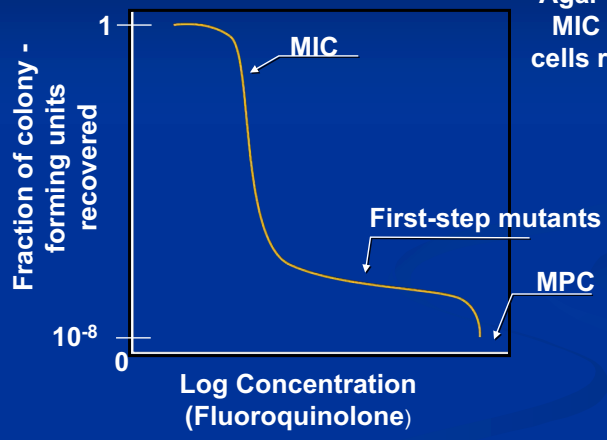
Mutant Prevention Concentration (MPC)

- MPC defines the antimicrobial drug concentration threshold that would require an organism to simultaneously possess two resistance mutations for growth in the presence of the drug
  - Prevents the selection of first step resistant mutants
  - MIC of most resistant cell in the bacterial population
  - Applies only to organisms deemed susceptible by current CLSI guidelines

Blondeau, 2016

MPC Measurement

Method:
Agar dilution as for MIC but apply 10^{10} cells rather than 10^5



Y. Dong et al. (1999) Antimicrob Agents Chemother. 43:1756 – 8.

How Many Bacterial Cells Should We Test to Determine Susceptibility?

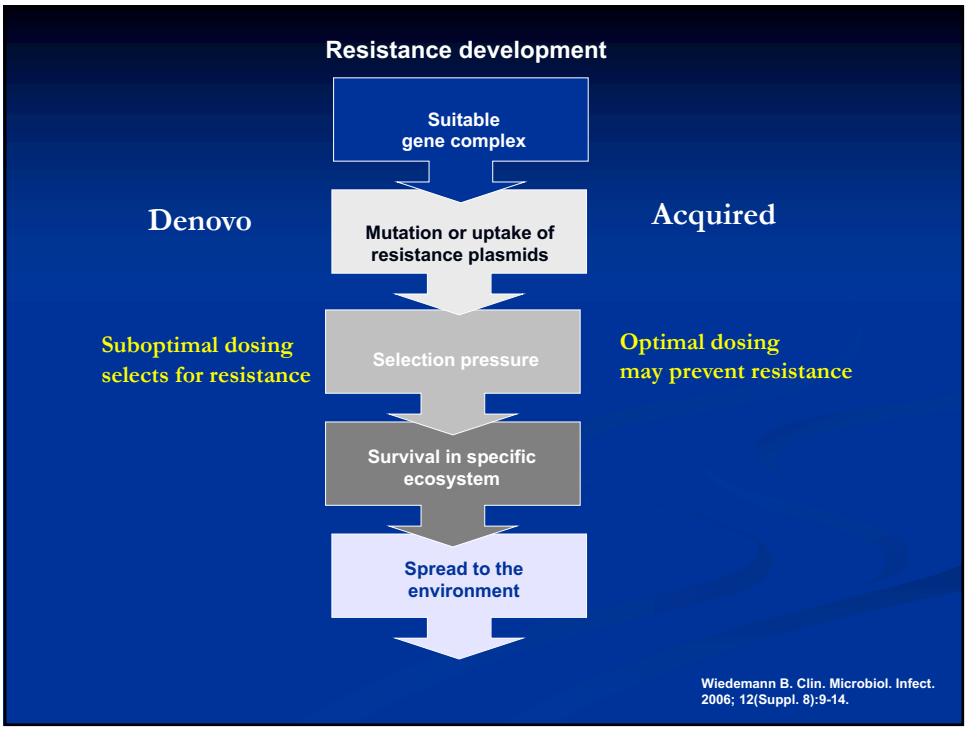
Numbers that may not represent bacterial burdens during infection

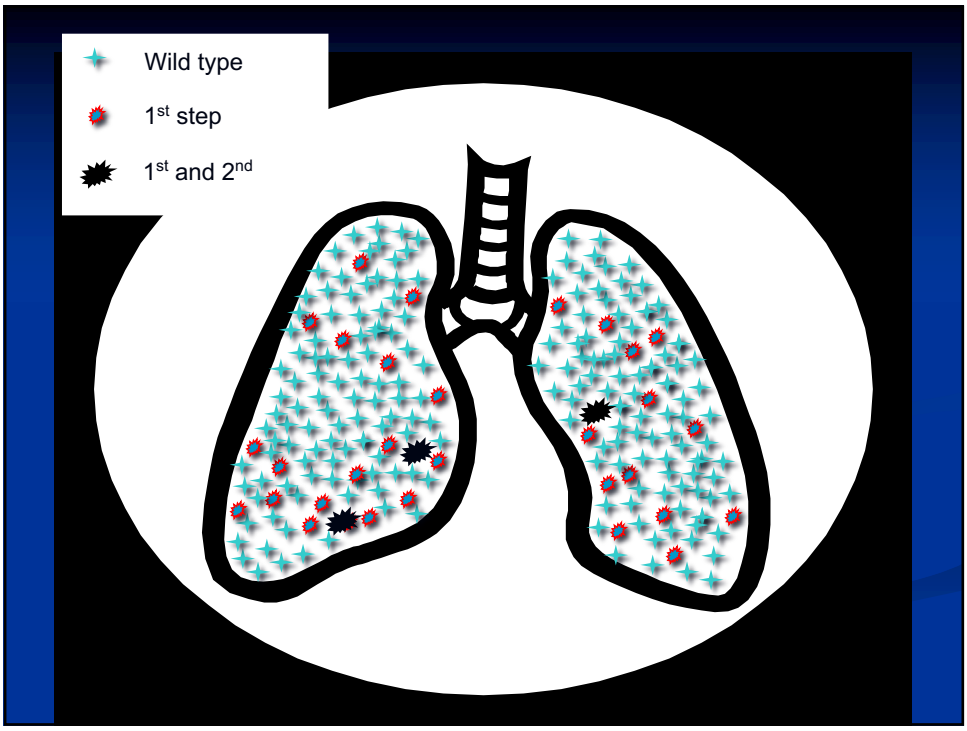
i.e. MPC Testing

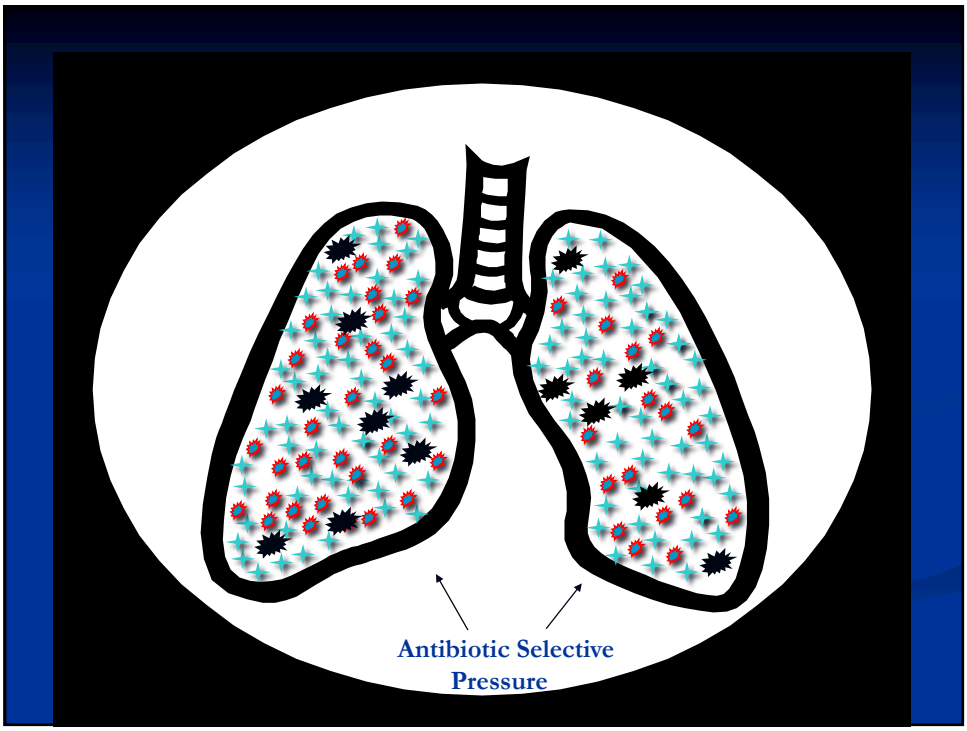
i.e. MIC Testing

Numbers representing bacterial burdens during infection

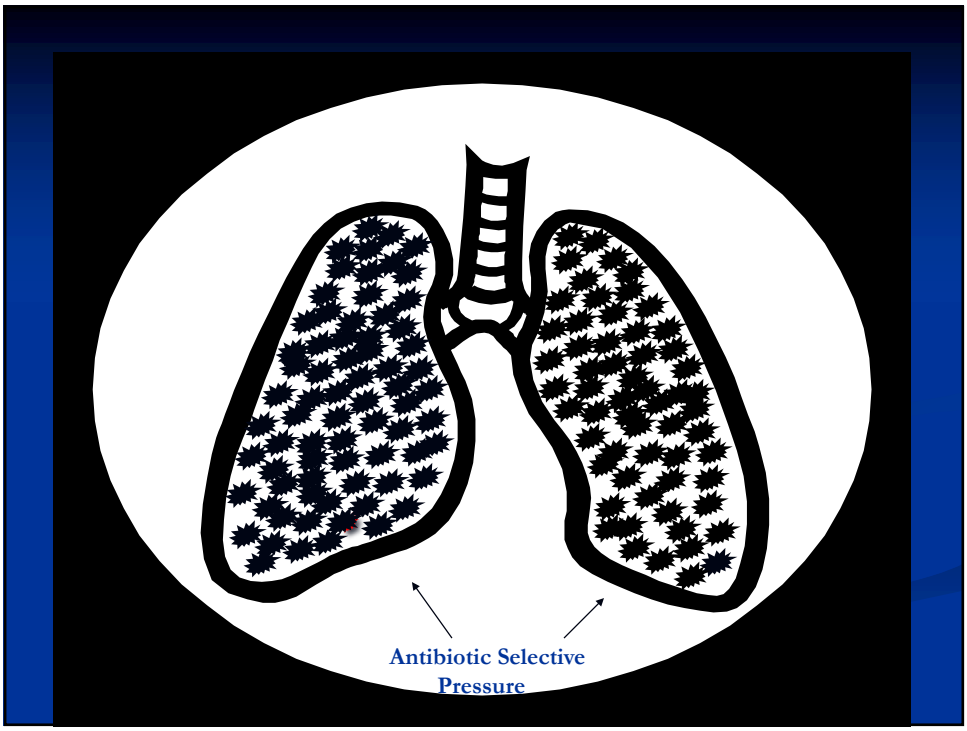
Blondeau, JM, 2012


Resistance development
Suitable gene complex
Denovo
Mutation or uptake of resistance plasmids
Acquired
Suboptimal dosing selects for resistance
Selection pressure
Optimal dosing may prevent resistance
Survival in specific ecosystem
Spread to the environment
Wiedemann B. Clin. Microbiol. Infect. 2006; 12(Suppl. 8):9-14.


Wild type
1st step
1st and 2nd


Antibiotic Selective
Pressure


Antibiotic Selective
Pressure

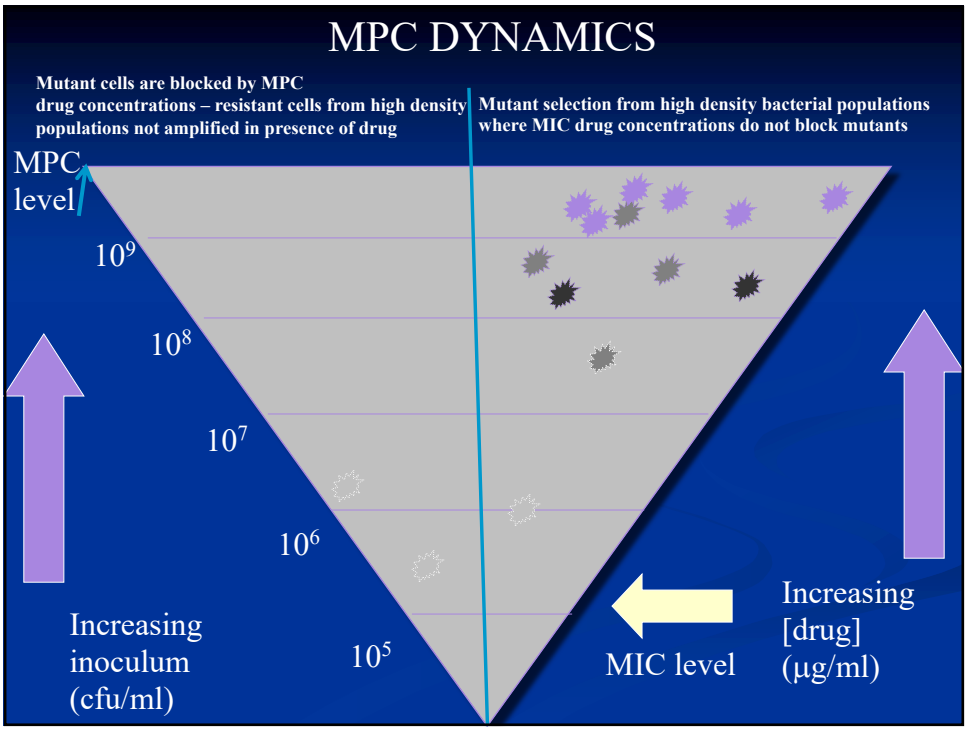


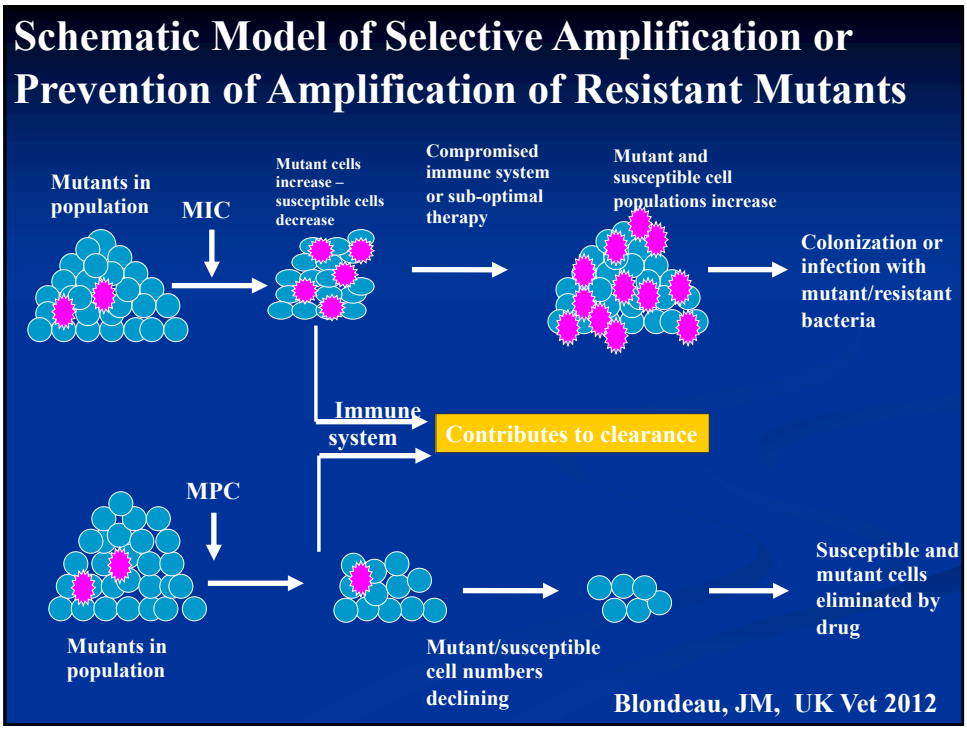
Case 1

- 64 yo M
  - previously good health
  - presented with history and clinical findings of CAP
  - no prior hx of FQ use
  - treated with Lfx 500 mg po 10d
  - sputum grew *S. pneumoniae*
- One week after completing therapy
  - diagnosed with recurrent pneumonia
  - sputum grew *S. pneumoniae*

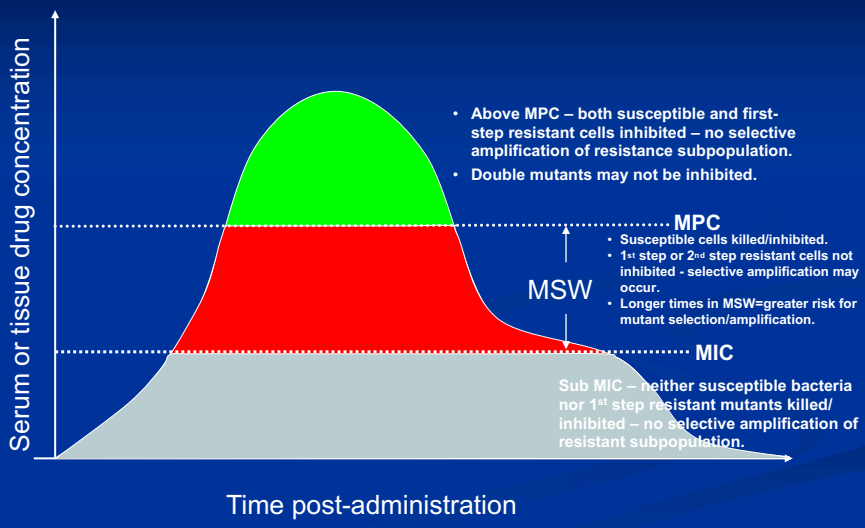
		MICs (µg/ml)			Mutations	
Sputum isolate	PFGE pattern	Levo	Pen	Eryth	*parC*	*gyrA*
Pre-Tx	A	1	<0.06	<0.25	-	-
Post-Tx	A	8	<0.06	<0.25	S79F	S81F

Davidson et al., NEMJ, 2002


MPC DYNAMICS
Mutant cells are blocked by MPC drug concentrations – resistant cells from high density populations not amplified in presence of drug
Mutant selection from high density bacterial populations where MIC drug concentrations do not block mutants
MPC level
10^9
10^8
10^7
10^6
10^5
Increasing inoculum (cfu/ml)
MIC level
Increasing [drug] (µg/ml)

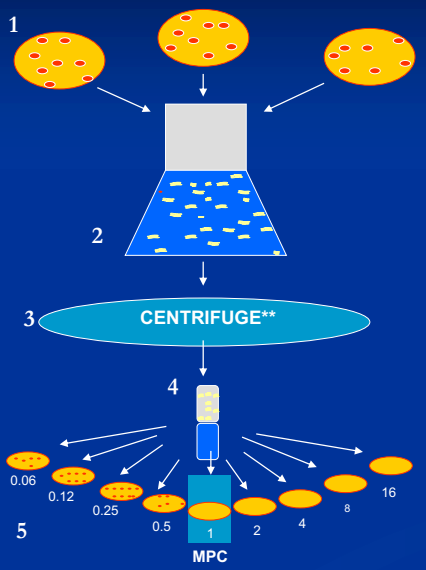

Schematic Model of Selective Amplification or Prevention of Amplification of Resistant Mutants
Mutants in population
MIC
Mutant cells increase – susceptible cells decrease
Compromised immune system or sub-optimal therapy
Mutant and susceptible cell populations increase
Colonization or infection with mutant/resistant bacteria
Immune system
Contributes to clearance
MPC
Mutants in population
Mutant/susceptible cell numbers declining
Susceptible and mutant cells eliminated by drug
Blondeau, JM, UK Vet 2012

Mutant Selection Window (MSW)



Blondeau et al, J. Chemo, 2004; Updated 2009

Schematic Overview of MPC Testing



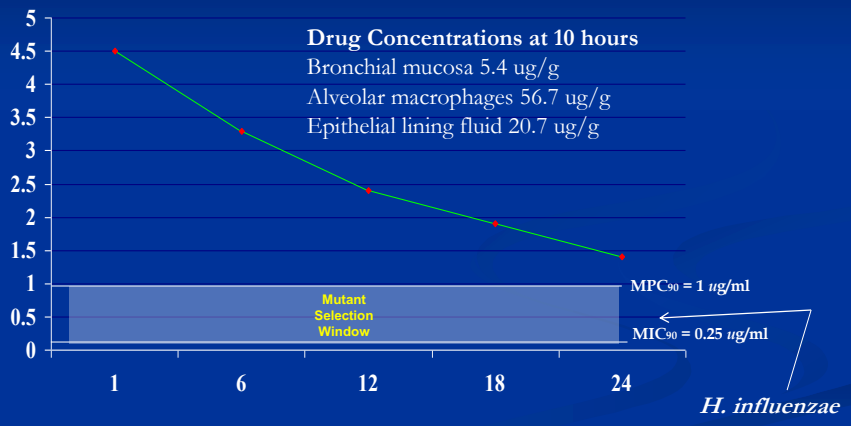
Basic Method (Varies by organism)

- Inoculate plates & incubate
- Transfer to fresh media (~100ml)
- Centrifuge and re-suspend in fresh media
- Inoculate drug containing plates with 10^{10} CFUs.

1. Inoculate 3* plates per organism; incubate 18-24 hrs at 35-37°C in O_2.
2. Transfer contents of plates to flask with 100 ml fresh media. Incubate 18-24 h at 35-37°C in O_2.
3. Centrifuge** culture media at 5000 xg for 30 min at 4°C.
4. Re-suspend in 3 ml of media.
5. Inoculate drug containing plates with 10^{10} organisms; incubate for 18-24 h in O_2, examine for growth, re-incubate for 18-24 h in O_2 and re-examine. The lowest drug concentration preventing = MPC.

Organism	# Starter Plates Inoculated*	Centrifugation Required**
E. coli	2-3	No
S. intermedius	2-3	No
P. multocida	3-4	No
P. aeruginosa	2-3	No
M. haemolytica	4-5	Yes

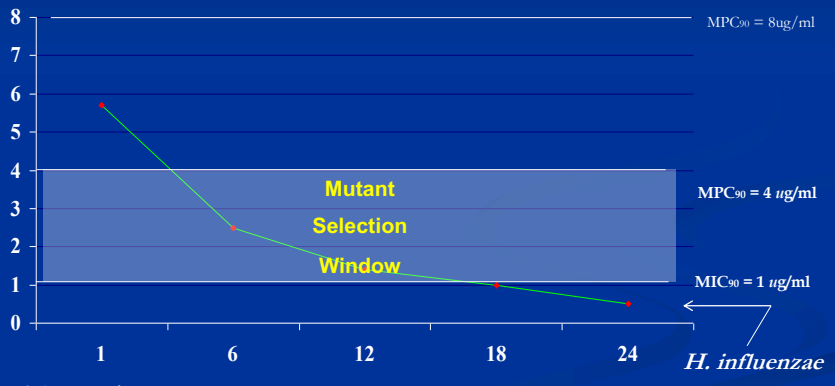
Relationship of serum concentration of moxifloxacin to MPC for *Streptococcus pneumoniae*



Wise, R. Clin Drug Invest 1999; 17:365-387.

Blondeau *et al*, ACC 2001; Hansen et al, AAC 2003; Blondeau et al, J. Chemo, 2004

Relationship of serum concentration of levofloxacin to MPC for *Streptococcus pneumoniae*



Fisher *et al*, 1999.

Blondeau *et al*, ACC 2001; Hansen et al, AAC 2003; Blondeau et al, J. Chemo, 2004

J Antimicrob Chemother 2013; **68**: 631–635
doi:10.1093/jac/dks461 Advance Access publication 20 November 2012

Journal of Antimicrobial Chemotherapy

Minimal inhibitory and mutant prevention concentrations of azithromycin, clarithromycin and erythromycin for clinical isolates of *Streptococcus pneumoniae*

Kelli Metzler[1], Karl Drlica[2] and Joseph M. Blondeau[1,3]*

[1]Departments of Pathology, Microbiology and Immunology and Ophthalmology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; [2]Public Health Research Institute Center and Department of Microbiology & Molecular Genetics, New Jersey Medical School, UMDNJ, Newark, NJ, USA; [3]Department of Clinical Microbiology, Royal University Hospital and the Saskatoon Health Region, Saskatoon, Saskatchewan, Canada

MPC of macrolides for *Streptococcus pneumoniae*

	T>MPC$_{90}$	T$_{MSW}$
Az	0	24
Cl	24	0
Er	1-5	13

JAC

Table 1. MIC/MPC distribution for azalide/macrolide compounds with clinical isolates of *Streptococcus pneumoniae* (n=191)

	MIC distribution data[a]											
Compound	≤0.16	0.031	0.063	0.125	0.25	0.5	1	2	4	≥8	MIC$_{50}$[b]	MIC$_{90}$[b]
Azithromycin	0	15	63	91	20	2					0.125	0.25
Clarithromycin	57	105	28	1							0.031	0.063
Erythromycin	1	23	111	49	7						0.063	0.125
	MPC distribution data[a]											
	≤0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	≥8	MPC$_{50}$[c]	MPC$_{90}$[c]
Azithromycin				1	10	46	63	37	18	16	1	4
Clarithromycin			49	61	45	17	10	3	5	1	0.125	0.5
Erythromycin			1	20	83	43	20	9	4	11	0.25	2

p=0.03-<0.0001

[a]The heading row shows drug concentrations (mg/L); for each drug, the number of isolates for a given concentration is listed in the body of the table.
[b]Drug concentration at which 50% or 90% of strains, respectively, are inhibited.
[c]Drug concentration at which growth was inhibited for 50% or 90% of strains, respectively, based on inoculum ≥10^9 cfu.

Veterinary Microbiology 160 (2012) 85–90

Contents lists available at SciVerse ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Comparative minimum inhibitory and mutant prevention drug concentrations of enrofloxacin, ceftiofur, florfenicol, tilmicosin and tulathromycin against bovine clinical isolates of *Mannheimia haemolytica*

J.M. Blondeau *, S. Borsos, L.D. Blondeau, B.J.J. Blondeau, C.E. Hesje

Department of Clinical Microbiology, Royal University Hospital and the Saskatoon Health Region, Departments of Microbiology and Immunology, Pathology and Ophthalmology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

	T>MPC90	T in MSW
Enro	~18 hours	~6 hrs
Ceft	?	?
Tul	0 hours	>24 hrs
Til	0 hours	>24 hrs

Table 1
Comparative MIC and MPC values for 285 *M. haemolytica* strains collected from cattle.

Drug	MIC/MPC distribution values (μg/ml)													
	≤0.008	0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	8	≥16	≥32	MIC$_{50}$/MIC$_{90}$
MIC distribution														
Ceftiofur[a]	17	22	2											0.016/0.016
Enrofloxacin	31	114	16	39	85									0.016/0.125
Florfenicol							5	120	160					2/2
Tilmicosin						3	64	56	82	38	42			2/8
Tulathromycin					2	15	53	98	117					1/2
MPC distribution														MPC$_{50}$/MPC$_{90}$
Ceftiofur[a]						2	1	19	15	4				1/2
Enrofloxacin			4	31	59	59	49	65	18					0.25/1
Florfenicol								8	64	142	55	16		4/8
Tilmicosin									1	60	58	87	79	16/≥32
Tulathromycin								3	61	138	77	6		4/8

MIC and MPC distribution values are shown. The calculation of MIC$_{50}$ and MIC$_{90}$ – the drug concentration at which 50% or 90% respectively of the strains are inhibited – allows comparison of the various agents for *in vitro* potency. Similarly, the calculation of MPC$_{50}$ and MPC$_{90}$ – the drug concentration preventing the growth of mutant subpopulation for 50% or 90% respectively of the strains tested – allows a similar comparison of *in vitro* potency for mutant prevention.
[a] Testing against 41 isolates.

PLOS ONE

Jan10th, 2019

RESEARCH ARTICLE

Mutant prevention and minimum inhibitory concentration drug values for enrofloxacin, ceftiofur, florfenicol, tilmicosin and tulathromycin tested against swine pathogens *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Streptococcus suis*

Joseph M. Blondeau[1,2]*, **Shantelle D. Fitch**[1]

1 Department of Clinical Microbiology, Royal University Hospital and the Saskatchewan Health Authority, Saskatoon, Saskatchewan, Canada, 2 Departments of Microbiology and Immunology, Pathology and Ophthalmology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

* joseph.blondeau@saskhealthauthority.ca

Check for updates

Table 1. MIC and MPC values for 67 *A. pleuropneumoniae* isolates from swine.

Drug	MIC/MPC Distribution Values (mg/L)													
	≤0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	≥64	
MIC Distribution														$MIC_{50/90}$
Ceftiofur	46	19	2											≤0.016/0.031
Enrofloxacin	67													≤0.016/≤0.016
Florfenicol					30	36	1							0.5/0.5
Tilmicosin							2	49	15	1				2/4
Tulathromycin						5	54	7		1				1/2
MPC Distribution														$MPC_{50/90}$
Ceftiofur	2	15	26	11	5	2	6							0.063/0.5
Enrofloxacin			25	18	14	10								0.125/0.5
Florfenicol					1	48	9	6	3					0.5/2
Tilmicosin										11	13	41	2	32/32
Tulathromycin										1	10	56		32/32

https://doi.org/10.1371/journal.pone.0210154.t001

Table 2. MIC and MPC values for 73 *P. multocida* isolates from swine.

Drug	MIC/MPC Distribution Values (mg/L)													
	≤0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	≥64	
MIC Distribution														$MIC_{50/90}$
Ceftiofur	72	1												≤0.016/≤0.016
Enrofloxacin	73													≤0.016/≤0.016
Florfenicol					21	48	4							0.5/0.5
Tilmicosin							7	35	25	4				2/4
Tulathromycin			1	9	38	21	4							0.25/0.5
MPC Distribution														$MPC_{50/90}$
Ceftiofur		14	16	22	17	1								0.125/0.25
Enrofloxacin		19	34	15										0.063/0.125
Florfenicol					1	12	59	1						1/1
Tilmicosin								2	13	38	15	4	1	8/16
Tulathromycin						19	47	3	3	1				1/1

https://doi.org/10.1371/journal.pone.0210154.t002

Blondeau and Fitch, PLOS ONE, Jan, 2019

Table 3. Comparative MIC values for 59 *S. suis* strains collected from swine.

Drug	MIC Distribution Values (mg/L)									$MIC_{50/90}$
	0.031	0.063	0.125	0.25	0.5	1	2	4	≥8	
Ceftiofur	6	29	3	1	3	3	4	1	9	0.063/1
Enrofloxacin		1	4	28	23	1		2		0.25/0.5
Florfenicol							29	30*		≥4/≥4
Tilmicosin						1			58	≥4/≥4
Tulathromycin									59	≥4/≥4

*≥4 mg/L

https://doi.org/10.1371/journal.pone.0210154.t003

Bactericidal effects of various concentrations of enrofloxacin, florfenicol, tilmicosin phosphate, and tulathromycin on clinical isolates of *Mannheimia haemolytica*

Joseph M. Blondeau PhD
Shantelle D. Shebelski BSc
Christine K. Hesje MSc

Received October 2, 2014.
Accepted January 8, 2015.

From the Department of Clinical Microbiology, Royal University Hospital (Blondeau, Shebelski), and the Departments of Microbiology and Immunology (Blondeau, Hesje), Pathology and Laboratory Medicine (Blondeau), and Ophthalmology (Blondeau), College of Medicine, University of Saskatchewan, Saskatoon, SK S7N 5B4, Canada; and the Saskatoon Health Region, 701 Queen St, Saskatoon, SK S7N 0W8, Canada (Blondeau).

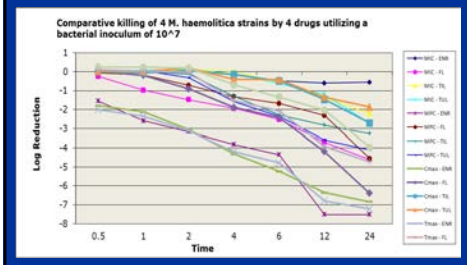
Address correspondence to Dr. Blondeau (joseph.blondeau@saskatoonhealthregion.ca).

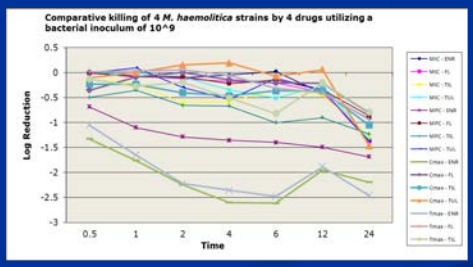
OBJECTIVE
To determine bactericidal effects of enrofloxacin, florfenicol, tilmicosin, and tulathromycin on clinical isolates of *Mannheimia haemolytica* at various bacterial densities and drug concentrations.

SAMPLE
4 unique isolates of *M haemolytica* recovered from clinically infected cattle.

PROCEDURES
Minimum inhibitory concentration (MIC) and mutant prevention concentration (MPC) were determined for each drug and isolate. *Mannheimia haemolytica* suspensions (10^6 to 10^9 CFUs/mL) were exposed to the determined MIC and MPC and preestablished maximum serum and tissue concentrations of each drug. Log_{10} reduction in viable cells (percentage of cells killed) was measured at various points.

RESULTS





MPC 2 hrs Enro vs Til p=0.04
MPC 12 hrs Enro vs Flor, Til, Tul p<0.0001-0.0007
MPC 24 hrs Enro vs Til, Tul p=0.001-0.01
Cmax 2,4,6 12 hrs Enro vs Flor, Til, Tul p <0.0001-0.05
Cmax 12, 24 hrs Flor vs Til Tul p<0.0001-0.001
Cmax 24 hrs Enro vs Til, Tul p<0.0001

Cmax 1,2, 4, 6, 12 Enro vs Flor, Til, Tul p <0.0001-0.001
Cmax 24 hrs Enro vs Flor p=0.007
Tiss max 1, 2,4,6,12, 24 hrs Enro vs Til, Tul p<0.0001-0.02

AJVR • Vol 76 • No. 10 • October 2015

Veterinary Dermatology

Vet Dermatol 2016; **27**: 267–e63 DOI: 10.1111/vde.12334

Comparative *in vitro* killing of canine strains of *Staphylococcus pseudintermedius* and *Escherichia coli* by cefovecin, cefazolin, doxycycline and pradofloxacin

Joseph M. Blondeau*† and Shantelle D. Shebelski*

*Division of Clinical Microbiology, Royal University Hospital and Saskatoon Health Region, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8, Canada.
†Departments of Microbiology and Immunology, Pathology and Ophthalmology, University of Saskatchewan, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8, Canada.
Correspondence: Joseph M. Blondeau, Division of Clinical Microbiology, Royal University Hospital and Saskatoon Health Region, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8, Canada. E-mail: joseph.blondeau@saskatoonhealthregion.ca

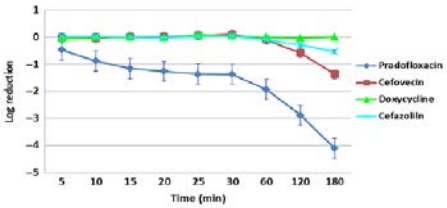


Figure 4. Log_{10} reduction in *Staphylococcus pseudintermedius* viable cells exposed to cefazolin, cefovecin, doxycycline and pradofloxacin at the maximum tissue drug concentration*. *Statistically significant observations: (i) pradofloxacin versus cefazolin ($P = 0.0043$), cefovecin ($P = 0.0522$), doxycycline ($P = 0.0014$); (ii) pradofloxacin versus cefazolin, cefovecin and doxycycline at lines 15, 20, 25, 30 and 60 min (*P*-values ranged from ≤0.0001 to 0.0008); (iii) pradofloxacin versus cefazolin ($P = 0.0002$) and doxycycline ($P = ≤0.0001$) at 120 min; (iv) pradofloxacin versus cefazolin ($P = 0.015$) and doxycycline ($P ≤ 0.0001$) at 120 min; (v) doxycycline versus cefovecin ($P = 0.0003$) at 120 min.

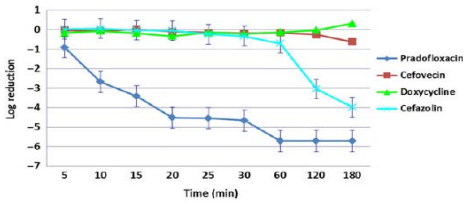
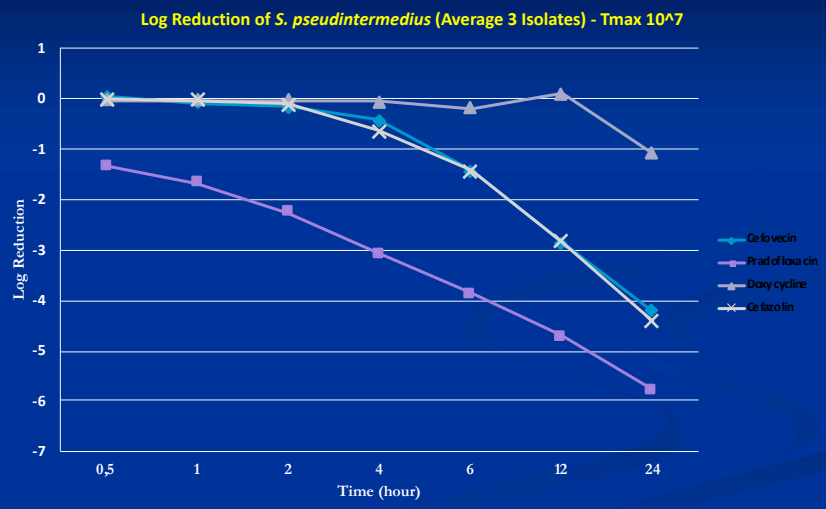
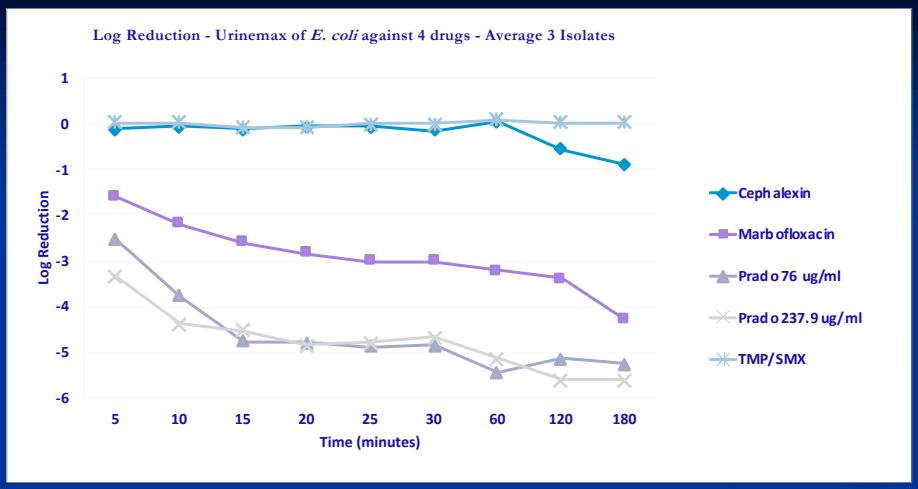


Figure 8. Log_{10} reduction in *Escherichia coli* viable cells exposed to cefazolin, cefovecin, doxycycline and pradofloxacin at the maximum tissue drug concentration*. *Statistically significant observations: (i) pradofloxacin versus cefovecin ($P = 0.0349$) at 5 min; (ii) pradofloxacin versus cefazolin, cefovecin and doxycycline at 10, 15, 20 and 25 min (*P*-values ranging from ≤0.0001 to 0.0181); (iii) pradofloxacin versus cefovecin ($P = 0.0033$) at 30 min; (iv) pradofloxacin versus cefovecin and doxycycline at 60 and 120 min (*P* value ranging from ≤0.0001 to 0.0012); (v) pradofloxacin versus doxycycline ($P ≤ 0.0001$) at 180 min; (vi) doxycycline versus cefazolin ($P ≤ 0.0001$) and cefovecin ($P = 0.0057$) at 180 min.

Currently under review in Vet Dermatology….



6 hours pradofloxacin vs doxycycline p=0.0001
12 hours cefazolin, cefovecin, pradofloxacin vs doxycycline p=0.0017-p<0.0001



5 minutes: pradofloxacin/marbofloxacin vs cephalexin/TMP/SMX, p<0.0001
180 minutes: pradofloxacin/marbofloxacin vs TMP/SMX, p<0.0001; cephalexin vs TMP/SMX p=0.0008

Veterinary Dermatology

Vet Dermatol 2014; **25**: 163–e43 DOI: 10.1111/vde.12118

Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases)

Andrew Hillier*, David H. Lloyd†, J. Scott Weese‡, Joseph M. Blondeau§, Dawn Boothe¶, Edward Breitschwerdt, Luca Guardabassi††, Mark G. Papich**, Shelley Rankin‡‡, John D. Turnidge§§ and Jane E. Sykes¶¶**

infection. Most studies evaluating the efficacy of AMDs indicate that SBF infections are resolved after 3 weeks or more of systemic AMD treatment; rapid improvement over the first 1–2 weeks is typically observed, but resolution of all lesions and prevention of rapid recurrence of disease requires 3–6 weeks of treatment.[17–22,28] Although there is no significant difference in the likelihood of resolution of MSSP after 3–4 weeks of systemic AMD treatment compared with MRSP infections, it has been reported that MRSP infections took longer to treat compared with MSSP infections.[60]

Journal of Veterinary Internal Medicine ACVIM Open Access

Guideline and Recommendation

J Vet Intern Med 2017;31:279–294

Antimicrobial use Guidelines for Treatment of Respiratory Tract Disease in Dogs and Cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases

M.R. Lappin, J. Blondeau, D. Boothe, E.B. Breitschwerdt, L. Guardabassi, D.H. Lloyd, M.G. Papich, S.C. Rankin, J.E. Sykes, J. Turnidge, and J.S. Weese

Monitoring Treatment of Bacterial Pneumonia

The current recommendation in most veterinary textbooks is to treat bacterial pneumonia for 4–6 weeks, but evidence to support this duration of treatment in either cats or dogs is lacking. Although such lengthy courses of antimicrobial treatment might be necessary for some animals with severe pulmonary involvement or

Research Article

Antimicrobial Use Guidelines for Treatment of Urinary Tract Disease in Dogs and Cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases

J. Scott Weese,[1] Joseph M. Blondeau,[2] Dawn Boothe,[3] Edward B. Breitschwerdt,[4] Luca Guardabassi,[5] Andrew Hillier,[6] David H. Lloyd,[7] Mark G. Papich,[4] Shelley C. Rankin,[8] John D. Turnidge,[9,10] and Jane E. Sykes[11]

Adequate evidence regarding duration of treatment is lacking, precluding the ability to make a specific recommendation for treatment duration. Typically, uncomplicated UTIs are treated for 7–14 days. However, the Working Group acknowledges the likelihood that a shorter treatment time (≤7 days) may be effective. Accordingly, in the absence of objective data, 7 days of appropriate antimicrobial treatment is reasonable. Clinical trials supporting shorter durations for treatment of UTIs in dogs and cats are strongly encouraged.

CMAJ • FEB. 17, 2004; 170 (4) 469

Research
Recherche

Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial

Thomas Vogel, René Verreault, Marie Gourdeau, Michèle Morin, Lise Grenier-Gosselin, Louis Rochette

Results: The proportion of patients with bacterial eradication at 2 days after treatment was 98% (91/93) in the 3-day group and 93% (83/89) in the 7-day group ($p = 0.16$). The frequency of adverse events, including drowsiness, headache, nausea or vomiting, and loss of appetite, was significantly lower in the 3-day group.

Interpretation: These results suggest that a 3-day course of antibiotic therapy is not inferior to a 7-day course for treatment of uncomplicated symptomatic UTI in older women, and that the shorter course is better tolerated.

Table 2: Therapeutic efficacy at 2 days and 6 weeks after completion of treatment

Measure of efficacy	No. (and %) of subjects: 3-day group	7-day group	*p* value
2 days after treatment			
Bacterial eradication	91/93 (98)	83/89 (93)	0.16
Symptom improvement*			
Nocturia (≥ 1/night)	64/73 (88)	57/69 (83)	0.86
Urgency	35/48 (73)	43/49 (88)	0.05
Frequency	24/33 (73)	27/35 (77)	0.44
Burning on micturation	31/31 (100)	33/34 (97)	0.99
Suprapubic pain	12/14 (86)	21/25 (84)	0.71
6 weeks after treatment			
Reinfection	13/93 (14)	16/89 (18)	0.54
Relapse	14/93 (15)	12/89 (13)	0.83

*Among subjects who presented the symptom at baseline (time of entry into the study) and who also provided information on symptom relief at follow-up.

Respiratory Medicine (2010) 104, 1396–1403

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

Short-course fluoroquinolone therapy in exacerbations of chronic bronchitis and COPD

Antonio Anzueto [a,*], Marc Miravitlles [b]

[a] Department of Medicine, Pulmonary Disease, 111E, 7400 Merton Minter Boulevard, The University of Texas Health Science Center at San Antonio, South Texas Veterans Health Care System, San Antonio, TX 78229, USA
[b] Fudació Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, 08036 Barcelona, Catalonia, Spain

Received 28 October 2009; accepted 26 May 2010

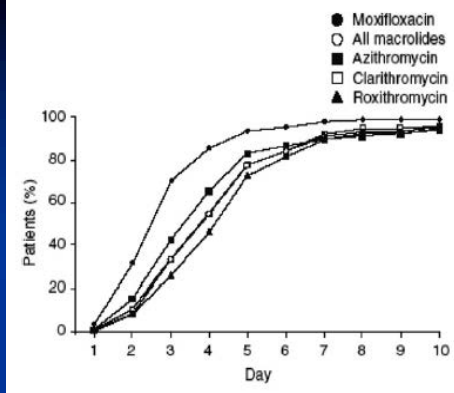


Figure 2 Improvement rate over the first 10 days of observation. Mean duration until improvement in moxifloxacin-treated patients was 3.2 days compared with 4.5 days in macrolide-treated patients. The difference of 1.2 days was statistically significant ($P < 0.0001$).[44] Reproduced with

greater clinical success. Evidence suggests that short-course antimicrobial therapy can be as effective as standard duration therapy (>7 days) in treating exacerbations. Randomized trials have shown that clinical and bacteriological success rates are comparable with both 5-day and standard antibiotic courses. Furthermore, 5-day fluoroquinolone therapy is associated with faster recovery, fewer relapses, prolonged duration between episodes, and less hospitalization when compared with standard therapy. Both moxifloxacin and gemifloxacin have received FDA-approval for 5-day therapy in AECB.

LUNG ALERT

Short course antibiotics in community acquired pneumonia

▲ El Moussaoui R, de Borgie CA, van den Broek P, *et al.* Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006;**332**:1355–8

This Dutch study, undertaken between November 2000 and July 2003, took adults with a pneumonia severity index score of ⩽110 and randomly assigned those who substantially improved after 72 hours of intravenous amoxicillin to either 750 mg oral amoxicillin (n = 63) or placebo (n = 56) three times daily for 5 days thereafter.

Clinical, bacteriological and radiological outcomes were assessed. The clinical success rate at day 10 (per protocol analysis) was 93% in both groups (50/54 in the 3 day treatment group and 56/60 in the 8 day treatment group: difference 0.1% (95% CI −9 to 10)). At day 28 clinical success rates were 90% (47/52) in the 3 day treatment group and 88% (49/56) in the 8 day treatment group (difference 2% (95% CI −9 to 15)). There was therefore little difference between the two groups.

This study suggests that a short course of antibiotic therapy is not inferior to a longer course in patients with mild to moderate-severe uncomplicated community acquired pneumonia who show clinical improvement after 3 days of intravenous antibiotics.

UROLOGIA DEL CANE

Valutazione della velocità di guarigione clinica e batteriologica della pradofloxacina nei cani affetti da **infezioni delle vie urinarie non complicate**

SUMMA animali da compagnia N° 5 Giugno 2017

Andrea Vercelli*, **José M. Mottet****
*Ambulatorio Veterinario Associato, Corso Traiano 99/d, Torino
**Bayer Animal Health GmbH, Monheim (Germany)

Figura 1. Distribuzione degli uropatogeni isolati dai cani affetti da UTI non complicata il giorno 0

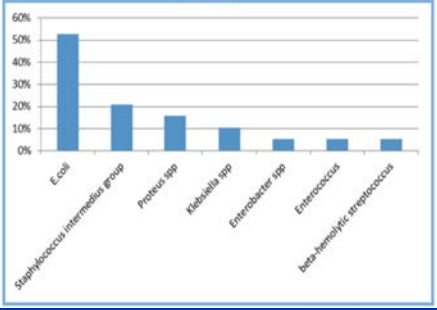
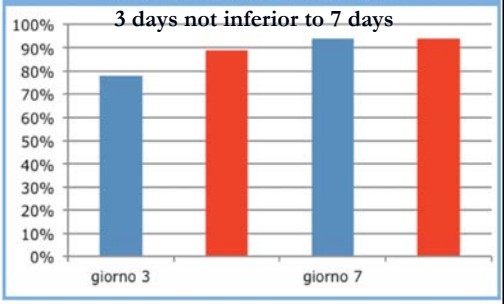


Figura 2. Tassi di cura clinica (colore blu) e batteriologica (colore rosso) dei cani trattati con pradofloxacina il giorno 3 ed il giorno 7



Are all antibiotics the same…

- NO
  - Bactericidal vs bacteriostatic
  - Distribution
  - Serum versus tissue
  - Rate of kill
  - Protein binding >60%
- Could choice of antibiotic influence duration of therapy?
  - Faster kill…shorter durations of therapy?

Change in Thinking!!!!!

Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.

Mandell LA, Wunderink RG, Anzueto A *et al.* Infectious Disease Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. *Clin. Infect. Dis.* 44(Suppl. 2), S27-S72 (2007).

Future MICROBIOLOGY

EDITORIAL

Antimicrobial resistance & 'Man's best friend': what they give to us we might be giving right back

"Antimicrobial resistance follows antimicrobial use…"

Joseph M Blondeau*[,1]

First draft submitted: 9 March 2017; Accepted for publication: 15 March 2017; Published online: 12 June 2017

Zoonotic Diseases: Animal to Human
Zooanthroponosis: Reverse Zoonotic Disease Transmission; Human to Animal

Future MICROBIOLOGY

Editorial

The 24-h clinical microbiology service is essential for patient management

Joseph M Blondeau*[,1,2] & Evgeny A Idelevich[3]
[1]Department of Clinical Microbiology, Royal University Hospital & Saskatchewan Health Authority; Saskatoon, Saskatchewan, Canada
[2]Departments of Microbiology & Immunology, Pathology & Ophthalmology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
[3]Institute of Medical Microbiology, University Hospital Münster, Münster, Germany
*Author for correspondence: Tel.: +1 306 655 6943; Fax: +1 306 655 6947; joseph.blondeau@saskhealthauthority.ca

"optimal patient care requires access to necessary laboratory testing including clinical microbiology. A rethinking of hours of operation is required to shorten time to accurate result reporting."

First draft submitted: 14 August 2018; Accepted for publication: 15 October 2018; Published online: 14 November 2018

Antimicrobial Stewardship and optimization of therapy requires timely information!

Key Points

- Antibiotics impact morbidity/mortality
- Misuse/overuse contributes to antimicrobial resistance
- MIC testing may contribute to resistance
- Not all antimicrobials are equivalent
- Durations of therapy may be too long for many infectious diseases---contributions to resistance?
- Mixed bacterial infections…impact on antibiotics (ECCMID, 2019…1st abstract)
- Drug combinations?