

Emergence of extensive drug resistance among Gram-negative bacilli in South Africa

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Introduction

- Until recently, extensive drug resistance (XDR) restricted to *Mycobacterium tuberculosis*.
- Emergence of multi- (MDR) and pan-drug resistant (PDR) Gram-negative healthcare-associated pathogens confined to **non-fermenters**
- Increasing reports of infections due to XDR **fermentative** Enterobacteriaceae

Our worst nightmare?

- **MDR, or PDR Gram-negative non-fermenters**
- **MDR, XDR, or PDR Gram-negative fermenters**



Scope of presentation

- New proposed definitions
- Surveillance data
- XDR fermenters
- Impact on outcome
- Treatment options

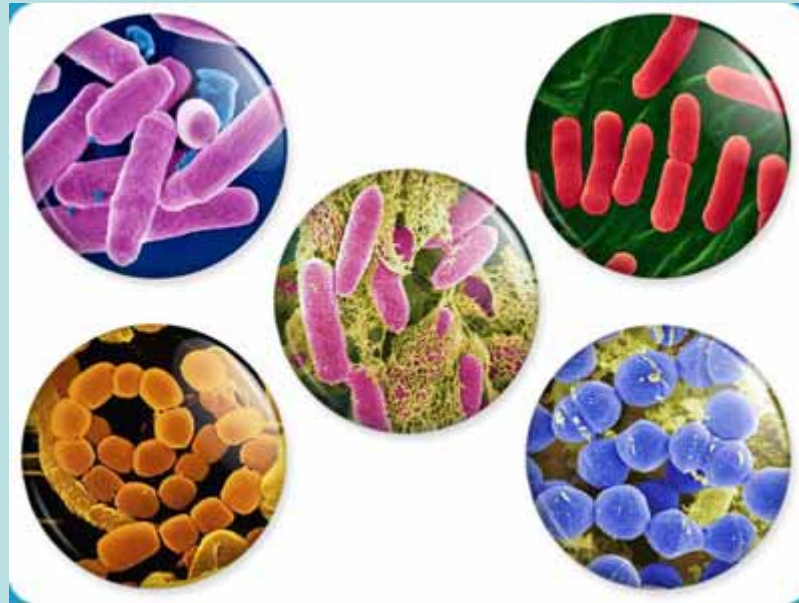
Antibiotic classes

- **Anti-pseudomonal cephalosporins (ceftazidime or cefepime)**
- **Carbapenems (ertapenem, imipenem or meropenem)**
- **Beta-lactam/ β -lactamase inhibitor combination (piperacillin/tazobactam)**
- **Fluoroquinolones (ciprofloxacin or levofloxacin)**
- **Aminoglycosides (amikacin, gentamicin or tobramycin)**
- **Aztreonam**
- **Polymyxin E**
- **Tigecycline (Wyeth/Pfizer, filed for registration in South Africa)**

Definitions

- **MDR: Resistance to 3 or more classes**
- **XDR: susceptibility to 2 or less classes**
- **PDR: diminished susceptibility to all classes (no options for treatment)**

Surveillance data in private institutions in South Africa



Bacteraemic isolates of *A. baumannii* Private sector SA Jan-June 2008

	Overall % sensitive	Range	Number
Ceftazidime	31	0-67	284
Cefepime	32	0-71	284
Pipercillin-tazobactam	32	0-67	284
Ciprofloxacin	32	0-67	284
Amikacin	61	51-100	284
Tobramycin	69	0-89	230
Imipenem	38	0-78	284
Meropenem	37	0-78	284

Bacteraemic isolates of *P. aeruginosa* Private sector SA Jan-June 2008

	Overall % sensitive	Range	Number
Ceftazidime	53	48-100	469
Cefepime	52	47-100	469
Piperacillin-tazobactam	52	25-100	469
Ciprofloxacin	50	45-100	469
Amikacin	61	56-100	469
Tobramycin	58	34-100	344
Imipenem	53	42-100	469
Meropenem	49	33-100	469

Our Worst Nightmare?

XDR Gram-negative Fermenters



National Private surveillance

- The study was conducted from 1st July 2007 to 31st December 2007.
- All private institutions in 7 major cities
- Over this period a total of 1241 blood culture isolates were tested;
E.coli (n=503)
K.pneumoniae (n=548)
Enterobacter spp (n=190)

% resistance			
	<i>E.coli</i> (n=503)	<i>K.pneumoniae</i> (n=548)	<i>Enterobacter</i> spp (n=190)
Antibiotic	Overall (Range)	Overall (Range)	Overall (Range)
Ampicillin	82 (65-90)	100 (-)	100 (-)
Co-amoxiclav	39 (0-57)	62 (31-73)	99 (91-100)
Cefuroxime	18 (0-33)	62 (31-72)	83 (0-96)
Ceftriaxone/Cefotaxime	7 (0-15)	57 (43-66)	62 (44-91)
Cefepime	5 (0-14)	54 (50-64)	26 (10-46)
Piperacillin-tazobactam	9 (0-23)	49 (26-67)	38 (17-66)
Ciprofloxacin	16 (0-36)	39 (18-64)	16 (0-40)
Levofloxacin	16 (0-36)	39 (28-64)	16 (0-40)
Gentamicin	14 (0-32)	31 (0-43)	25 (10-52)
Amikacin	6 (0-15)	25 (8-50)	6 (0-16)
Ertapenem	2 (0-8)	2 (0-8)	5 (0-17)
Imipenem	1 (0-6)	1 (0-1)	1 (0-5)
Meropenem	1 (0-6)	1 (0-1)	1 (0-5)
% ESBL production	5 (0-11)	50 (33-59)	23 (9-37)

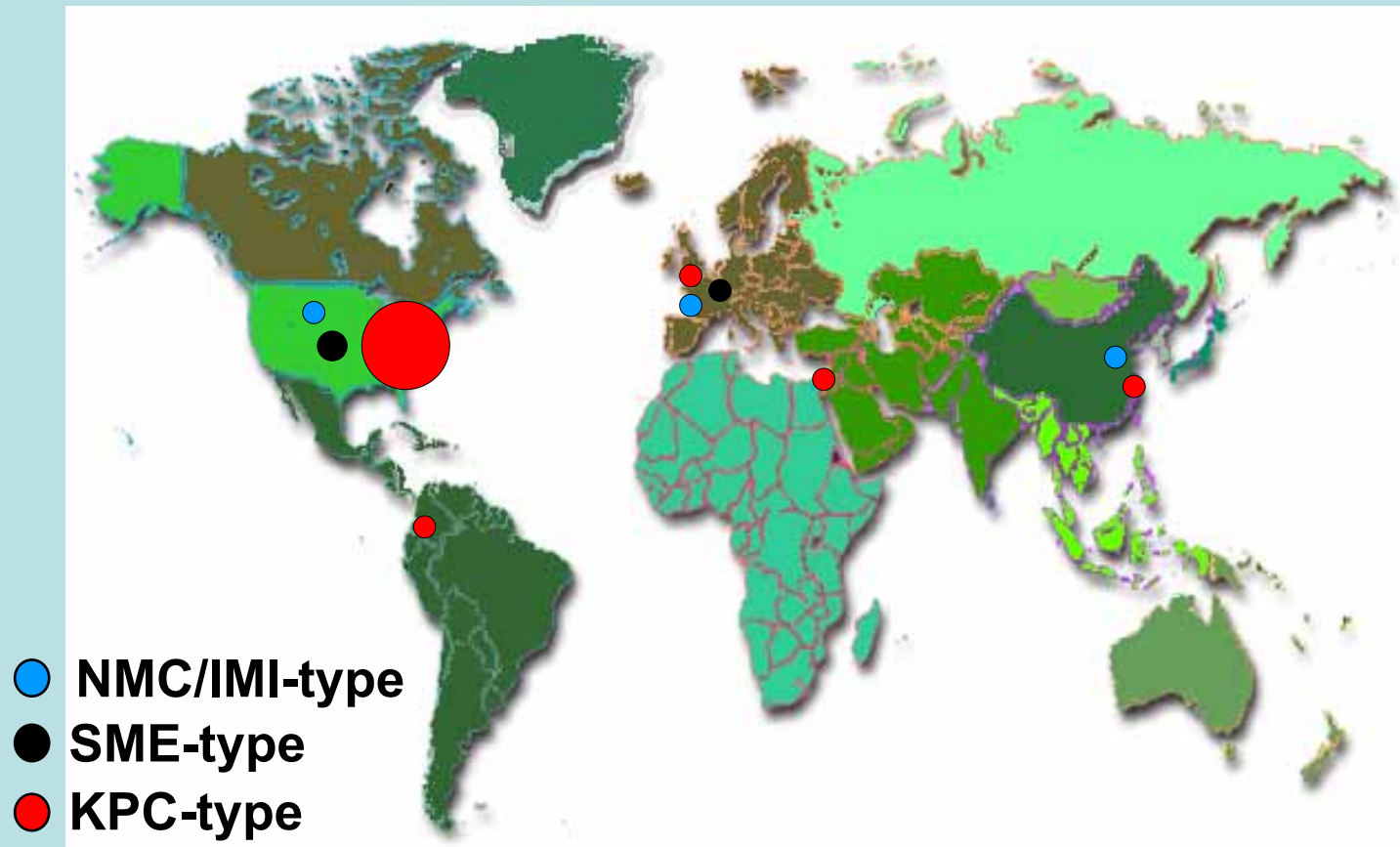
XDR

Extensive drug resistance amongst these species can be conferred by several resistance mechanisms:

- **Carbapenemases (KPC)**
- **Metallo- β -lactamases (MBL)**
- **ESBL/Amp C plus porin loss (impermeability)**

Acquired Class A serine-carbapenemases in *Enterobacteriaceae* – An Update

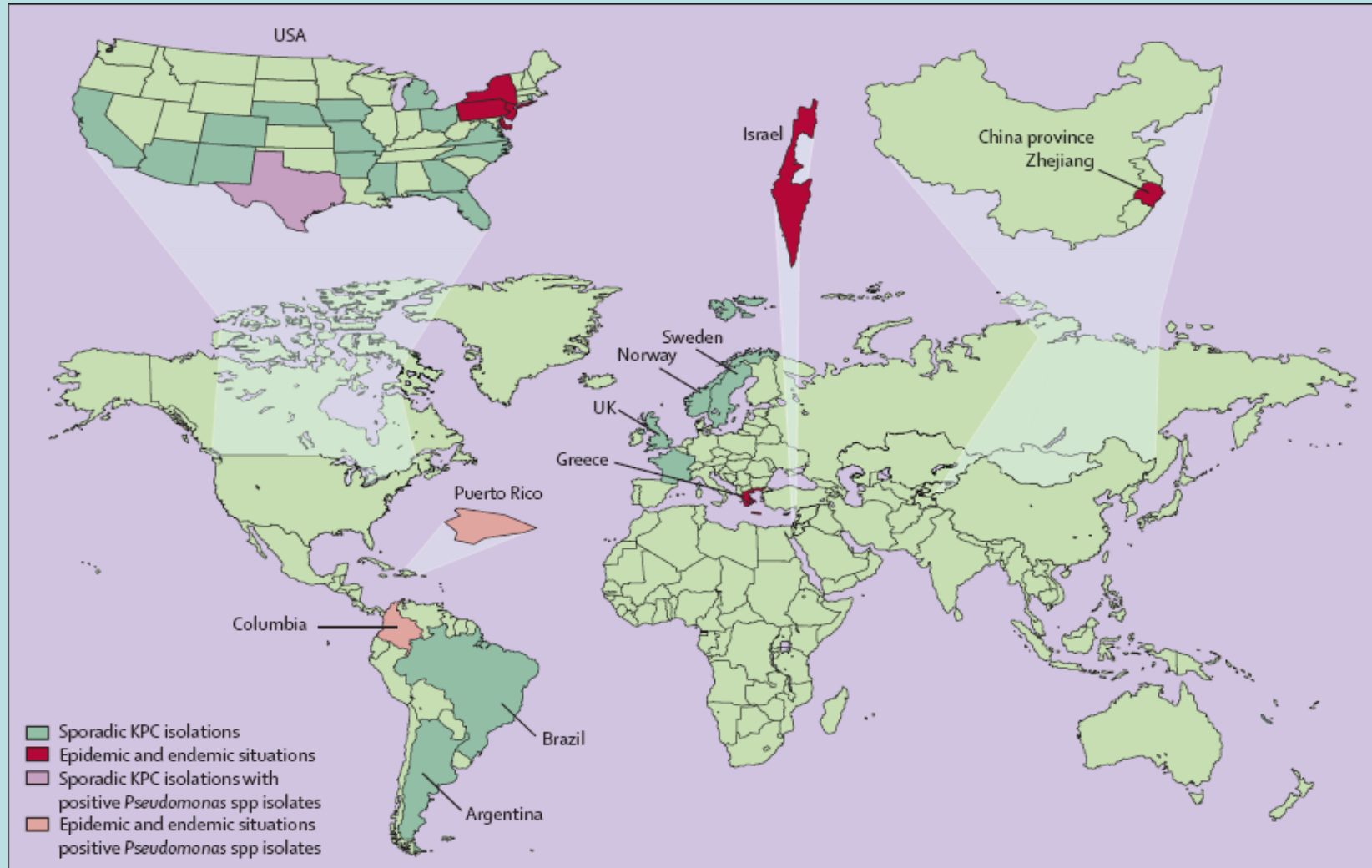
KPC = *K. pneumoniae* carbapenemase



Navon-Venezia et al. *Antimicrob Agents Chemother.* 2006; 50:3098

Villegas et al. *Antimicrob Agents Chemother.* 2007 29 Jan 2007

Geographic distribution of KPC



Epidemiology of KPC

- Mostly *Klebsiella pneumoniae*
- *Escherichia coli*
- Reported extensively in other genera of Enterobacteriaceae
 - *Proteus*
 - *Serratia*
 - *Salmonella*
 - *Citrobacter*
- *Pseudomonas*



Carbapenem-resistant *E. coli*

- **NY**
- **Emergence amongst long-term care facilities**
- **XDR UTI`s**
- **Harboring KPC-2 & 3**
- **Resistant to all antibiotics except tigecycline and colistin**

Carbapenem resistant *Enterobacter*

- **Tel Aviv, Apr 2003 - Dec 2006, 33 cases**
- **3 distinct clones, KPC-2**
- **Multivariate analysis: high-invasive device ($P=0.02$) remained a predictor of carbapenem resistance**
- **Mortality 33% vs 9% among controls (carbapenem-susceptible *Enterobacter*) $P=0.043$**
- **Delayed Rx, effective therapy often not possible**

Emergence of metallo- β -lactamases

- **MBL: Zn containing enzymes that can hydrolyse carbapenems**
- **Greece: 3 teaching hospitals, 2004 – 2006**
- **Bloodcultures *K. pneumoniae* (n=178)**
- **38% positive for MBL [*bla*(VIM-1)]**
- **There are no commercially available MBL inhibitors.**

Emergence of metallo- β -lactamases

- Spain: Hospital outbreak of VIM producing Enterobacteriaceae
- March 2005-September 2006 -25 patients (52% from ICU), 7 wards & ICUs
- Infected and/or colonized with single or different MBL-producing Enterobacteriaceae isolates
 - *K. pneumoniae*, 14 pts (1 clone)
 - *E. cloacae*, 12 pts (6 clones)
 - *E. coli*, 1 pt
 - *K. oxytoca*, 1 pt.
- *bla*(VIM-1) MBL present in all isolates
- *bla*(SHV-12) ESBL-gene present in *K. pneumoniae* and *E. coli*

ESBL plus porin loss

- Cape Town¹
- ***In vivo* development of ertapenem resistance in strain of ESBL-producing *K.pneumoniae***
 - CTX-M in conjunction with porin-deficiency
 - Ertapenem MICs increased from 0.5 to >16
 - Imipenem MICs increased from 0.125 to 0.5
 - Meropenem MICs increased from 0.5 to >16

1. Elliott E et al CID 2006;42:e95-98

2. Segal H and Elisha BG SAJEI
2006;21:41-44

ESBL plus porin loss

- **Groote Schuur Hospital²**
- **Similar phenomenon in pts on meropenem Rx**
- **4-fold increase in imipenem MICs**
- **8-fold increase in meropenem MICs**

1. Elliott E et al CID 2006;42:e95-98

2. Segal H and Elisha BG SAJEI
2006;21:41-44

More XDR in private practice?

- 6 other clinical strains from private hospitals in Cape Town have confirmed that both hyper production of an ESBL in association with porin deficiency is one mechanism by which these pathogens may become XDR (Pathcare, unpublished data).
- Several XDR strains of *K.pneumoniae* have now also been isolated from patients in 4 private hospitals in Johannesburg (Ampath, unpublished data).
- The underlying mechanism(s) of resistance is under investigation.

Impact on outcome

- **Attributable morbidity and mortality of increasingly resistant organisms is difficult to quantify.**
- **Clinical outcome in ESBL-producing *K. pneumoniae* bacteraemic infections appears to be worse than that for patients with non-ESBL-producing isolates**
 - **Mortality rate in an ESBL group 52% (25/48) vs 29% (29/99) in the non-ESBL group (P<0.007, OR 2.62)¹**
 - **Meta-analysis of bacteraemia caused by ESBL-producing *Enterobacteriaceae* demonstrated an increased risk for delay in effective therapy (pooled RR, 5.36; 95% CI, 2.73 to 10.53)**

Impact on outcome?

- **In the Spanish outbreak the overall mortality rate among patients infected with an MBL-harboring organism was very high (45%), and it was estimated that 67% of these deaths were attributable to the presence of the resistant organism**
- **Increased mortality due to increased likelihood that initial therapy would be inappropriate**
- **MBL and KPC-producing organisms may appear to be susceptible to carbapenems, clinical response may be poor.**

Antibiotic management of MDR, XDR and PDR Gram-negatives

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Antibiotic management of MDR, XDR and PDR Gram-negatives

- **Older antibiotics**
- **New antibiotics**
- **Combination therapy**
- **Novel approaches**

Is polymixin the answer?

- **Mechanism of action:**
~ disruption of the permeability barrier of the outer membrane of gram negative organisms
- **Peak:MIC or AUC:MIC appears the PK/PD modality best predicting outcome^{1,2}**
- **No studies ever performed to characterize PK profile in critically ill**
- **Optimal dosing regimen for such patients completely unknown (RSA recommended dose = 1-2 million U 8-hourly, max=6 million U/day)**

1Kethireddy et al. Abstract A-4. 47th ICAAC, Chicago, 17-21 September 2007

2Dudhani et al. Abstract A-5. 47th ICAAC, Chicago, 17-21 September 2007

Is polymixin with rifampicin the answer?

- ***In vitro* synergy against pan-resistant *A.baumannii*¹**
- **Efficacy of colistin/rifampicin in an experimental rat model of sepsis due to MDR *P.aeruginosa*²**
- **Adding to body of experimental evidence for the beneficial effect of combination³**
- **Clinical outcome/efficacy recorded in 2 studies^{4,5}**

1.Pantopoulou *et al. Int J Antimicrob Agents* 2007;29:51-55

2.Cirioni *et al. Crit Care Med* 2007;35:1717-1723

3.Rahal JJ. *Clin Infect Dis* 2006;43:S95-99

4.Motaouakkil *et al. J Infect* 2006;53:274-278

5.Petrosillo *et al. Clin Microb Infect* 2005;11:682-683

Fosfomicin?

- Discovered almost 40 years ago
- UTIs
- Beyond UTIs
- MDR non-fermenters¹
 - *Pseudomonas aeruginosa*
- XDR fermenters²
 - Carbapenem-resistant *Klebsiella pneumonia*
 - Critically ill ICU pts given ivi fosfomicin

1. Falagas et al. Int J Antimicrob Agents 2009 (34):111-120

2. Michalopoulos et al. ECCMID 2009 Abstract P750

The pipeline today

Compound	Class	Novel MOA	Formulation	Status
Dalbavancin	Lipoglycopeptide	No ^b	IV	Filed
Iclaprim	Diaminopyrimidine	No	IV	Phase 3
Oritavancin	Glycopeptide	No	IV	Phase 3
Telavancin	Lipoglycopeptide	Yes ^c	IV	Phase 3
Ceftobiprole	Cephalosporin ^d	No	IV	Filed
Cethromycin	Ketolide	No	Oral	Phase 3
Doripenem	Carbapenem	No	IV	Approved
Faropenem	Penem	No	Oral	Filed ^e
Prulifloxacin	Quinolone	No	Oral	Phase 3

Tigercycline?

- First glycylycylcycline
- Role in XDR GNB infections?
- Review of micro and clinical effectiveness vs ESBLs, Amp C enzymes and carbapenemases in Enterobacteriaceae¹
 - Clinical studies 70% cure
 - Almost all MDR/XDR *E coli*
 - Great majority of ESBL or MDR/XDR *Klebs*

1. Kelesidis et al. JAC 2008 62 (5):895-904

PDR *Klebsiella pneumoniae*

- Case 1
 - 70 year old female
 - with indwelling catheter
 - UTI
 - KPC – producing *Klebsiella pneumoniae*
 - Polymixin B MIC = 96
 - Tigercycline MIC = 4, then 8
 - Urine still culture positive >1 year later

PDR *Klebsiella pneumoniae*

- Case 2
 - 67 year old male
 - Post Whipple's
 - Hepatic abscess grew
 - KPC – producing *Klebsiella pneumoniae*
 - KPC – producing *Enterobacter cloacae*
 - Blood cultures grew
 - KPC – producing *Klebsiella pneumoniae*
 - Polymixin B MIC = 0.75, then 12
 - Tigecycline MIC ≥ 8

Continuous infusions

- Dr Brink to discuss

Combination vs monotherapy

- **Meta-analysis of published studies**
- **Documented Gram-negative bacteraemia in cases receiving monotherapy or two or more antibiotics**
- **17 studies met inclusion criteria**
- **No mortality benefit for combination Rx: OR = 0.96 [0.70-1.32]**
- **Subgroup analyses adjusting for year of publication, study design, and severity of illness did not change the results**

Combination vs monotherapy

- Analysis of *Pseudomonas aeruginosa* bacteraemia showed a significant mortality benefit for combination Rx OR = 0.50 [0.30-0.79]¹
- In contrast in a recent study, combination vs mono Rx in *P.aeruginosa* VAP there was no difference in outcome²
- Δ Initial empiric combination Rx switching to monotherapy once susceptibility is documented
- In most institutions, when a β-lactam is resistant, an aminoglycoside will be more likely than a quinolone to be susceptible

Thank you.

