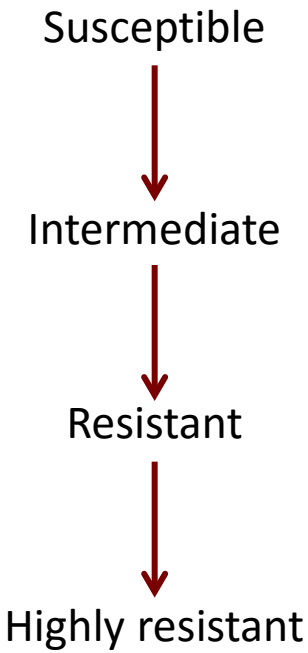
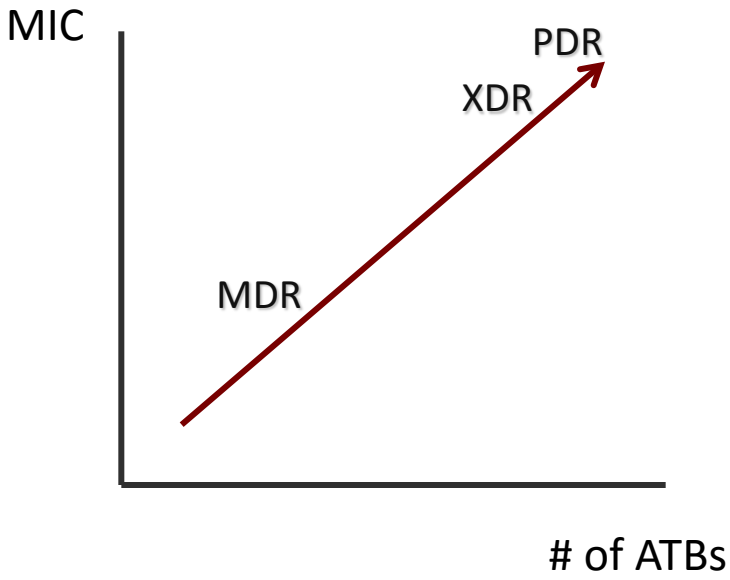
Infections à *P. aeruginosa* :

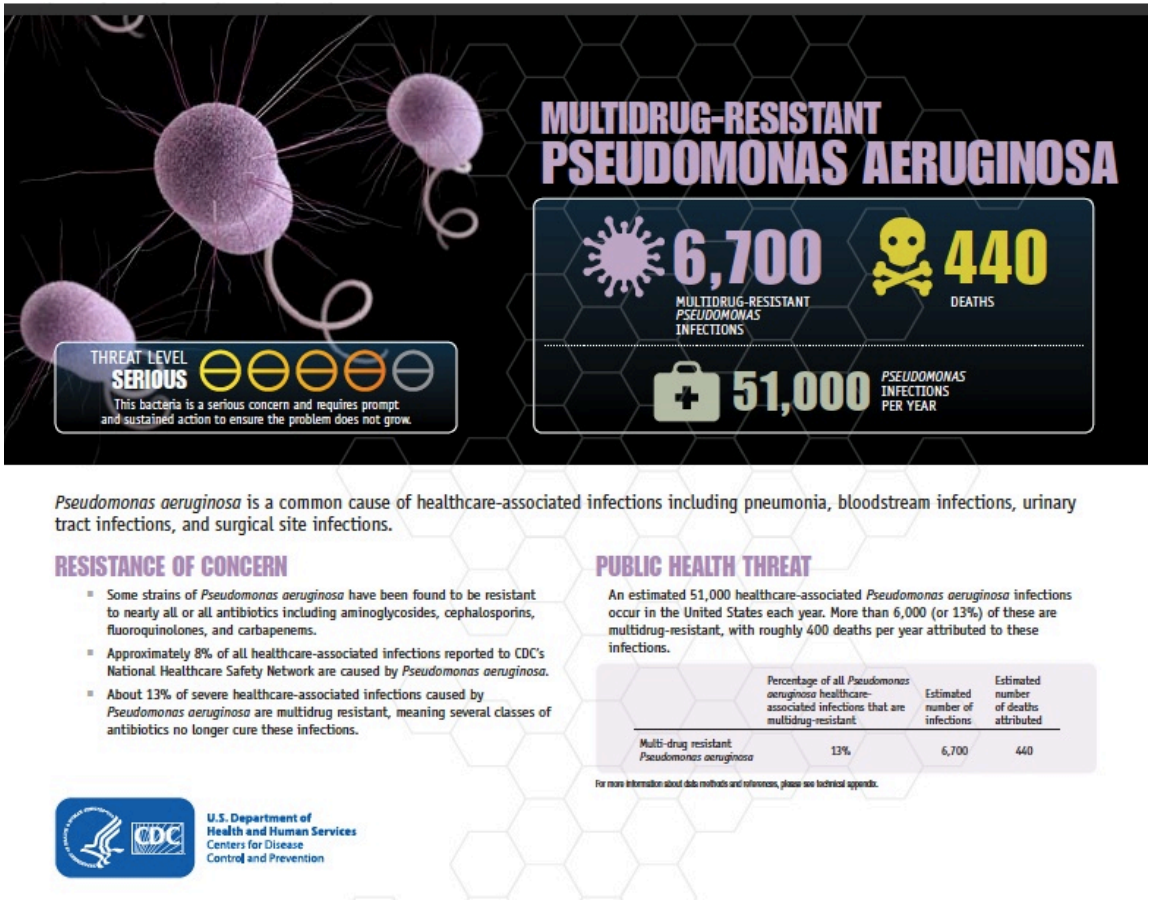
Quand la monothérapie s'impose

P. Plésiat
National Reference Center for Antibiotic Resistance
Minjoz University Hospital
Besançon, France

Trends in evolution of antibiotic resistance







BURDEN 2012, France:

Carbapenem^{r} *P. aeruginosa* responsible for:

- 36,757 out of 157,652 nocomial infections with mdr bacteria (23.3%)
- 6,610 out of 12,500 deaths (53.3%)

CDC 2014

DRUGS	EUCAST	
	S ≤	R >
Piperacillin ± tazobactam	16	16
Ticarcillin ± clavulanate	16	16
Cefepime	8	8
Ceftazidime	8	8
Imipenem	4	8
Meropenem	2	8
Doripenem	1	4
Aztreonam **(I)**	1	16
Ciprofloxacin	0.5	1
Levofloxacin	1	2
Amikacin	8	16
Gentamicin	4	4
Netilmicin	4	4
Tobramycin	4	4
Colistin	4	4
Fosfomycin (IV)	128	128

Magiorakos *et al.* CMI 2011, 18:268

DRUGS	EUCAST	
MDR	S ≤	R >
Piperacillin ± tazobactam	16	16
Ticarcillin ± clavulanate **R**	16	16
Cefepime	8	8
Ceftazidime	8	8
Imipenem	4	8
Meropenem	2	8
Doripenem	1	4
Aztreonam **(I)**	1	16
Ciprofloxacin	0.5	1
Levofloxacin **I/R**	1	2
Amikacin	8	16
Gentamicin **R**	4	4
Netilmicin	4	4
Tobramycin	4	4
Colistin	4	4
Fosfomycin (IV)	128	128

DRUGS	EUCAST	
XDR	S ≤	R >
Piperacillin ± tazobactam R	16	16
Ticarcillin ± clavulanate **R**	16	16
Cefepime R	8	8
Ceftazidime	8	8
Imipenem I/R	4	8
Meropenem I/R	2	8
Doripenem	1	2
Aztreonam **(I)**	1	16
Ciprofloxacin I/R	0.5	1
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Gentamicin **R**	4	4
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Tobramycin R	4	4
Colistin	4	4
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DRUGS	EUCAST	
PDR	S ≤	R >
Piperacillin ± tazobactam R	16	16
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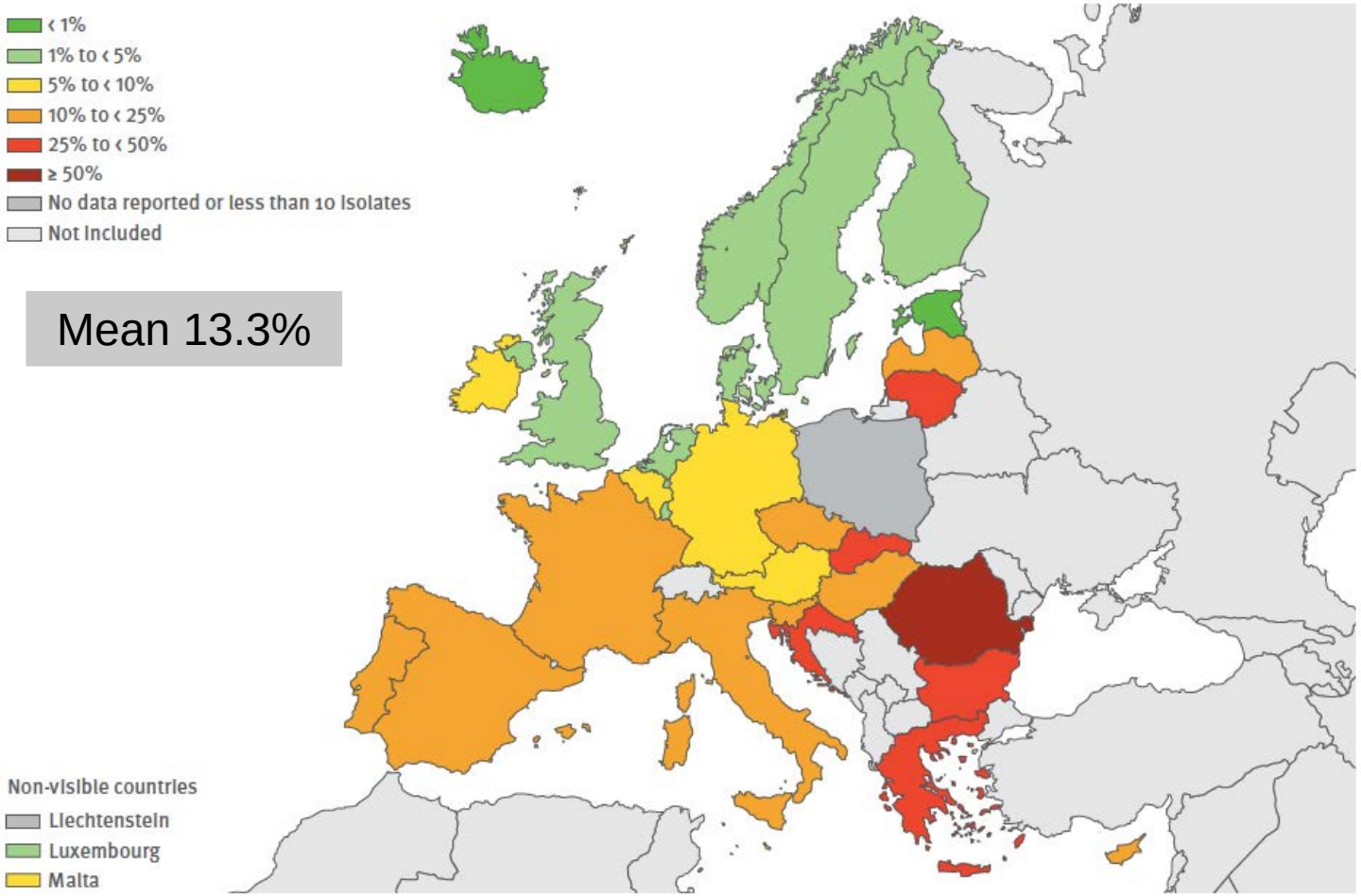
Cefepime R	8	8
Ceftazidime R	8	8
Imipenem I/R	4	8
Meropenem I/R	2	8
Doripenem I/R	1	2
Aztreonam I/R	1	16
Ciprofloxacin I/R	0.5	1
Levofloxacin I/R	1	2
Amikacin I/R	8	16
Gentamicin R	4	4
Netilmicin R	4	4
Tobramycin R	4	4
Colistin R	4	4
Fosfomycin (IV) R	128	128

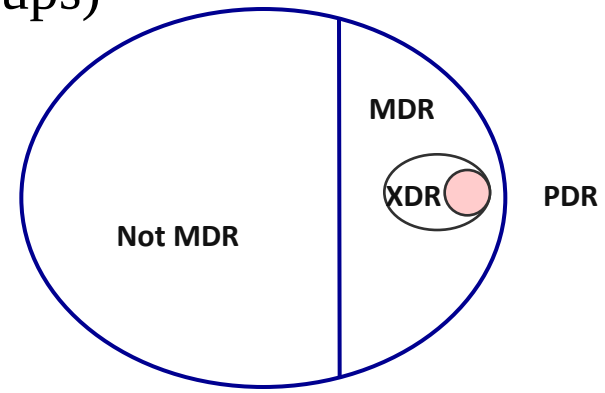
Resistance rates to ≥3 antibiotic groups



EARS-Net 2014

Resistance rates in Europe

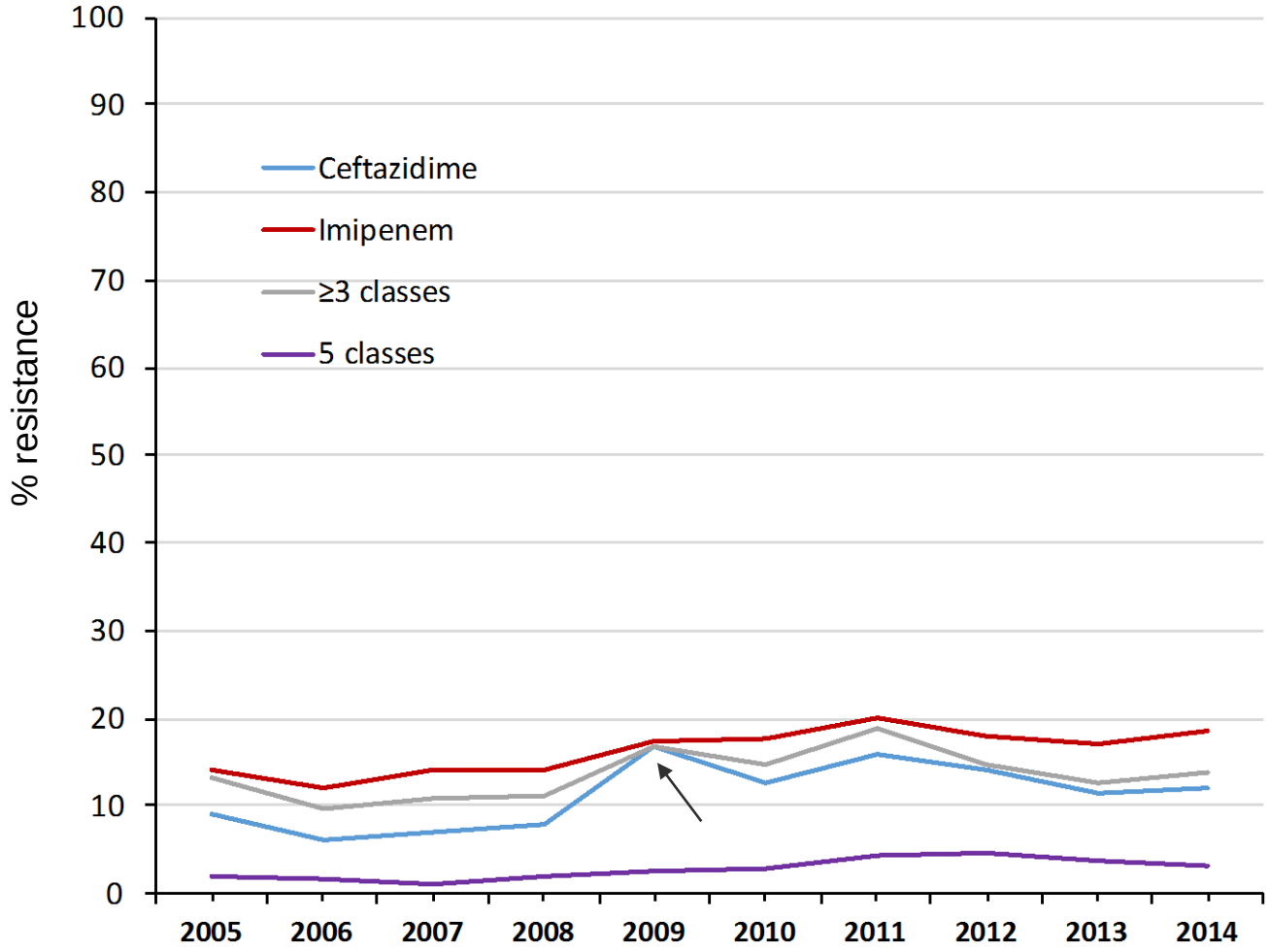
- MDR : from 0% to 59.6% in 2014
- XDR : 5.5% (rce to 5/5 antibiotic groups)
- PDR : < 1% ?
- Colistin resistance: 2%



- Poor response to treatments
- Use of nonconventional drug combinations
- Prolonged hospital stays
- Deaths (impacted by underlying disease)
- Increased hospital costs

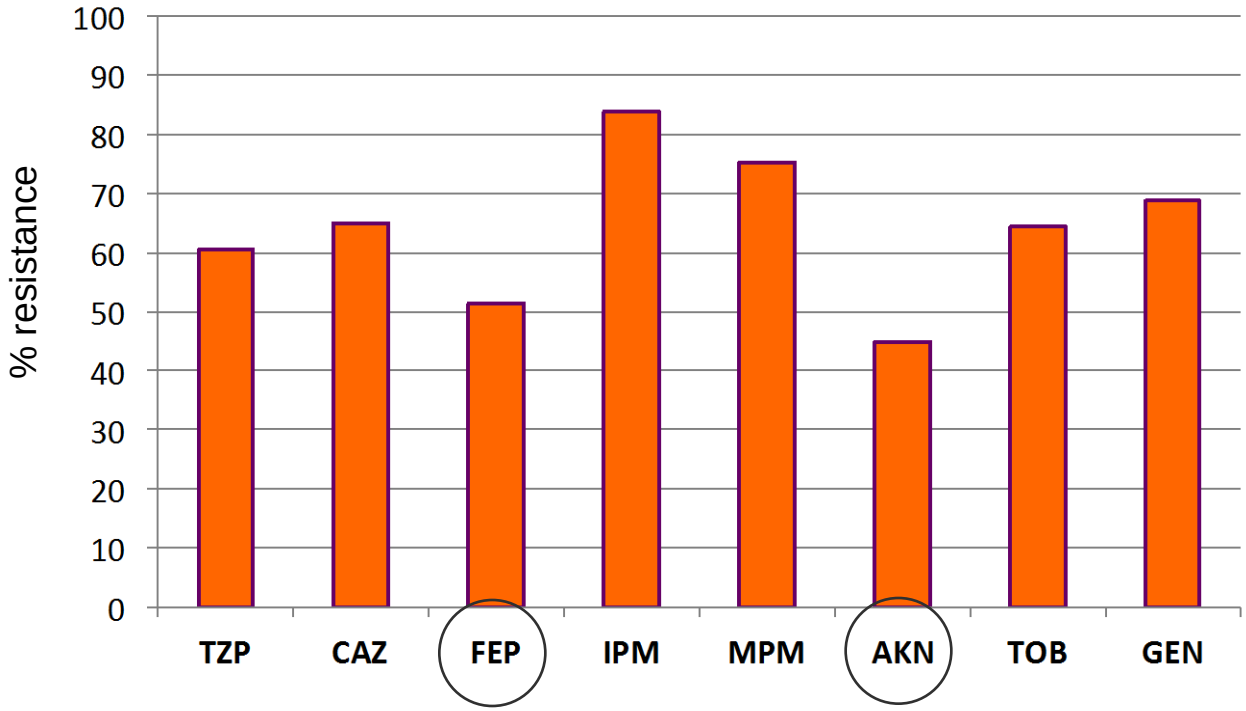
EARS-Net 2014

EARS-Net France: 2005-2014 trends



MDR *P. aeruginosa:* resistance rates

NRC data 2010-2014 (*n*=1,426 isolates)



ESBL and carbapenemase *Pae* in France

Survey	Year	# hospitals	Strains			% ESBLs		% Carbapenemases	
			Number	Origin	Criteria	collection	estimates/France	collection	estimates/France
GESPA	1999-2004	6	120	bacteremias	non replicate	0	< 1%	0	< 1%
ONERBA	2007	85	140	diagnostic samples non CF	non replicate CAZ^R	7.9%	1%	2.9%	0.4%
GESPAR	2010	26	109	ICU	non replicate $IPM^{I/R}$	3.7%	0.7%	6.4%	1.2%

Cephalosporins

-AmpC ↑+++

-ESBLs +

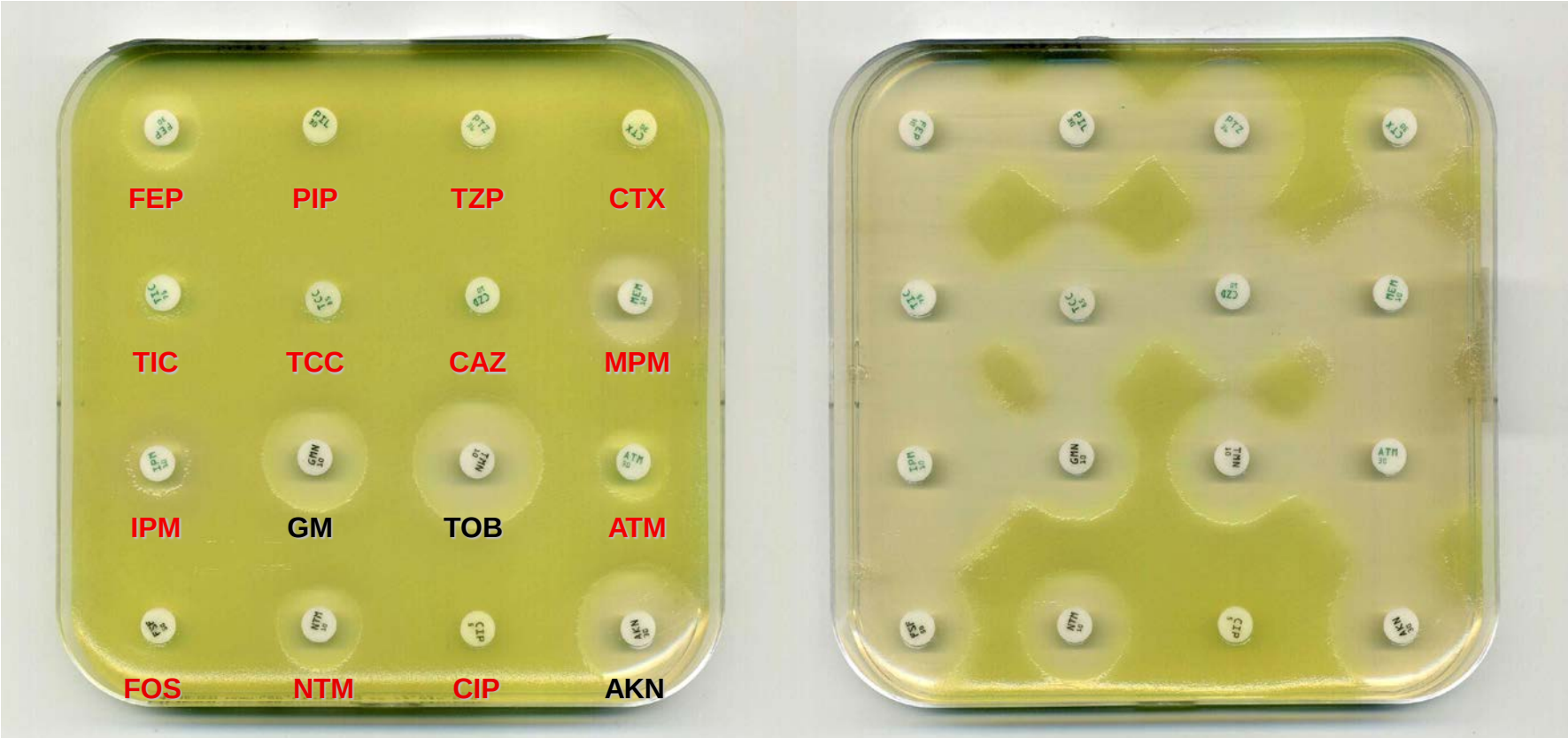
-Carbapenemases +

Carbapenems

-OprD ↓+++

-Carbapenemases +

Phenotype AmpC^{++} OprD^{-}



16.3488

16.3488 / cloxacillin 2,000

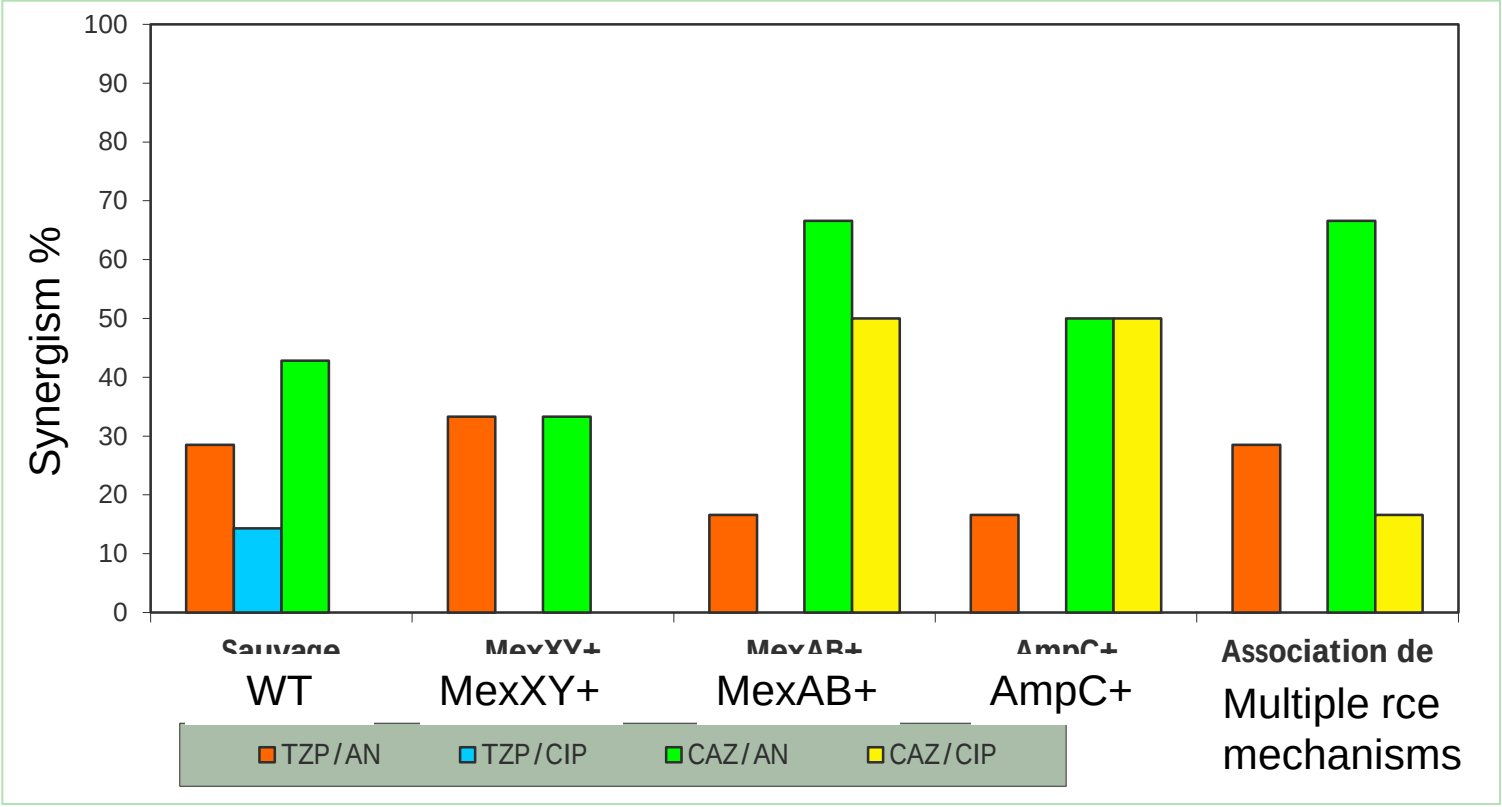
Synergistic drug combinations

- 128 drug combinations on 32 *P. aeruginosa* strains
  - ✓ *Only 2 discordances between E-test and checkerboard methods*
  - ✓ *33 (25.8%) synergistic, 97 (74.2%) additive, 0 antagonistic combinations*

	AMK	CIP
CAZ	48.6% (16)	21.2% (7)
TZP	24.2% (8)	6.0% (2)

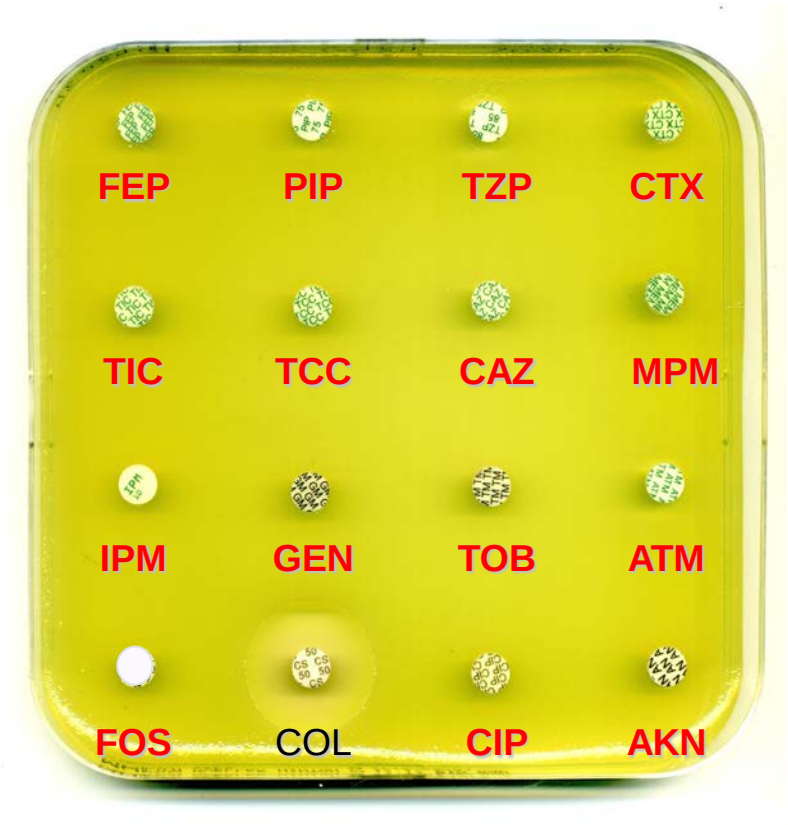
- Combination β-lactam-amikacin (18.75%) more often synergistic than β-lactam-ciprofloxacin (4.7%)

Unpredictable effects of antibiotic combinations



- Independent of resistance levels
- Independent of resistance mechanisms

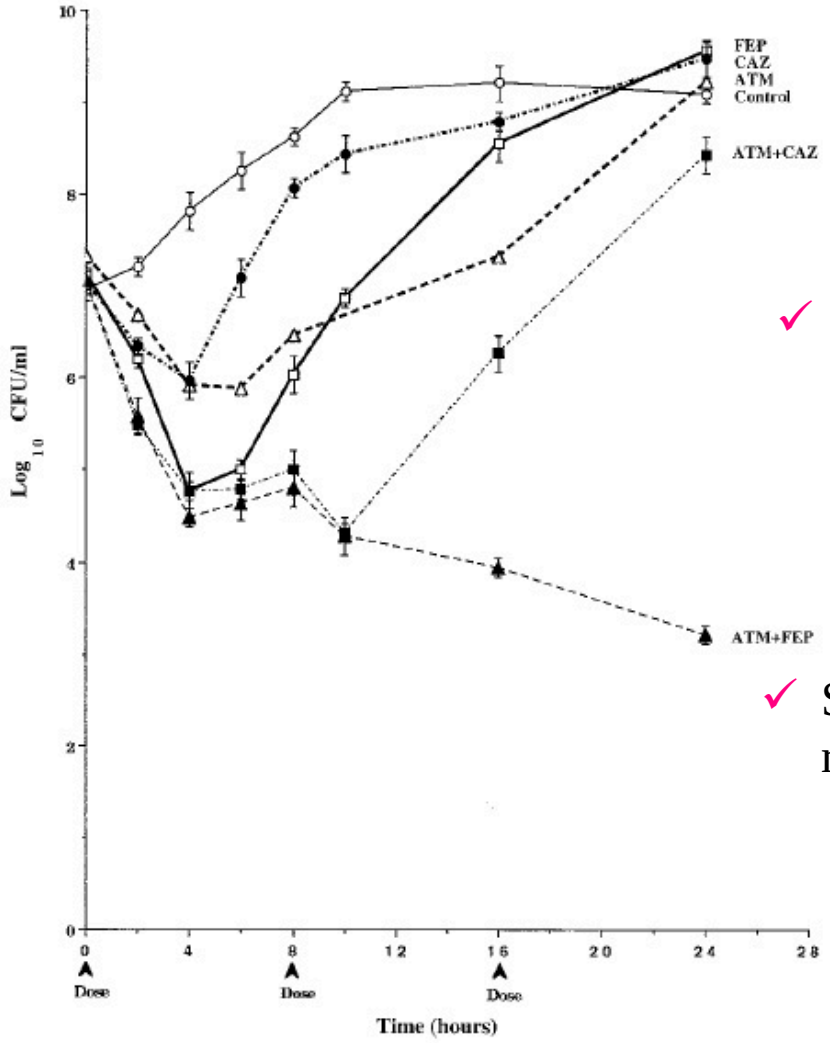
How to combat XDR strains ?



XDR = MIC

- CAZ, FEP, IPM, MPM, AKN (E-tests)
- ATM (E-test, MBL strains)
- COL (microdilution, COS strains)
- FOS (E-test, MIC <128, UTI)
- Ceftolozane-tazobactam (CA-SFM 2016)

Aztreonam-cefepim



- ✓ Aztreonam: inhibitor of ß-lactamase AmpC
  Non systematic synergy with FEP on $AmpC^{+}$ mutants

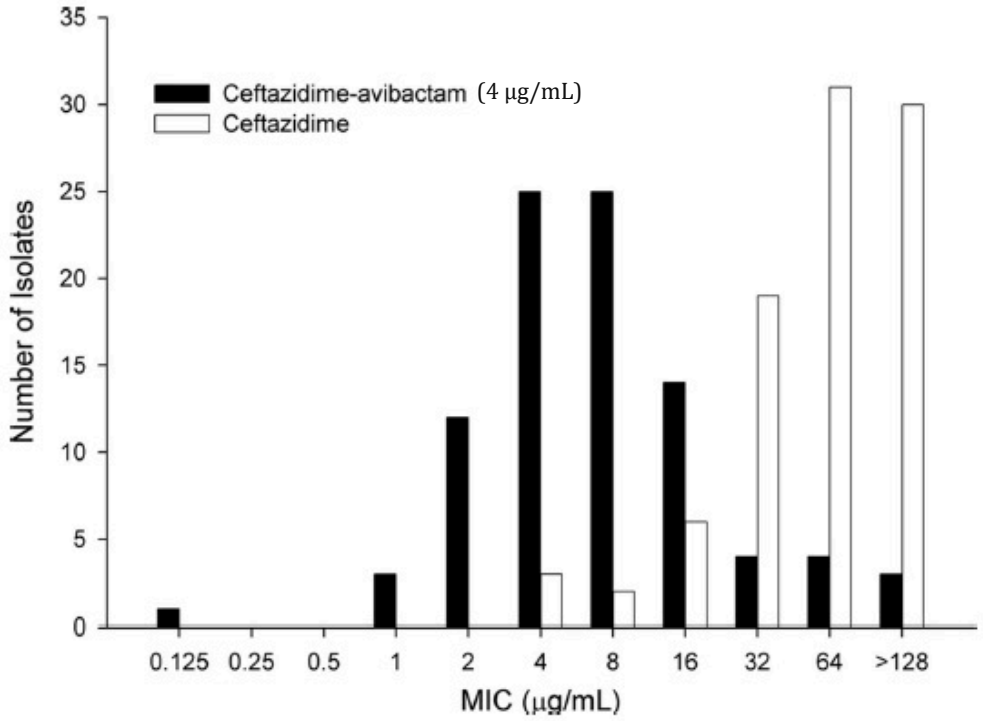
Lister *et al.* AAC 1998, 42:1610

- ✓ Synergistic combination on 50% strains resistant to IMP

Sader HS *et al.* IJAA 2005, 25:380
Dupont H *et al.* Anaesth.Crit.Pain.Care 2015, 34:141

Dose = 1 g

Ceftazidime-avibactam (NXL-104)



- ✓ Avibactam: inhibitor of class A (ESBL) and class C (AmpC) ß-lactamases
- ✓ CAZ 2g + AVI 0.5g x 3/d > CAZ 2g x 3/d in various infection models with Mdr strains

Crandon J.L. *et al.* AAC 2012, 56:6137
Housman S.T. *et al.* AAC 2014, 58:1365

Ceftolozane (CXA-101, FR264205)

E 1. Antibacterial activity of FR264205 against clinical isolates of *P. aeruginosa*

Strain (no. of isolates)	Compound	MIC (μg/ml)		
		Range	50%	90%
P. aeruginosa (193)	FR264205	0.25–4	0.5	1
	CAZ	0.125–128	2	16
	IPM	0.125–64	2	16
	CIP	≤0.0313–>128	0.25	8
P. aeruginosa, CAZ resistant (13)	FR264205	1–4	2	4
	CAZ	32–128	64	128
	IPM	1–32	16	32
	CIP	0.0625–64	2	64
P. aeruginosa, IPM resistant, CAZ susceptible (35)	FR264205	0.5–1	0.5	1
	CAZ	1–16	4	16
	IPM	16–64	16	32
	CIP	0.0625–32	1	8
P. aeruginosa, CIP resistant (30)	FR264205	0.5–4	1	2
	CAZ	1–128	8	64
	IPM	1–32	8	16
	CIP	4–>128	8	64

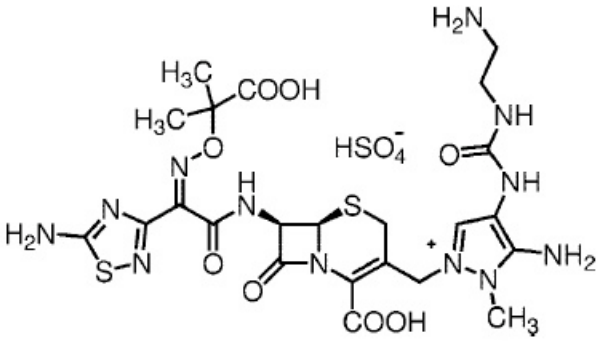
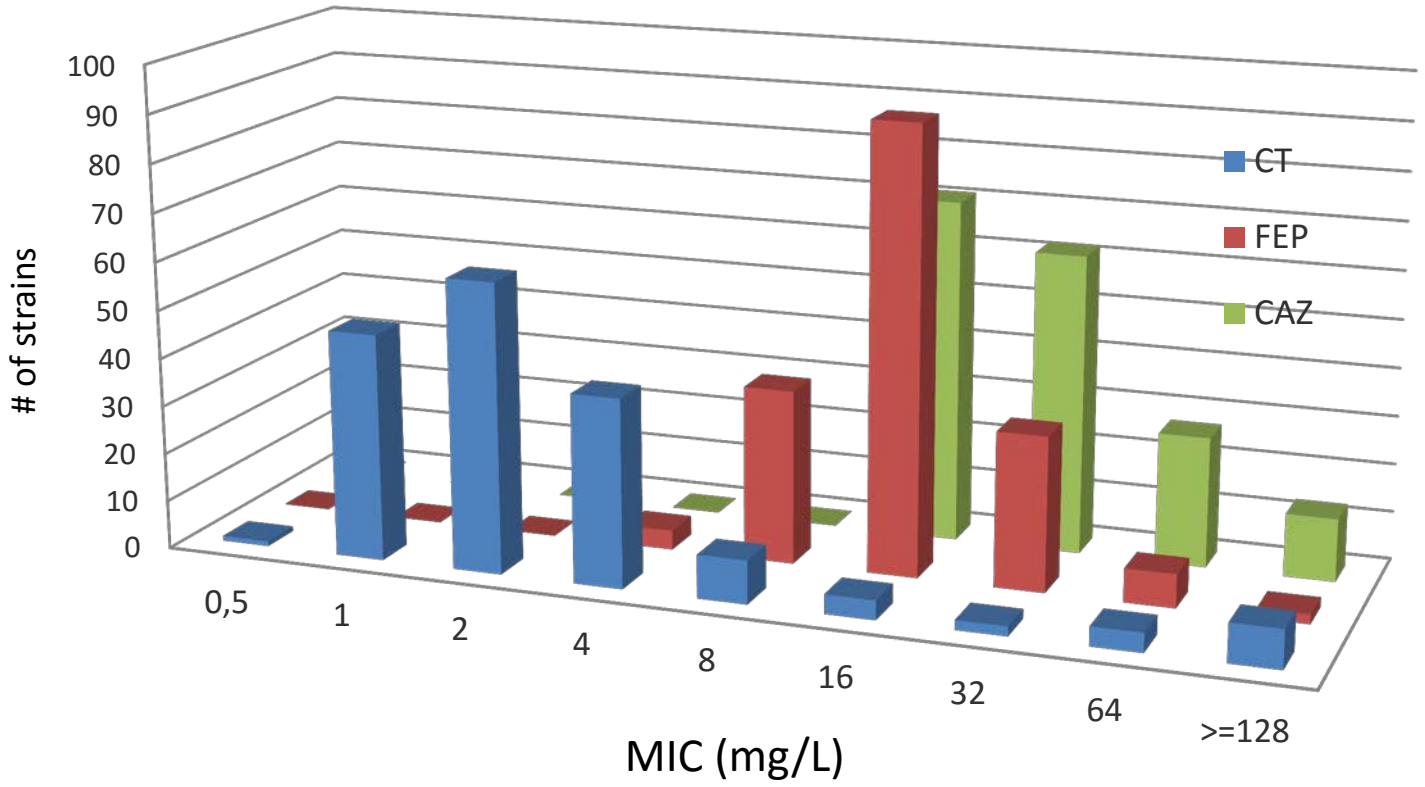


FIG. 1. Chemical structure of FR264205.

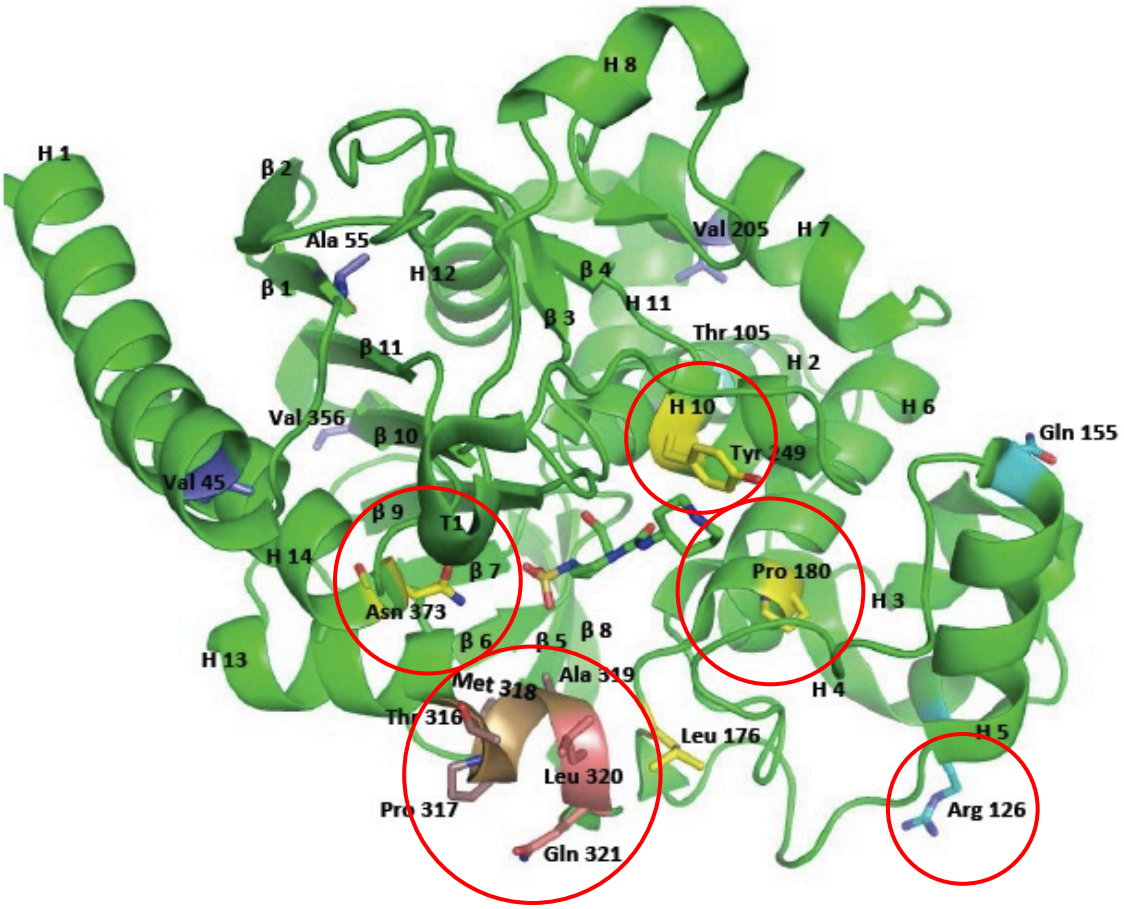
✓ Activity of tazobactam on ESBLs

Takeda S. AAC 2007, 51: 826
Juan C. AAC 2010, 54: 846
Moya B. AAC 2010, 54: 1213
Bulik C. C. AAC 2010, 54:557

GERPA 2015


100
90
80
70
60
50
40
30
20
10
0
# of strains
0,5
1
2
4
8
16
32
64
>=128
MIC (mg/L)
CT
FEP
CAZ

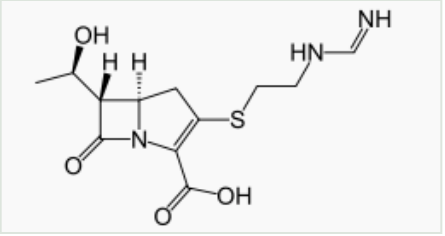
AmpC variants (ESACs)



Berrazeg M. *et al.* AAC 2015, 59: 6248

Mutational modulation of AmpC activity

Site	TIC	TZP	ATM	CAZ	FEP	CZ/T	IPM
G1 (Ω loop)	↑	↓	↑	↑	-	↑	-
G2 (R2 loop)	-	↓	-	↑	↑	↑	-
G3 (YSN loop)	-	-	-	↑	-	↑	-
G4 (N347I)	-	↓	-	↑	↑	↑	-

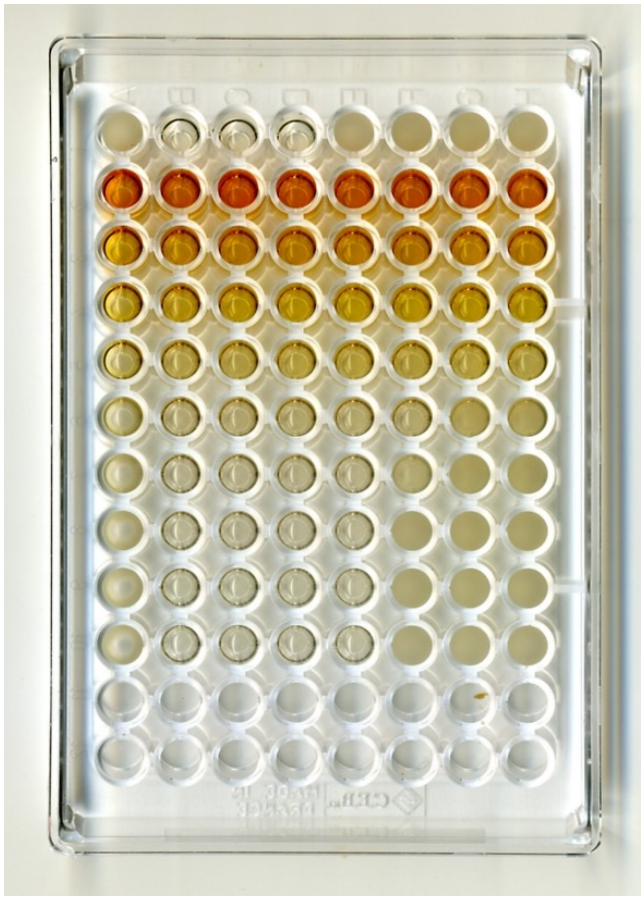


Other *in vitro* synergic drug combinations

- Colistin-rifampicin
- Colistin-carbapenem
- Colistin-azithromycin
- Colistin-ceftazidime
- Colistin-tobramycin (biofilm)
- Fosfomycin-tobramycin
- Fosfomycin-carbapenem
- Tobramycin-clarithromycin (biofilm)

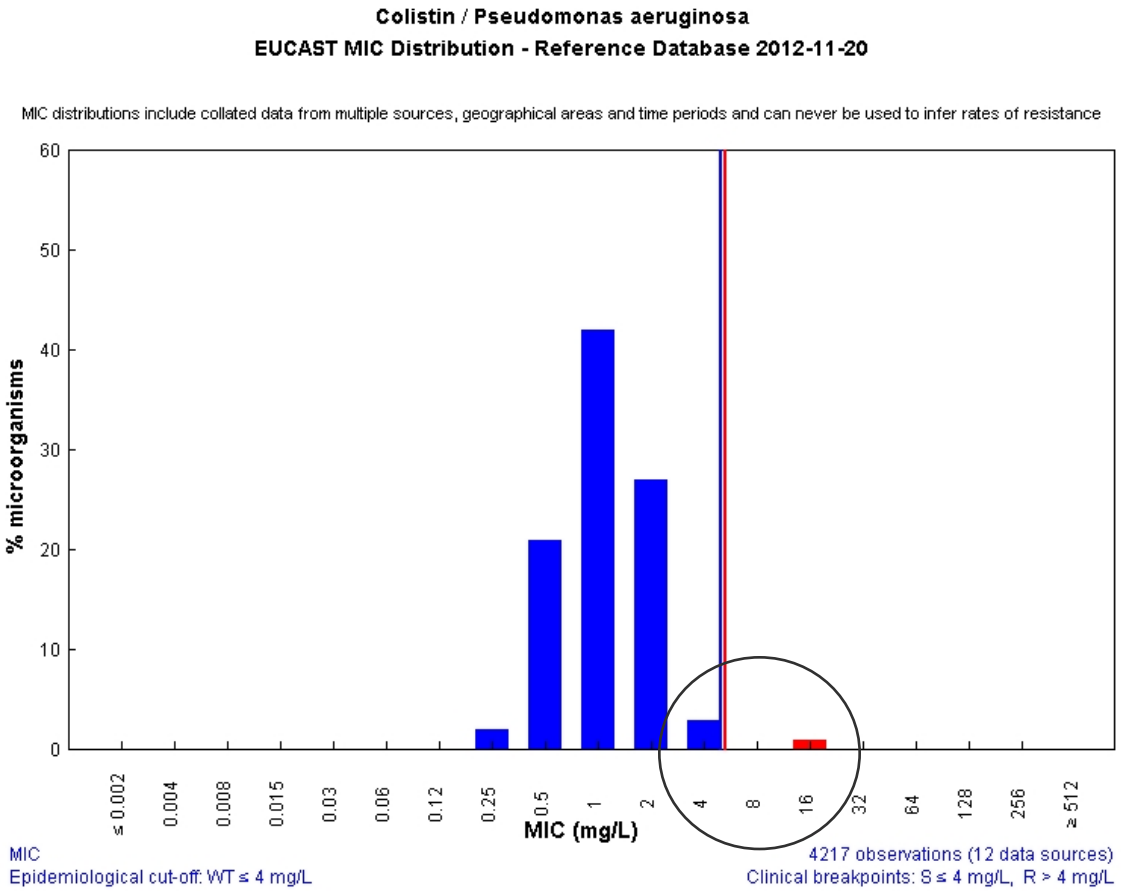
- Equivocal results *in vitro* et *in vivo* (Petrosillo *et al.* CMI 2008, 14:816; Yahav D *et al.* CMI 2011, 18:18)
- Results dependent on type of *in vitro* method (Zusman *et al.* AAC 2013, 57:5104)
- Synergy effect around the MIC (RIF 32 µg/mL, FOS 64-128 µg/mL)
- Non inferiority of colistin monotherapy *vs* combination therapy in animal models and clinical studies (Petrosillo *et al.* CMI 2008, 14:816)

Cherckerboard method

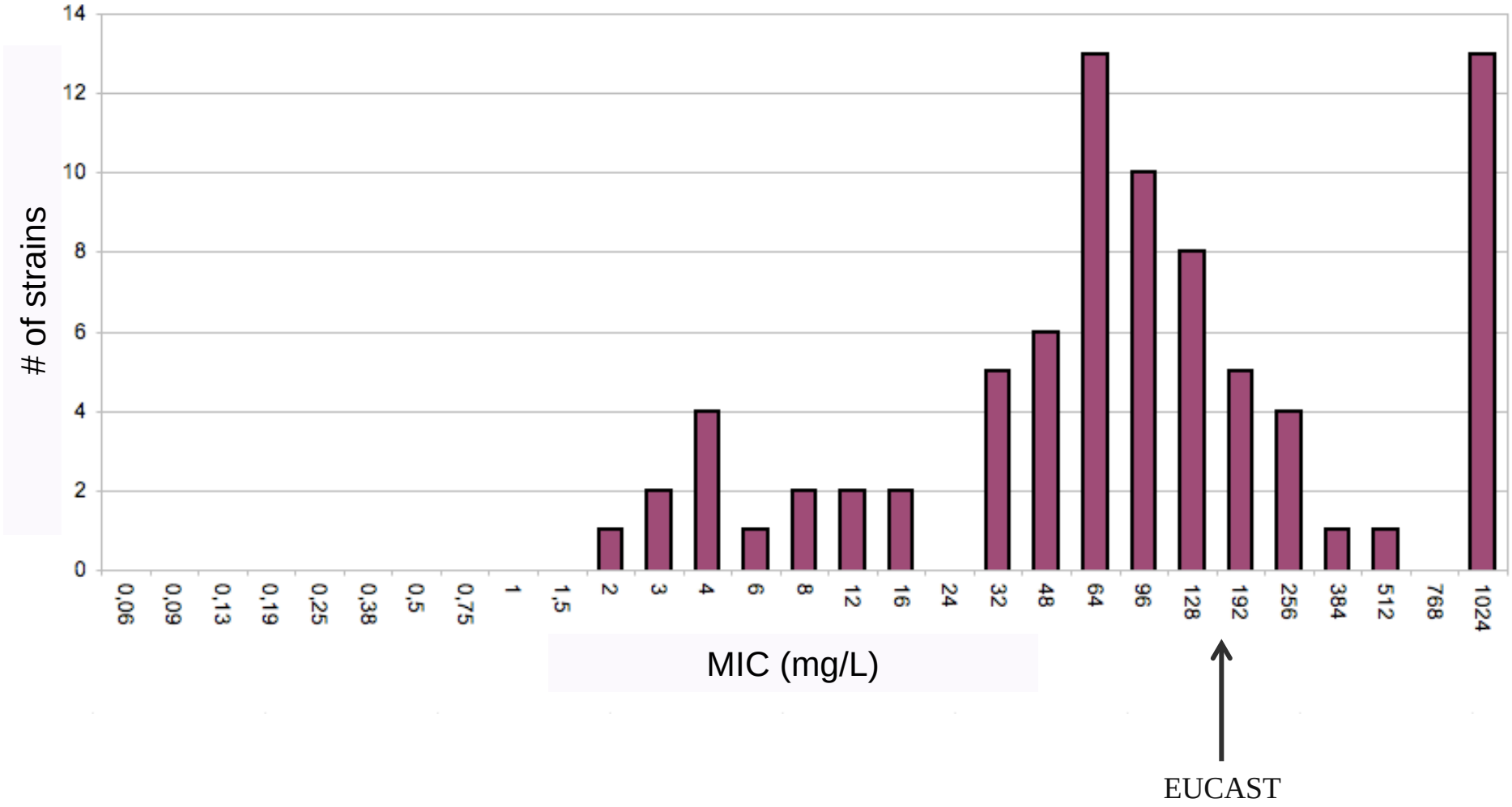


Rifampicin – Colistin
(FIC index)

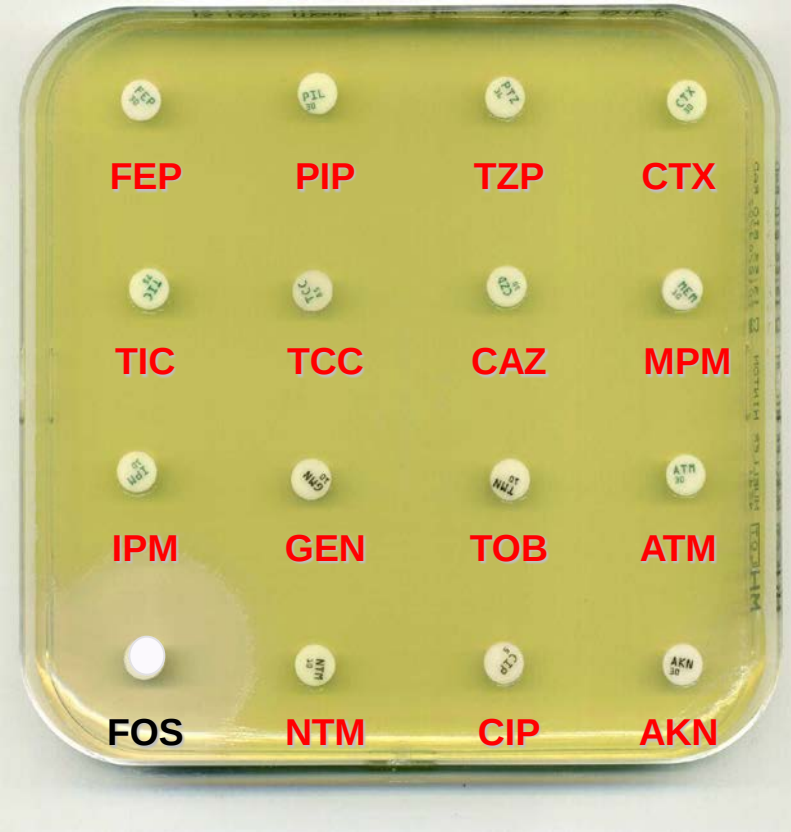
Colistin MIC distribution



Fosfomycin MIC distribution



XDR Fosfo^{S} Coli^{S}



13.1333
VIM-30, PER-1, PSE-1, OXA-4

Conclusions

- XDR strains of *P. aeruginosa* are increasingly reported worldwide
- No clinically-validated strategy to combat XDR strains
- MIC determination is highly recommended as rational approach to choose optimal antipseudomonal molecules
- Resistance to colistin remains rare (<2%) but should be investigated *in vitro* at least retrospectively
- Ceftolozane-tazobactam and ceftazidime-avibactam are interesting options against AmpC derepressed mutants
- *In vitro* tests cannot predict the clinical efficacy of non conventional drug combinations (colistin, fosfomycin)
- High dose combined therapy is the rule if based on MIC values.

.../...

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

Acknowledgments

Present

Biologists
Katy Jeannot
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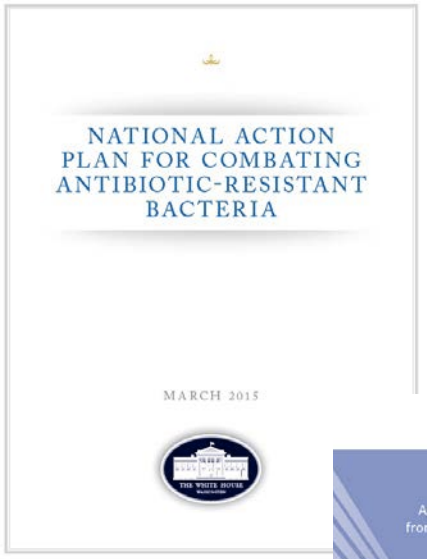

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA
MARCH 2015
THE WHITE HOUSE


Review on Antimicrobial Resistance
Tackling drug-resistant infections globally
Tackling a global health crisis: initial steps


The evolving threat of antimicrobial resistance
Options for action
World Health Organization

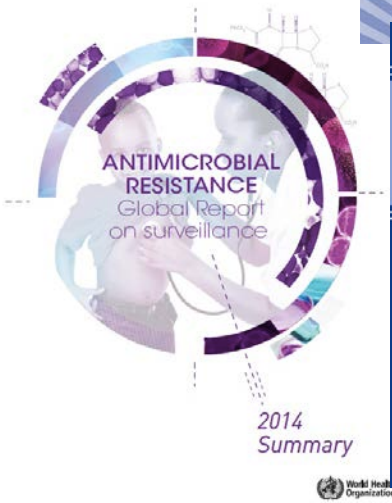

ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013
CDC

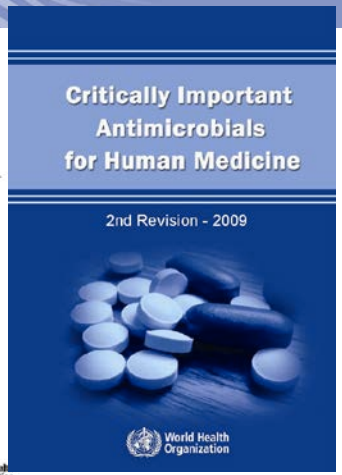

Action Plan Against the rising threats from Antimicrobial Resistance: Road Map


European Commission

Communication from the Commission to the European Parliament and the Council
Action plan against the rising threats from Antimicrobial Resistance
COM (2011) 748


Prévention de la transmission croisée des Bactéries Hautement Résistantes aux antibiotiques émergentes
(BHRe)


ANTIMICROBIAL RESISTANCE
Global Report on surveillance
2014 Summary
World Health Organization


Critically Important Antimicrobials for Human Medicine
2nd Revision - 2009
World Health Organization


NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA
September 2014
THE WHITE HOUSE