The Treatment of Resistant Bacterial Infection in Children

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South African Antibiotic Stewardship Programme

SAPA/SAAPS Congress 10 Sept 2014

The Treatment of Resistant Bacterial Infection in Children (and adults…)

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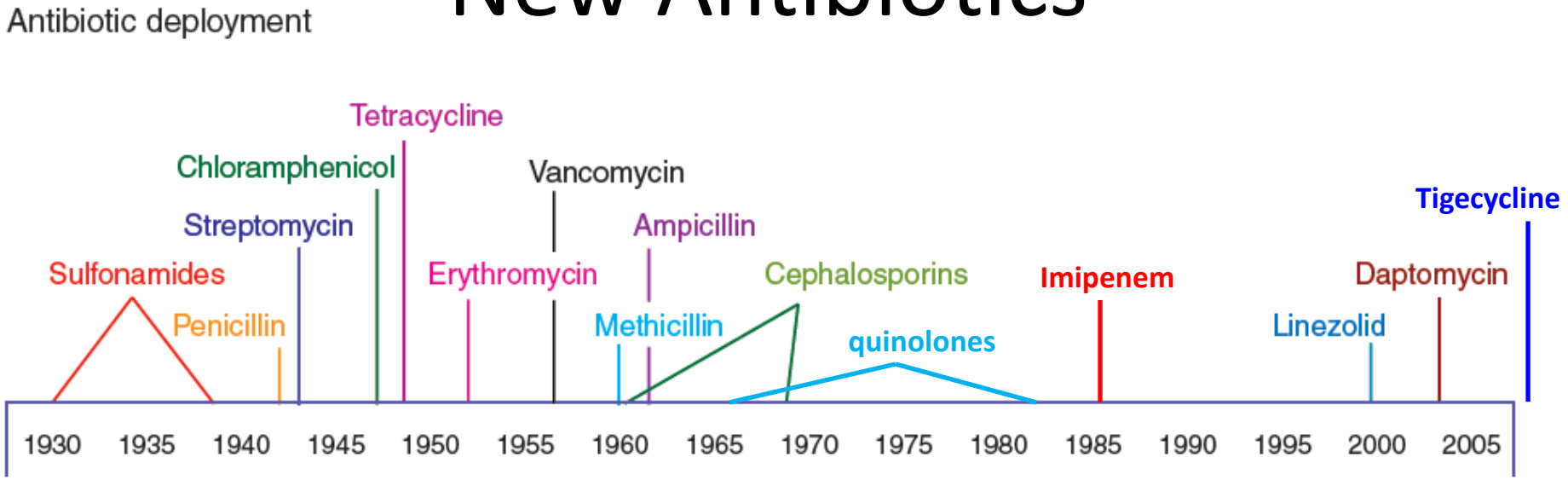
One of the biggest challenges…

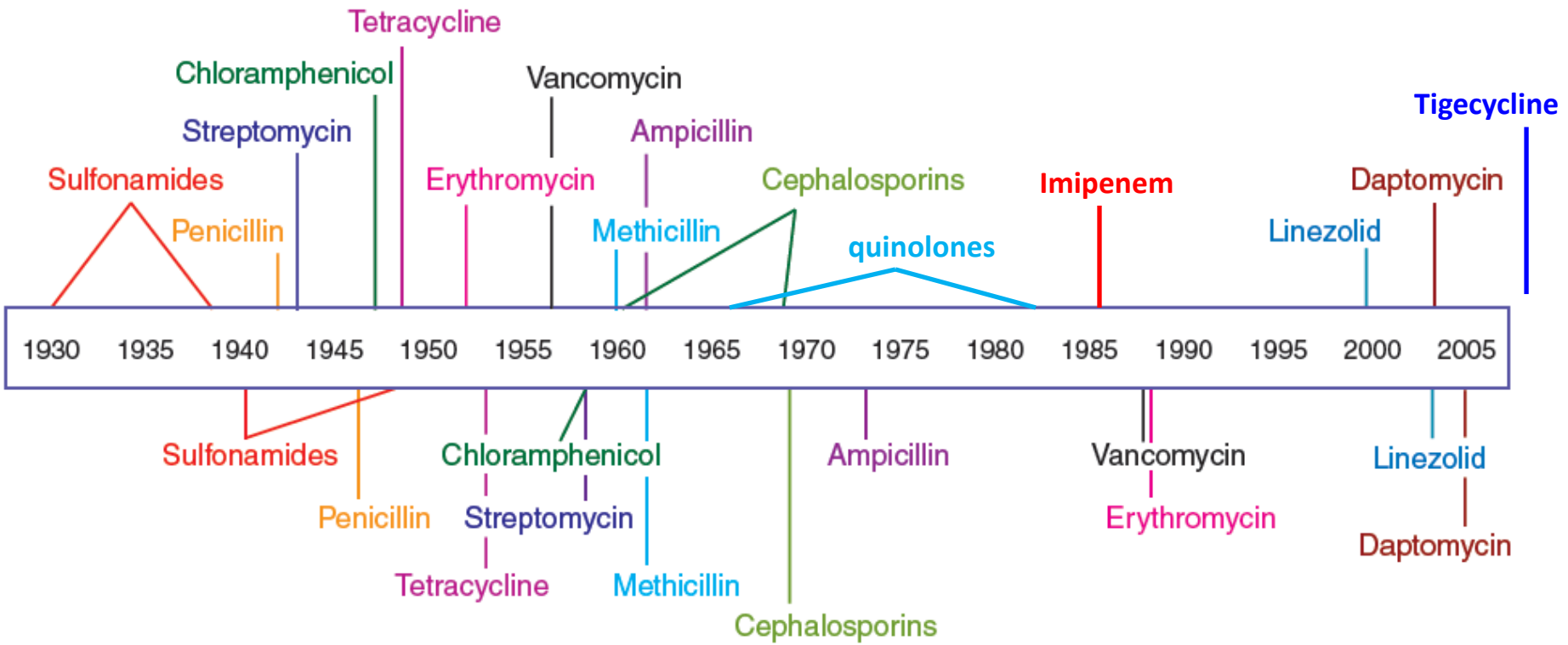
Children are not small adults

New Antibiotics



Nature Chemical Biology, 2007

Antibiotic deployment



Antibiotic resistance observed

Nothing in the pipeline for another decade or more…

Do we know what's out there?

Paediatric BSI

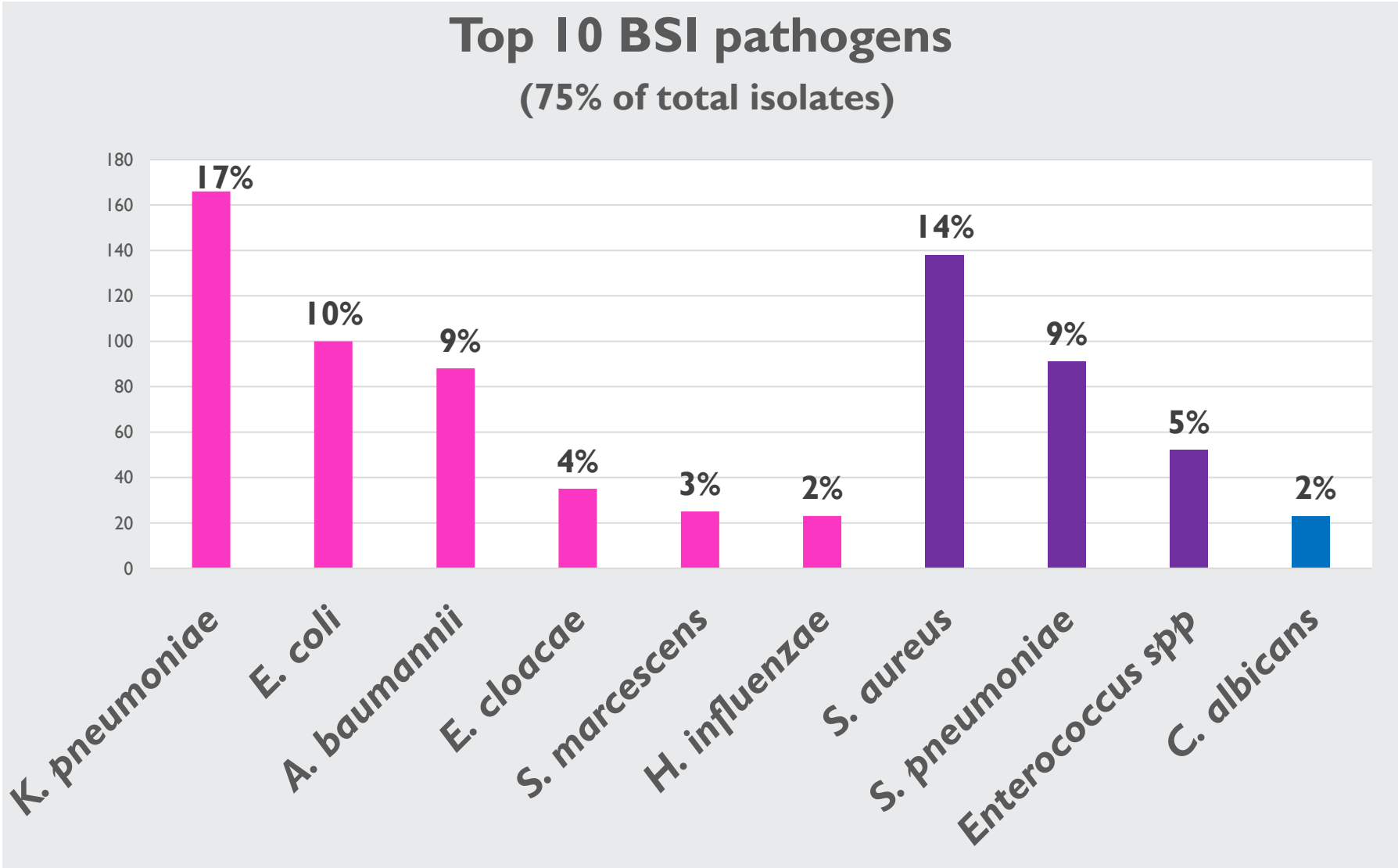
Table 2. Spectrum of common pathogens on blood culture

	2008	2009	2010	2011	2012
Gram-positive, %					
Total, *N*	271	255	234	190	133
Streptococcus pneumoniae	34.3	36.4	26.5	22.1	14.3
Staphylococcus aureus	33.9	32.2	42.3	40.5	42.1
Streptococcus group B	6.3	5.1	6.8	5.8	4.5
Enterococcus faecium	4.8	7.1	3.4	5.3	11.3
Enterococcus faecalis	6.3	7.5	4.7	14.7	10.5
Gram-negative, %					
Total, *N*	338	408	376	325	232
Klebsiella pneumoniae	31.3	27.2	27.9	21.2	22
Escherichia coli	21.9	19.1	17	14.5	22
Acinetobacter baumannii	12.4	17.2	17.8	25.2	8.2
Serratia marcescens	2.4	7.1	7.4	7.1	10.3
Other, %					
Total, *N*	43	43	43	42	36
Candida albicans	73.8	77.5	53.5	32.5	55.6
Candida parapsilosis	14.3	17.5	18.6	27.5	11.1
Candida krusei	4.7	-	-	11.9	19.4
Candida lusitaniae	-	5	4.7	2.4	-
Candida tropicalis	2.3	-	16.3	-	5.6
Candida dubliniensis	-	-	2.3	12.5	-
Mycobacterium tuberculosis complex	2.3	7	-	4.8	2.8

Red Cross Hospital, 2008-2012

Lochan, SAMJ, 2013

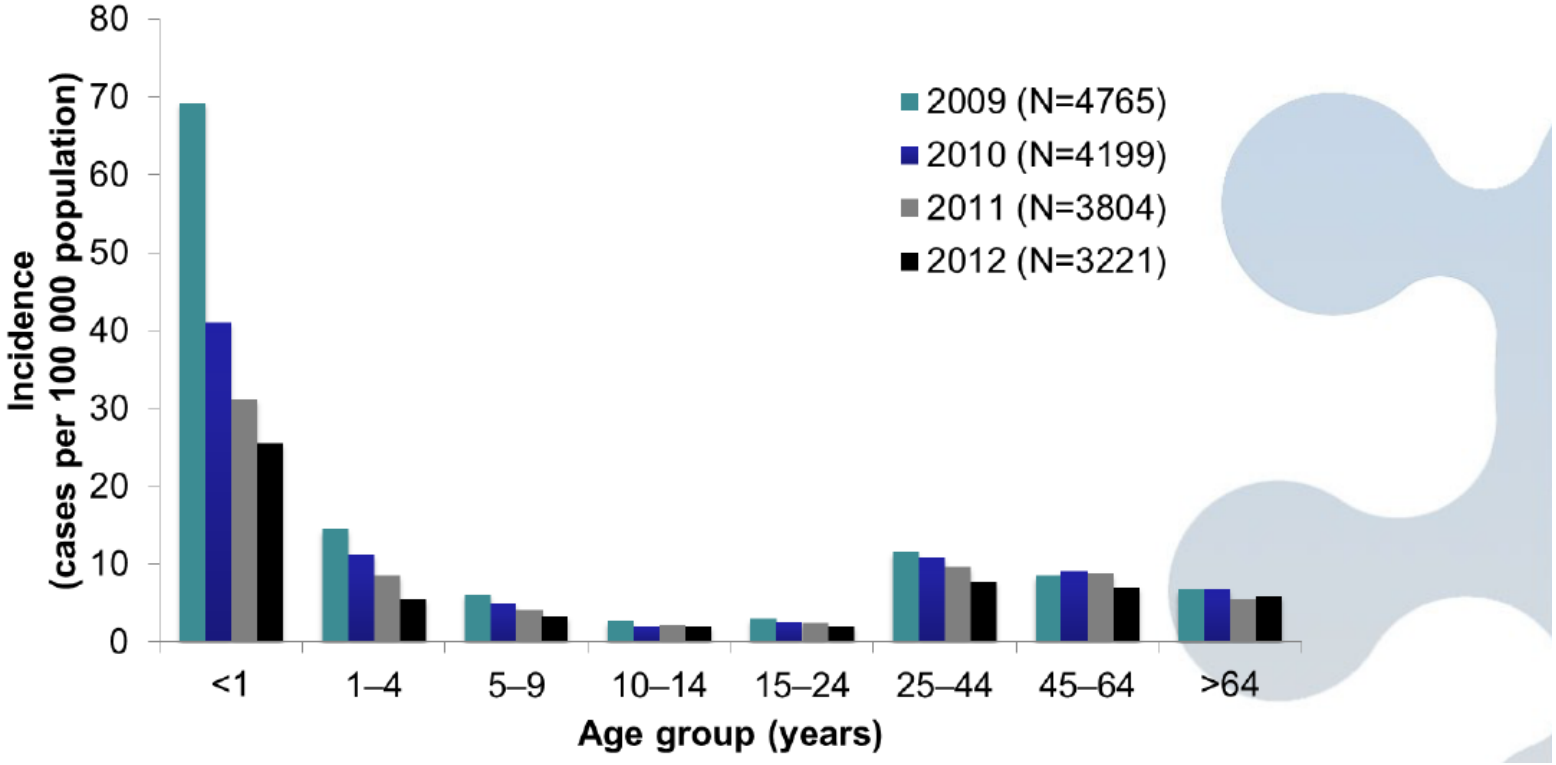
Paed bacteraemia TBH (2008-2013)



Gram negatives (61.1%) **Gram positives (31.6%)** **Fungi (7.3%)**

Slide courtesy A Dramowski, TBH.

Pneumococcal infections



Age-specific incidence rates for laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, South Africa, 2009 through 2012

GERMS-SA Annual report 2012

MDR Invasive pneumococcal diseases

- Associated with
  - Younger age (<1; 2-5)
  - HIV infection
  - Previous antibiotics (incl TB treatment)
  - PCV13 seroypes
- Not associated with
  - Gender
  - Site of infection
  - Outcome

Crowther-Gibson AAC 2012; 56: 5088

Resistance

	2010	2011	2012
Penicillin non-susceptible	42%	34%	28%
Penicillin non-susceptible (<5yrs old)	61%	44%	35%
Ceftriaxone non-susceptible	8%	5%	5%

Reduction thought to be related to reduction in vaccine serotypes

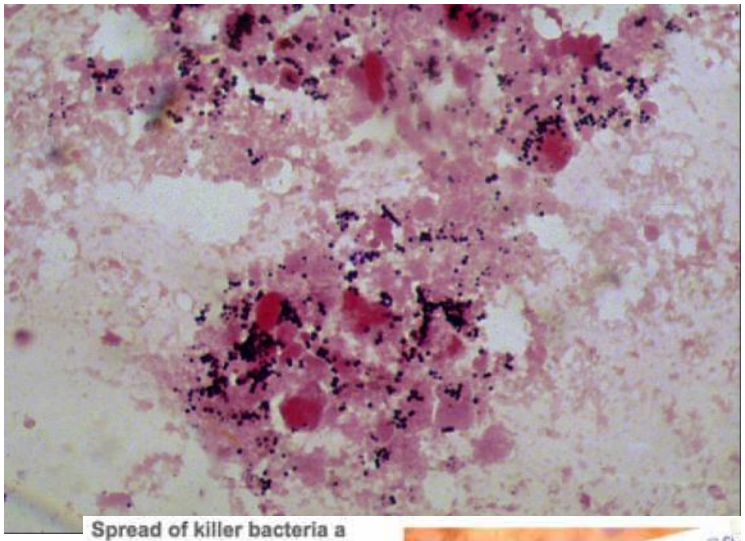
For respiratory infections:

- Penicillin/amoxicillin still appropriate
- High level penicillin resistance (MIC >2) rare – about 5%

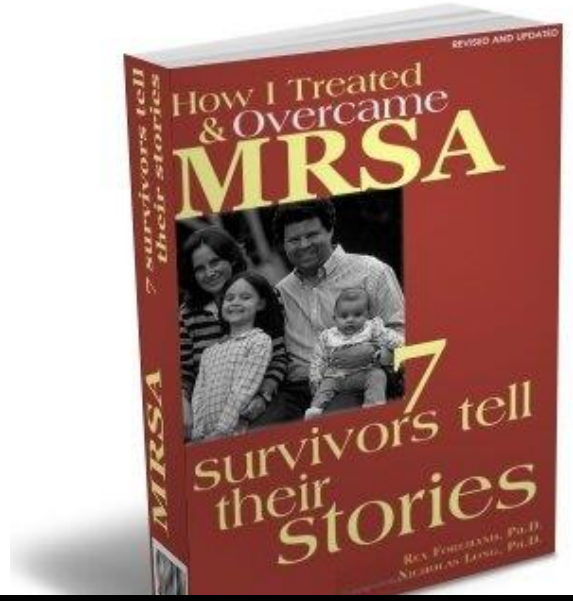
For meningitis:

- Ceftriaxone empirically
- If ceftriaxone MIC >1 – ceftriaxone plus vancomyin; or moxifloxacin plus rifampicin

S. aureus




Spread of killer bacteria a threat to public
Health region fears superbug will hit general population
Michelle Lang, Calgary Herald
Published: Sunday, February 10
Science News
'Superbug' Infections More Than Doubled In Hospitals, Study Finds
TIMESONLINE
NEWS | COMMENT | BUSINESS | SPORT | LIFE & STYLE | ARTS & ENTERTAINMENT
CAREER & JOBS | DRIVING | EDUCATION | FOOD & DRINK | HEALTH | PROPERTY | TRAVEL
Where am I? Home Life & Style Health
From The Sunday Times
March 23, 2008
MRSA and C difficile superbug deaths at 10,000 a year


How I Treated & Overcame MRSA
7 survivors tell their stories
MRSA


World MRSA Day
Saturday, October 1st
10:30am
Loyola University
Stritch School of Medicine
2160 S. First Ave
Maywood, IL 60153
MRSA

Resistance - community

Review

Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Saharan Africa and Asian low and middle income countries

Elizabeth A. Ashley[1,2], Yoel Lubell[1,3], Nicholas J. White[1,3] and Paul Turner[1,3,4]

1 *Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand*
2 *Imperial College NHS Trust, London, UK*
3 *Centre for Tropical Medicine, University of Oxford, Oxford, UK*
4 *Shoklo Malaria Research Unit, Mae Sot, Thailand*

Trop Med Int Health, 2011

- 2004 onwards
- Urine and blood
- >1 month old patients

Definition of community acquired not stringent

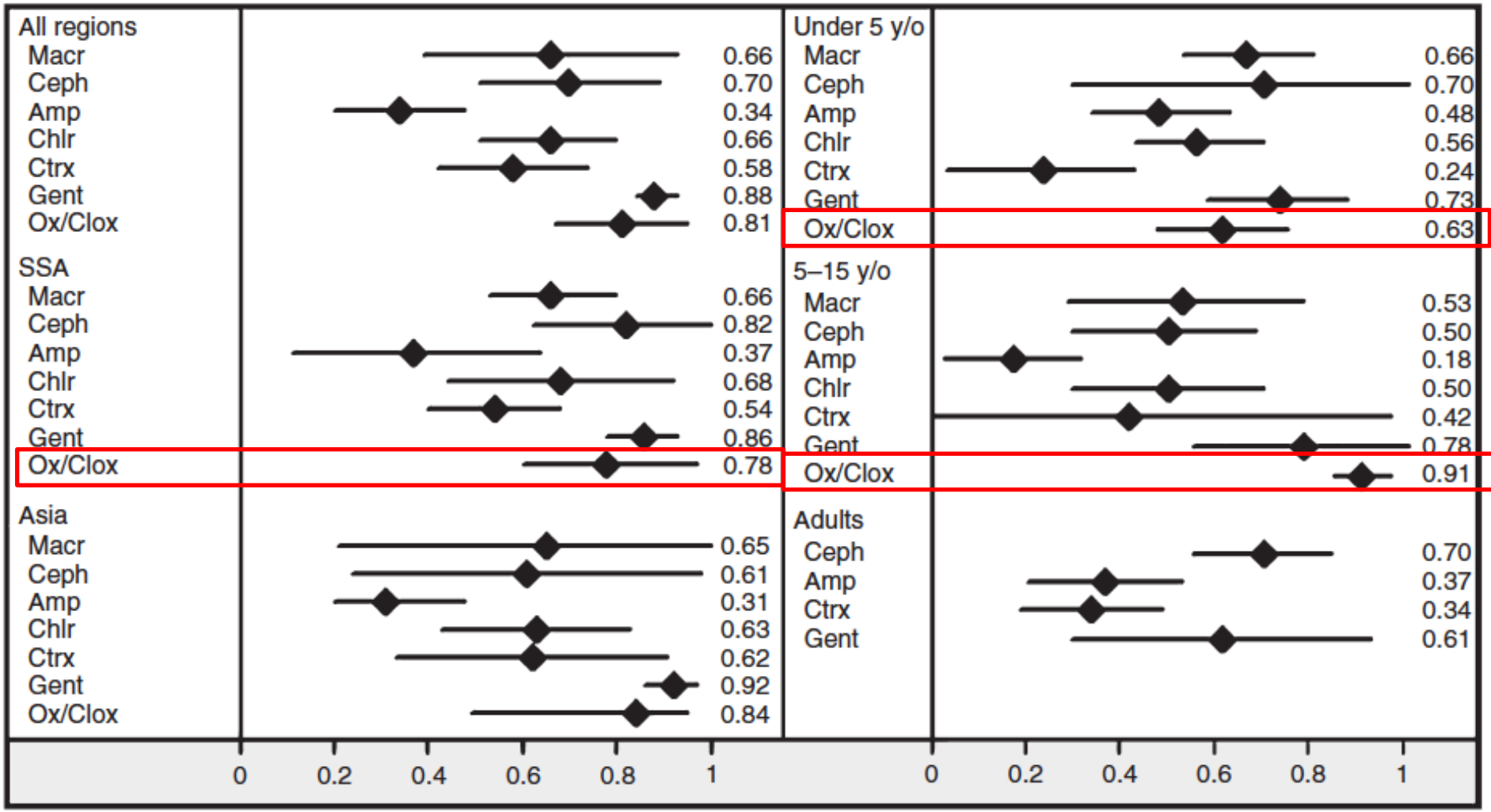


Figure 2 Proportion susceptible of *S. aureus* by region (left) and age group (right). Macr – macrolides; Ceph – **third** generation cephalosporins; Amp – aminopenicillins; Chlr – chloramphenicol; Ctrx – co-trimoxazole; Gent – gentamicin; Ox/Clox – oxacillin/cloxacillin.

Ashley, TMIH, 2011

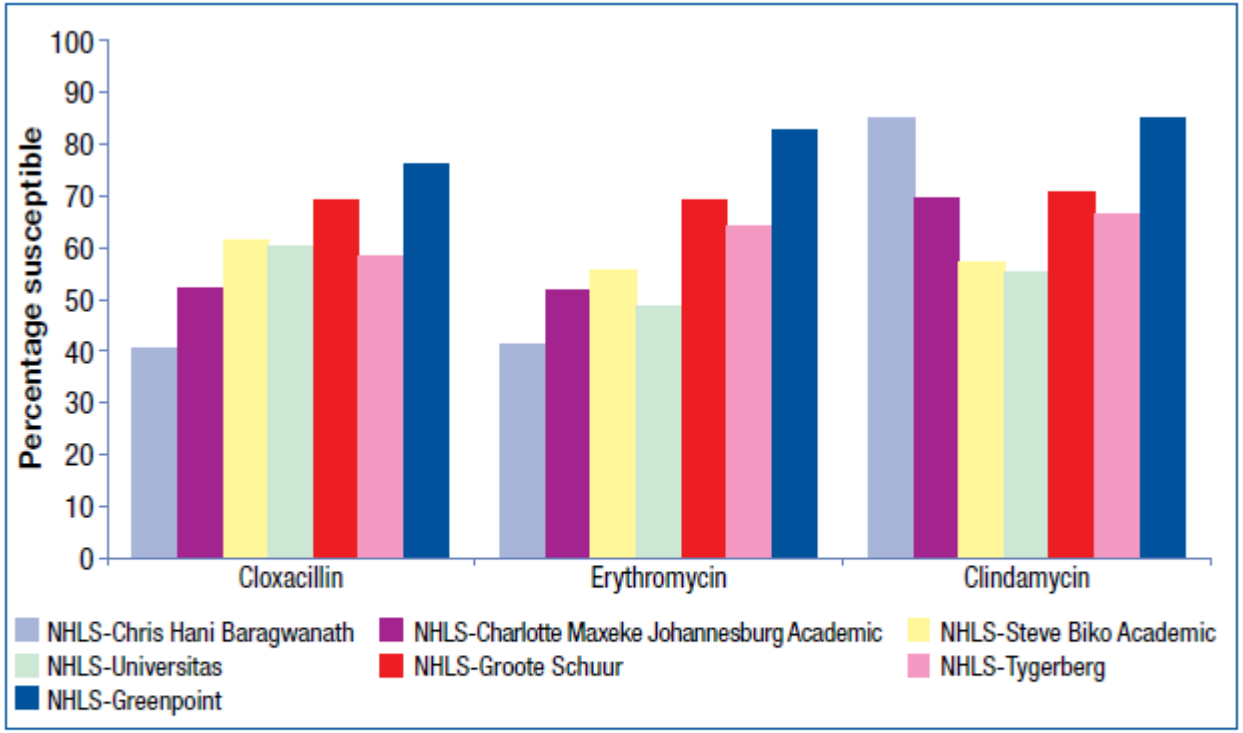
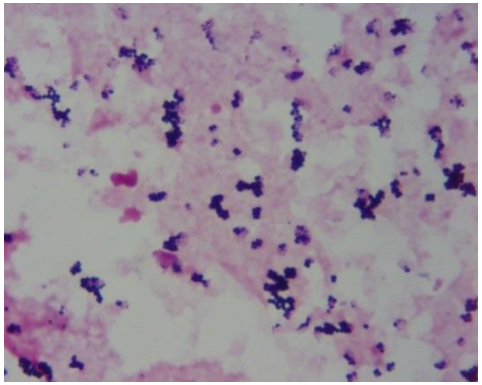


Figure 6: Susceptibility of *Straphylococcus aureus* isolated from blood to selected antimicrobial agents at seven participating laboratories, South Africa, 2010

Combined adults and children
Combined community and hospital acquired

Bamford et al, SA J Epi and Infect 2011

MRSA



- Baragwanath Hosp, Jhb, 2005-2006
  - 39% of CA SAB were MRSA (n=161)
  - Many had been hospitalised in previous year
  - CA defined as pos BC within 48 hrs of admission
- Red Cross Children's Hospital, CT, 2007-2011
  - 3% CA SAB were MRSA
  - 72% of nosocomial SAB were MRSA
  - CA defined as pos BC within 48 hrs admission, with none of the CDC defined risks for HA MRSA

Groome, Paed & Int Child Health, 2012
Naidoo, PLoS One, 2013

MRSA outcome and vanc MIC

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%
Test for overall effect: Z = 2.65 (P = .008)

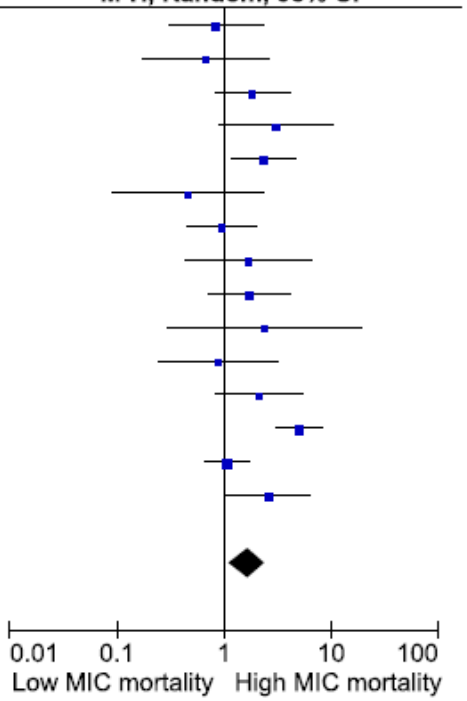


Figure 2. Forest plot (using Mantel-Haenszel analysis) of events denoting methicillin-resistant *S. aureus* mortality (irrespective of source of infection and minimum inhibitory concentration [MIC] methodology used) comparing high vancomycin MIC (≥1.5 µg/mL) with low MIC (<1.5 µg/mL) infections. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

Van Hal, CID, 2012

Table 2. Eligible Studies Examining the Association Between Mortality and Vancomycin Minimum Inhibitory Concentration (MIC) Classified by MIC Categories 1.5 μg/mL and 2 μg/mL Separately

	Study Population	Number of MRSA, (MSSA) Isolates	Source	MIC Method	Mortality% (n) Vancomycin MIC (μg/mL) ≤1	1.5	≥2	Comments
Bae et al [12]	See Table 1	65 (0)	IE	Etest	39% (11/28)	29% (9/31)	67% (4/6)	
Haque et al [19]	See Table 1	158 (0)	HAP	Etest	23%[a] (10/43)	30%[a] (26/86)	52%[a] (15/29)	
Holmes et al [23]	See Table 1	199 (324)	BSI	Etest	12%[a] (7/57)	13%[a] (35/272)	27%[a] (48/179)	Mortality rates were similar for MIC results 1 vs 1.5 μg/mL

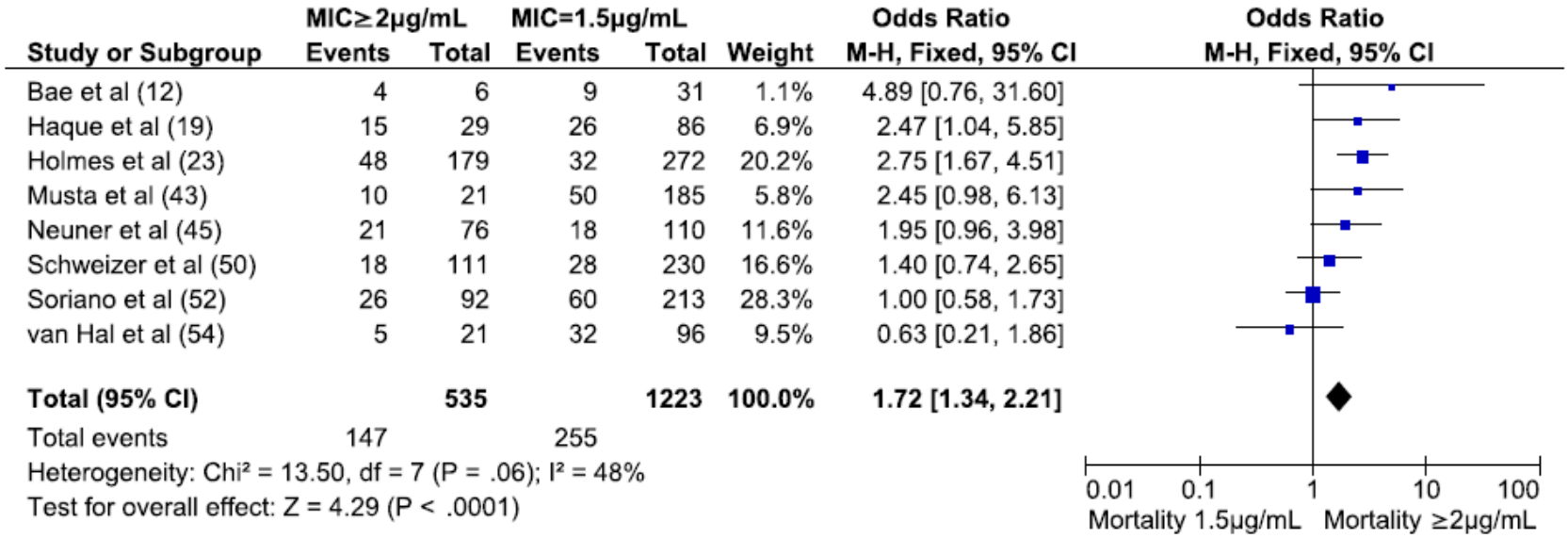


Figure 4. Forest plot (using Mantel-Haenszel analysis) of events denoting *S. aureus* mortality (irrespective of source of infection) comparing Etest vancomycin minimum inhibitory concentrations (MIC) of 1.5 μg/mL with MIC ≥2 μg/mL. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

Van Hal, CID, 2012

MRSA and vancomycin

- Increasing numbers of MRSA with vanco MICs >1,5ug/ml
- Need to monitor levels
  - troughs 15-20 ug/ml
  - No need to monitor peak levels
- Dose 15mg/kg 6 hourly (10mg/kg if renal impairment)
- Debate about continuous infusion
  - Clinical outcomes similar, but fewer SE, better drug levels
- Use alternatives esp if vanco MIC>=2
  - Cotrimoxazole, linezolid, clindamycin

Cataldo. J Antimicrob Chemo 2012; 67: 17

Vancomycin and toxicity

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	9.8%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	7.2%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	6.5%	1.85 [0.69, 4.96]
Hermsen et al. (30)	5	16	4	39	3.6%	3.98 [0.91, 17.46]
Hidayat et al. (13)	11	63	0	32	1.1%	14.24 [0.81, 249.87]
Jeffres et al. (15)	27	49	13	45	7.7%	3.02 [1.28, 7.11]
Kralovicova et al. (31)	21	60	29	138	9.8%	2.02 [1.04, 3.96]
Kullar et al. (32)	8	116	1	84	2.0%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	10.6%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	6.2%	3.13 [1.12, 8.69]
McKamy et al. (38)	16	57	8	110	7.0%	4.98 [1.98, 12.52]
Minejima et al. (39)	17	72	25	155	9.6%	1.61 [0.80, 3.21]
Prabaker et al. (43)	7	54	24	294	7.3%	1.68 [0.68, 4.11]
Wunderink et al. (50)	26	118	24	215	10.7%	2.25 [1.22, 4.13]
Zimmermann et al. (51)	8	12	0	33	1.0%	126.56 [6.19, 2585.90]
Total (95% CI)		**1039**		**1718**	**100.0%**	**2.67 [1.95, 3.65]**
Total events	256		201			

Heterogeneity: Tau² = 0.14; Chi² = 23.89, df = 14 (P = 0.05); I² = 41%
Test for overall effect: Z = 6.13 (P < 0.00001)

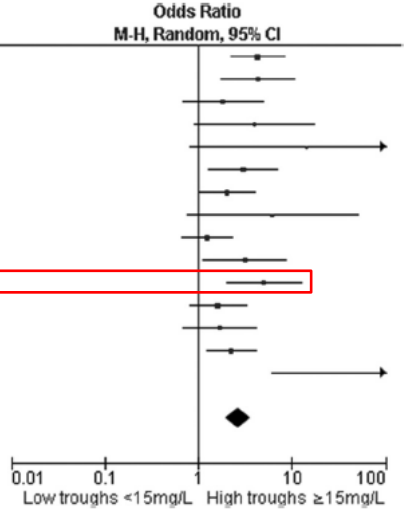


FIG 1 Forest plot (using Mantel-Haenszel [M-H] analysis) of events denoting nephrotoxicity associated with vancomycin, comparing rates for trough levels of ≥15 mg/dl and <15 mg/dl. Squares indicate point estimates, and the size of the square indicates the weight of each study.

Effect of concomitant nephrotoxins
Higher in ICU patients
Generally reversible

Guidelines on how to adjust dosages lacking

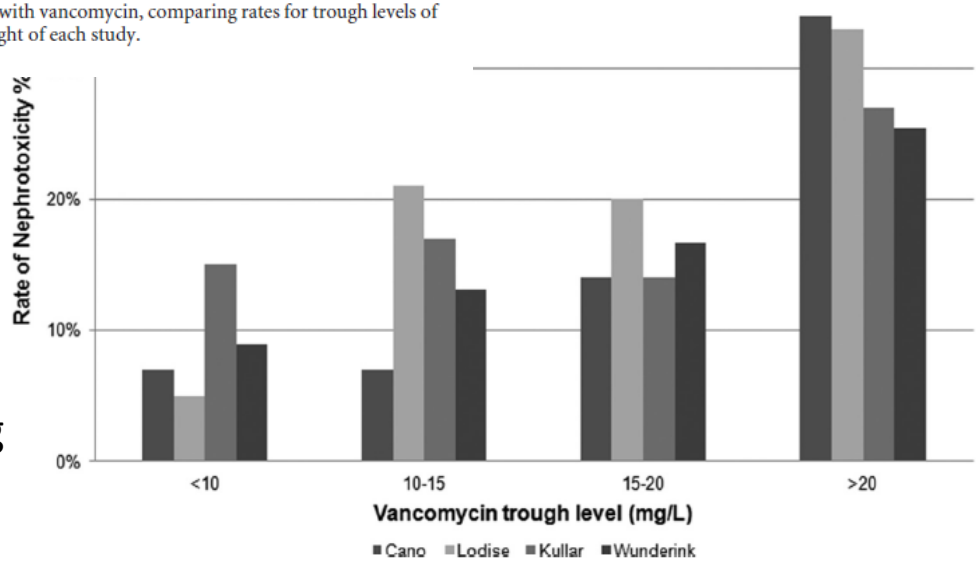


FIG 3 Incidence of vancomycin nephrotoxicity with rising trough levels (8, 22, 36, 50).

Van Hal. Antimicrob Agents Chemother 2013; 57: 734

If not vancomycin, then what?

- Daptomycin
  - SSI, R sided IE
  - NOT resp tract infection
- Linezolid
  - Possibly superior to vancomycin for HAP, VAP
  - Good oral bioavailability
  - Clinical cures in 75-93%
  - SE more common with prolonged therapy
- Don't forget clindamycin, cotrimoxazole, moxifloxacin
  - Probably better for minor infections, oral therapy
- SOURCE CONTROL

Gram negative bacilli

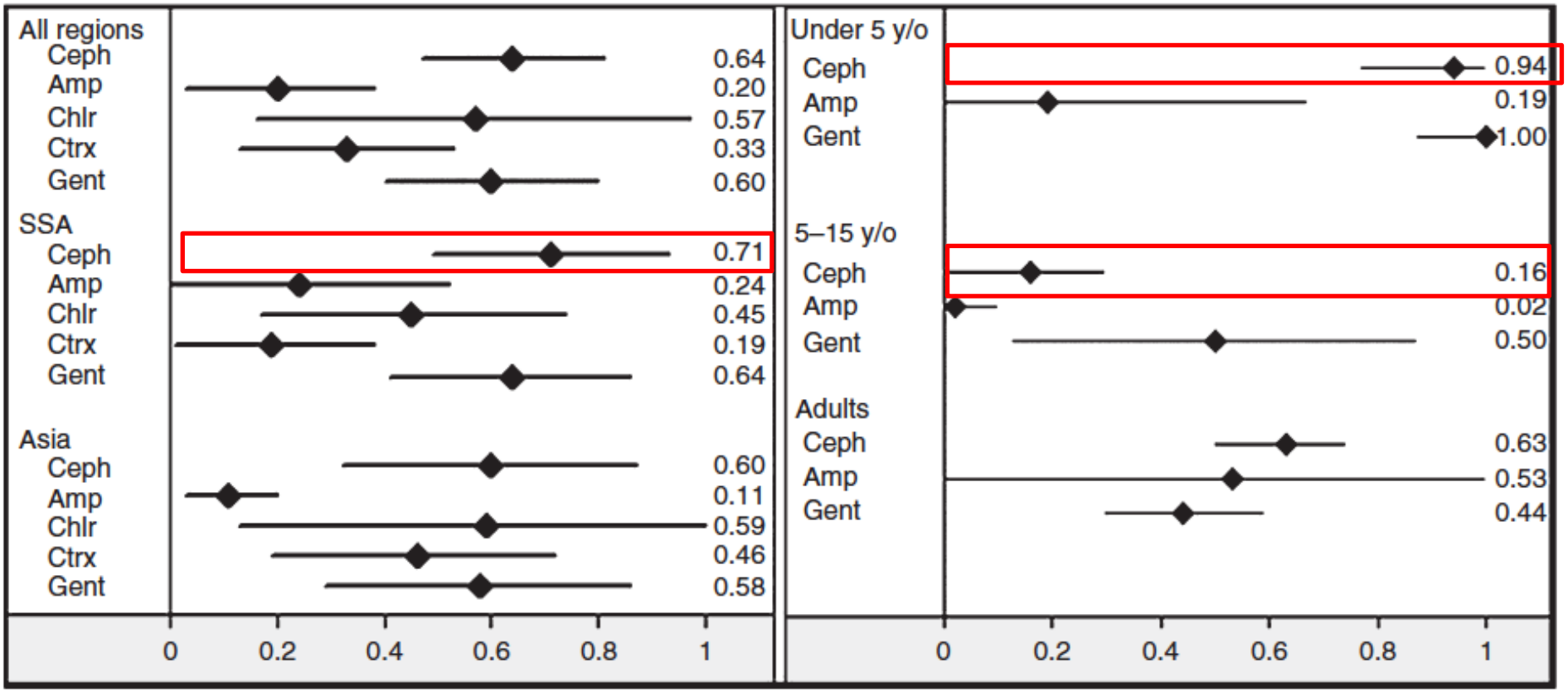


Figure 5 Proportion susceptible of *Klebsiella* spp. by region (left) and age group (right). Macr – macrolides; Ceph – **third** generation cephalosporins; Amp – aminopenicillins; Chlr – chloramphenicol; Ctrx – co-trimoxazole; Gent – gentamicin.

Ashley, TMIH, 2011

Bacteraemia data

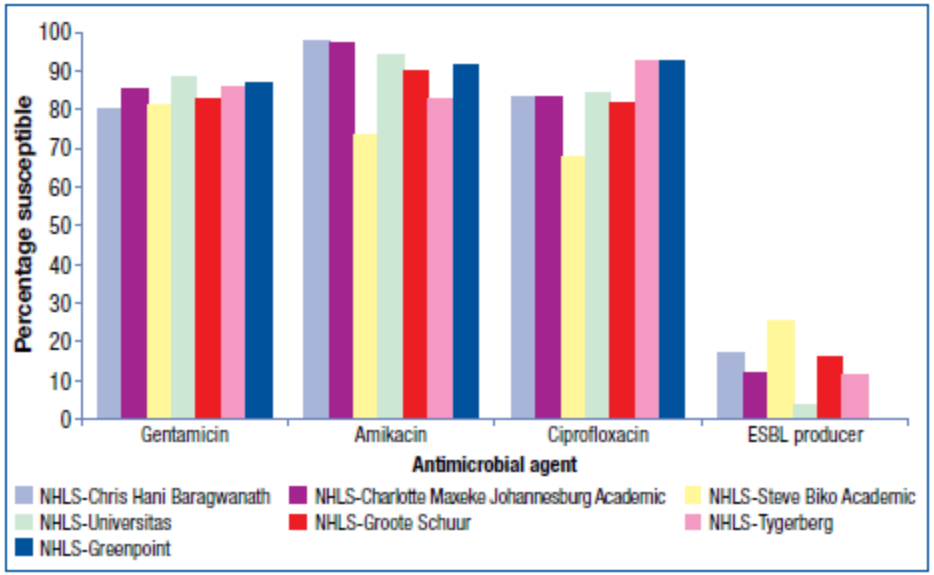


Figure 1: Susceptibility of *Escherichia coli* isolated from blood to selected antimicrobial agents at seven participating laboratories, South Africa, 2010

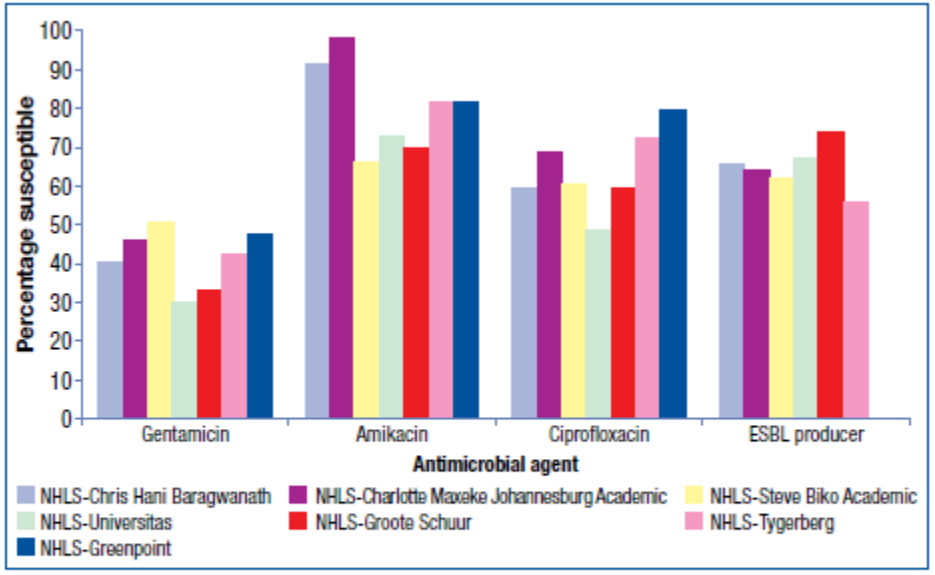


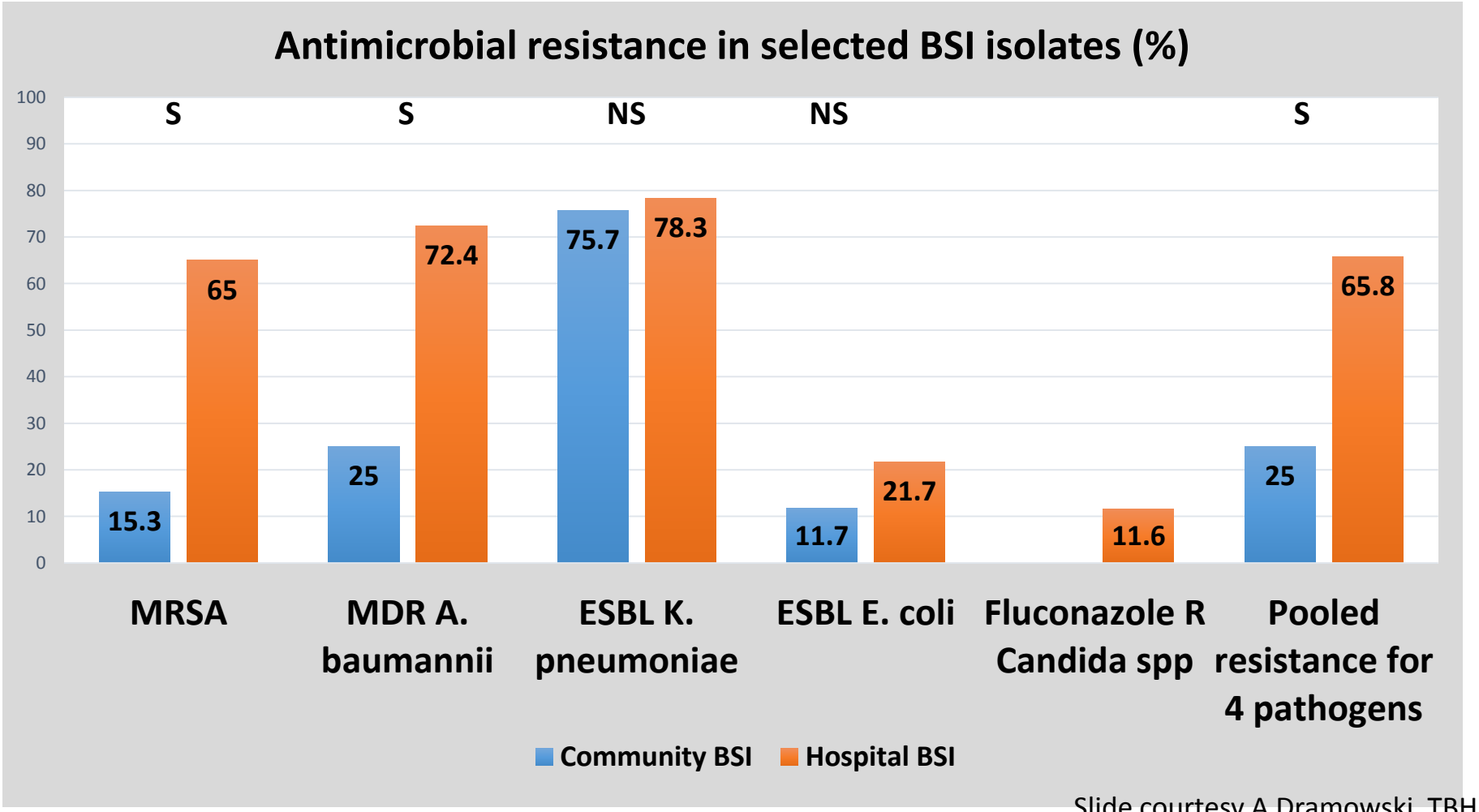
Figure 2: Susceptibiity of *Klebsiella pneumoniae* isolated from blood to selected antimicrobial agents at seven participating laboratories, South Africa, 2010

All pos BCs in state sector, adults and children
No differentiation between CA and HCA

Bamford et al, SA J Epi and Infect 2011

CA-ESBL

- Increasing concern in Europe, USA



Slide courtesy A Dramowski, TBH.

ESBL producing Enterobacteriaceae

- Carbapenems regarded as best option
  - Ertapenem narrower spectrum
  - Meropenem / imipenem in <3 month olds
  - Meropenem if CNS infection / CNS pathology
- Beta-lactamase inhibitor combinations
  - Poor quality data, very limited paediatric data
  - May be effective for UTIs

Ertapenem

Carbapenem stewardship: does ertapenem affect *Pseudomonas* susceptibility to other carbapenems? A review of the evidence

David P. Nicolau[a,*], Yehuda Carmeli[b], Christopher W. Crank[c], Debra A. Goff[d], Christopher J. Graber[e], Ana Lucia L. Lima[f], Ellie J.C. Goldstein[g,h]

Setting	Study period (addition of ertapenem)	Ertapenem use (DDD)	Group 2 carbapenem use (DDD before/after[a])	% carbapenem susceptible (pre versus post ertapenem introduction)
Single centre, ca. 300-bed tertiary centre/teaching hospital; USA [16][b]	March 2004 to December 2008 (July 2005)	58.4/1000 PD	37.5 to 21.0/1000 PD	*Pseudomonas*, 62.2 vs. 70.4 (*P* – N/S) Enterobacteriaceae, 82.5 vs. 88.6 (*P* – N/S)
Single centre, 344-bed teaching hospital; USA [6][c]	January 2002 to December 2005 (July 2003)	44/1000 PD (median)	30 to 25/1000 PD (median)	*Pseudomonas*, 69 vs. 88 Enterobacteriaceae, no change
Single centre, 770-bed teaching hospital; USA [7]	January 2002 to December 2007 (May 2003)	3.4 to 8.9/1000 PD	21.5 to 31.1/1000 PD	*Pseudomonas*, 69 vs. 88 Enterobacteriaceae, no change
Single centre, 770-bed teaching hospital; USA [14]	January 2003 to December 2008 (May 2003)			
Retrospective, longitudinal hospital database study of nine medical wards (400 beds, 139 185 patient admissions, 504 ward months); Israel [15][d]	2001 to 2005 (2001)	2130	4637	*Pseudomonas*, 3.8% annual increase in imipenem-resistant *Pseudomonas* (*P* – 0.001), associated only with group 2 carbapenem use (*P* – 0.0014)
Single-centre study using pharmacy purchase records and microbiology reports; USA [13]	2000 to 2007 (2003)	1670 (2003 to 2007)	1650 to 2295	*Pseudomonas*, 73.2 vs. 71.9 (*P* – N/S) (imipenem); 76.6 vs. 71.9 (*P* – 0.0001) (meropenem)
Single centre, 200-bed tertiary care centre; Brazil [10,11]	March 2005 to March 2007 (March 2006)	42.6/1000 PD	46.3 to 16.1/1000 PD	*Pseudomonas*, 20 to 0 (*P* – N/S)
Single centre, 200-bed, tertiary care centre; Brazil [12]	April 2006 to March 2008 (2006)	31.5/1000 PD	61.1 to 48.7 DDD/1000 PD	*Pseudomonas*, *Acinetobacter*, Enterobacteriaceae, no change
Multicentre (25 community and teaching hospitals), retrospective, data analysis; USA [8,9]	January 2000 to December 2008	7.3 to 15.9[e]	10.4 to 15.3[e]	*Pseudomonas*, 85.4 to 81.0 (*P* – N/S)

What else…

- Aminoglycosides
  - Mainly for UTI
- Quinolones, co-trimoxazole
  - Good options for de-escalation if isolate susceptible
- Fosfomycin
  - High urine concs after single dose
  - Poor serum / renal parenchyma levels – only for cystitis
  - IV form not available in SA (yet…)

Bacteraemia data

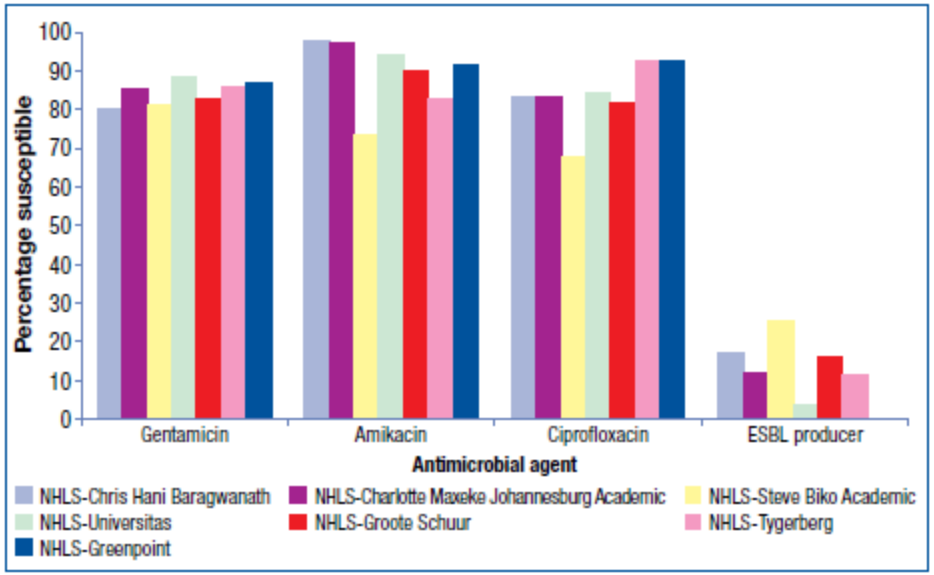


Figure 1: Susceptibility of *Escherichia coli* isolated from blood to selected antimicrobial agents at seven participating laboratories, South Africa, 2010

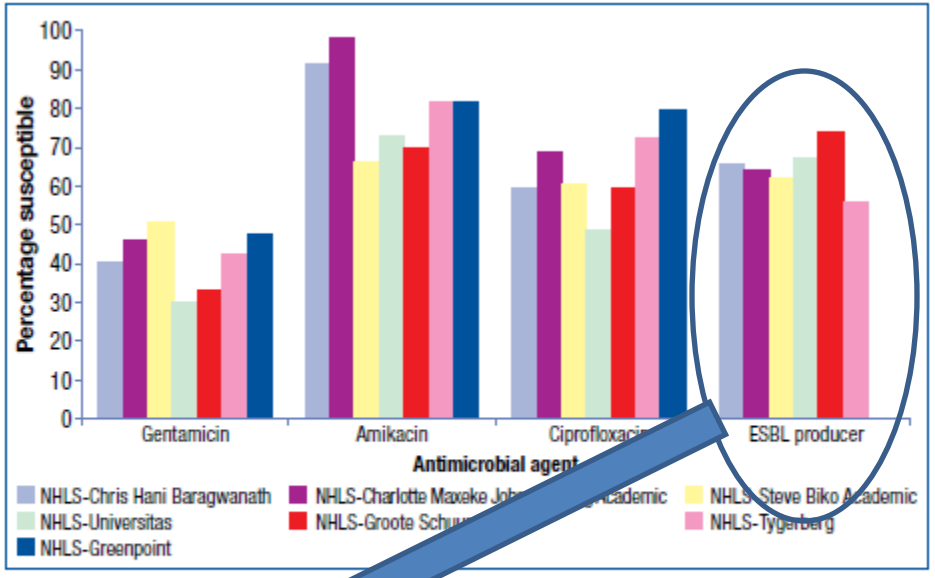


Figure 2: Susceptibi… *Klebsiella pneumoniae* isolated from blood to selected antimicrobial… at seven participating laboratories, South Africa, 2010

Carbapenems

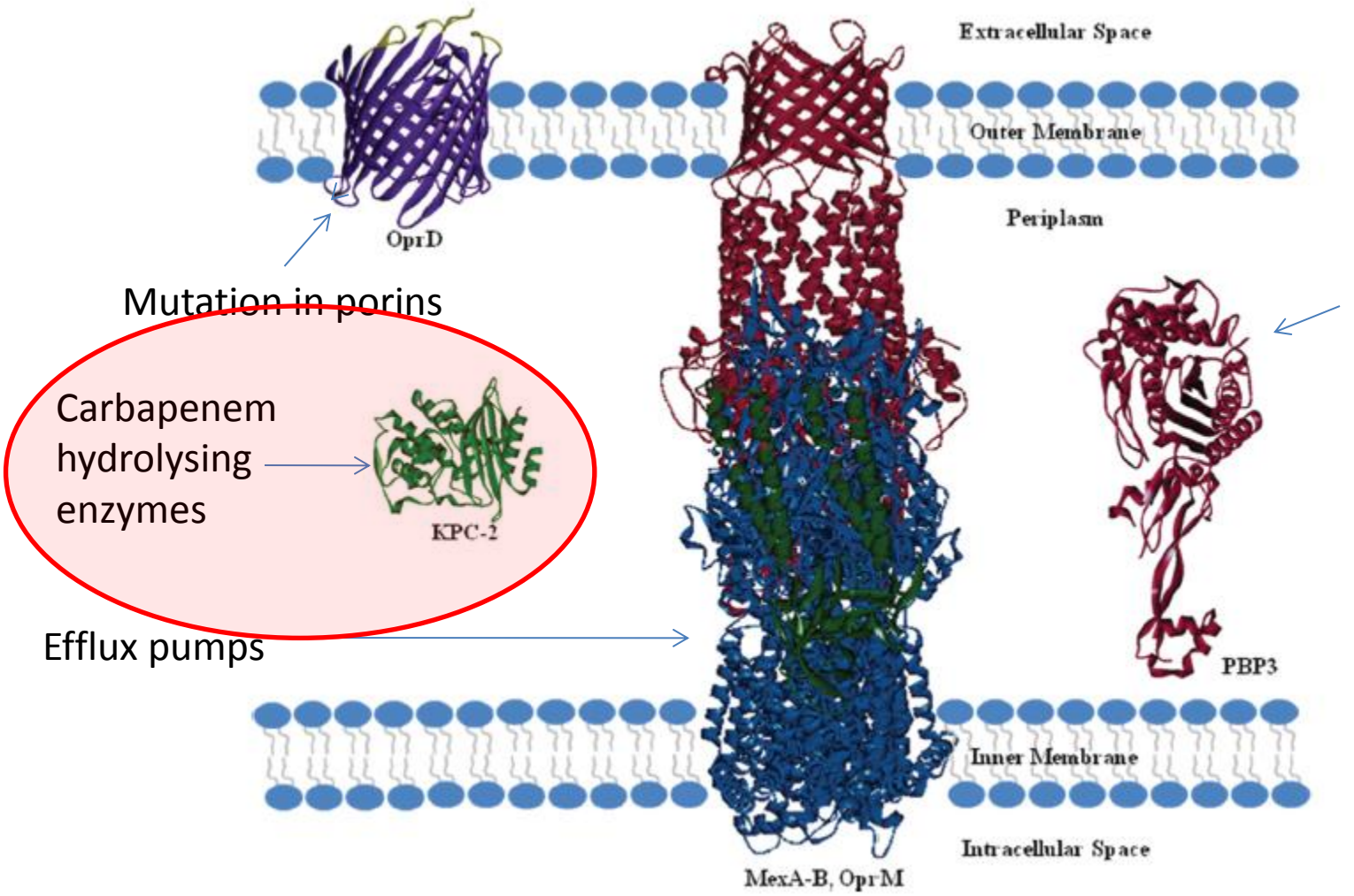
Bamford et al, SA J Epi and Infect 2011

Carbapenem resistance – beyond Acinetobacter and Pseudomonas

Klebsiella pneumoniae	2007 (n=1778)	2010 (n=1914)
ESBL producers – resistant to all cephalosporins	49%	65%
Gentamicin resistance	50%	43%
Fluoroquinolone resistance	28%	37%
Carbapenem resistance (ertapenem)	Not reported	2%

Data from:
Bamford. South Afr J Epidemiol Infect 2009; 24: 28-30
Bamford. South Afr J Epidemiol Infect 2011; 26 (Part II): 243-250

Carbapenem resistance



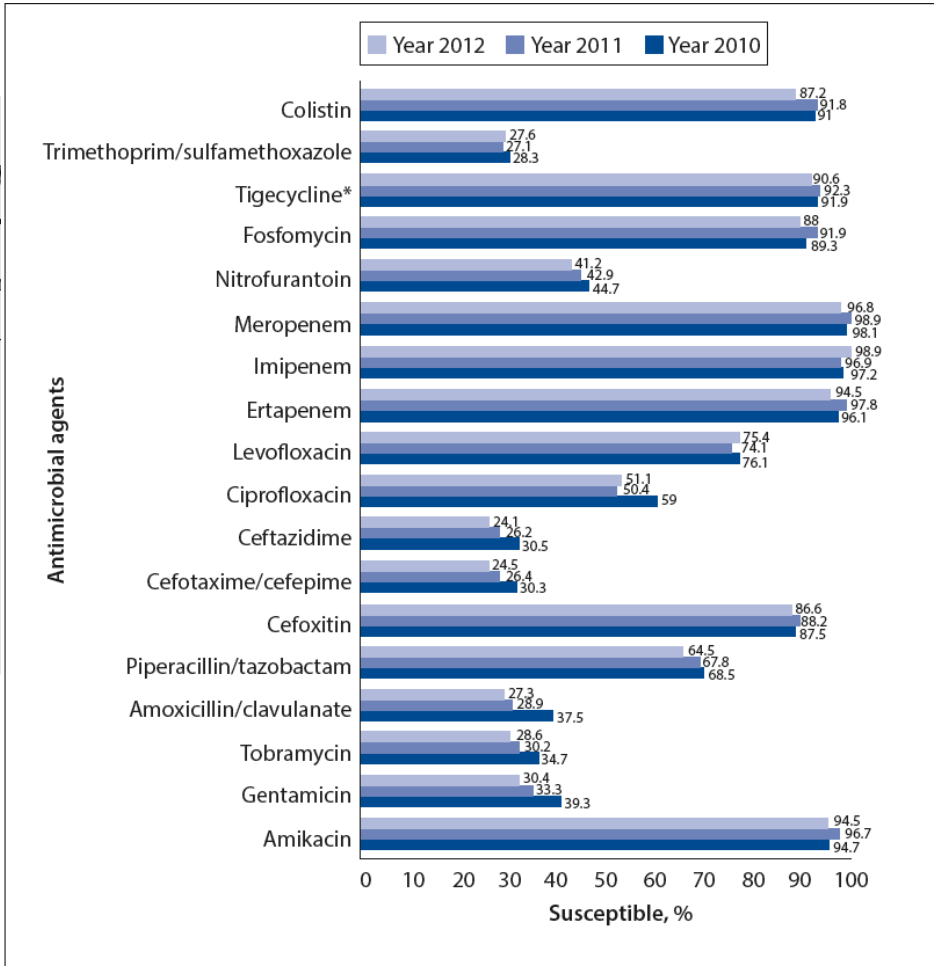
Antimicrob Agents Chemother, 2011, 55: 4943

National sentinel site surveillance for antimicrobial resistance in *Klebsiella pneumoniae* isolates in South Africa, 2010 - 2012

Table 2. Provinces of submission of *K. pneumoniae* isolates 2010 - 2012 and proportion of isolates found to be ESBL-positive or to have reduced susceptibility to carbapenems

Province	Isolates submitted 2010 - 2012, *N*	ESBL-positive isolates 2010 - 2012, *n* (%)	Reduced carbapenem susceptibility, *n* (%)
Gauteng	1 737	1 207 (69.5)	75 (4.3)
Western Cape	620	414 (66.8)	25 (4.0)
KwaZulu-Natal	268	203 (75.7)	15 (5.6)
Free State	134	59 (44.0)	7 (5.2)
Limpopo	15	12 (80.0)	2 (13.3)
Totals	2 774	1 895 (68.3)	124 (4.5)

ESBL = extended-spectrum beta-lactamase.



Perovic et al, SAMJ, 2014

Clinical Significance

- Not always easy to detect by susceptibilty testing – awareness!
- If present, often limited therapeutic options
  - ?combination therapy / alternative agents
    - Imipenem plus colistin
    - Aztreonam (not hydrolysed by most MBLs)
    - Tigecycline (but P. aeruginosa resistant)
    - Fosfomycin – no IV form locally
    - Carbapenem plus colistin plus tigecycline

Tigecycline

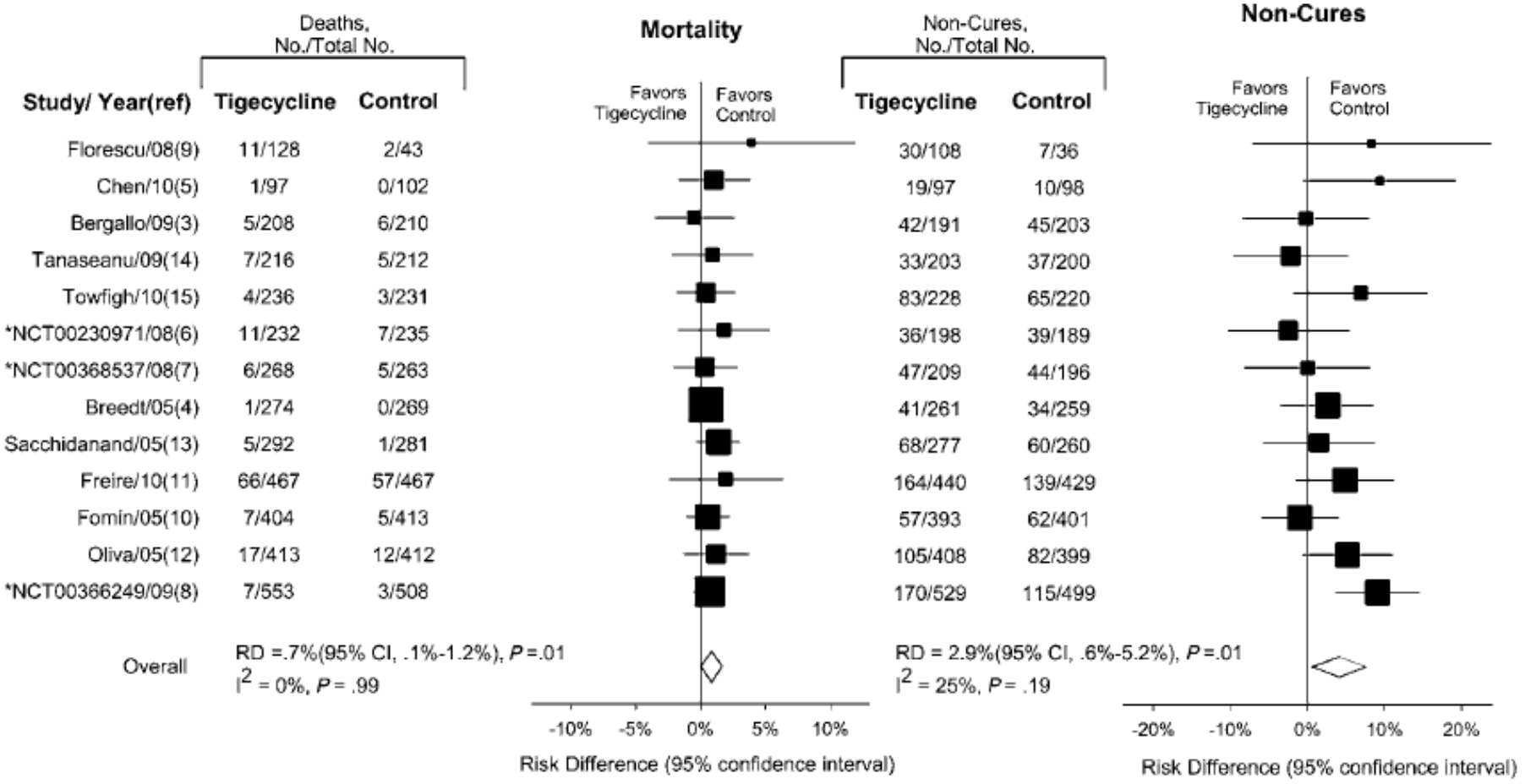
- Glycylcycline, related to tetracyclines
- Broad spectrum Gram pos and Gram neg cover
  - Not active against Pseudomonas
  - Tetracycline derivative – not registered for <8yr olds
- Response rates
  - 68%-84% (VAP - adults)
  - 75-90% (cSSSI, cIAI, CAP – children 8-11)
- Emergence of resistance on therapy
  - Large volume of distribution, low serum levels
  - Concern about treating bacteraemia
- Dose in children ?(1,2mg/kg bd suggested)

Garnaco-Montero. Cur Opin Infect Dis 2010; 23: 332
Gordon. JAC 2009; 63: 775
Purdy. Clin Therap 2012; 34: 496

Excess Deaths Associated With Tigecycline After Approval Based on Noninferiority Trials

Paritosh Prasad, Junfeng Sun, Robert L. Danner, and Charles Natanson

Clinical Infectious Diseases 2012;54(12):1699–709



Colistin - Efficacy

- Review of 5 retrospective case series
  - Clinical response 25-61% (>50% in 4/5 studies)
  - One study compared to imipenem – both 57%
  - Superinfection with colistin resistant organisms uncommon (3 pts)
  - Clinical response in extrapulm infection seems better (72-75%)
    - ?poor lung penetration

Colistin dosing

- Peak:MIC and AUC:MIC important predictors
- More is probably better
- Loading dose recommended
- Twice vs thrice daily?

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

Clinical Infectious Diseases 2012;54(12):1720–6

Colistin dosing

Number	Dose	Outcome	Ref
29 children / 38 courses	5mg/kg/day 75 000U/kg/day	79% good outcome	Korbuz, PIDJ, 2014
31 patients / 41 courses	5mg/kg/day	68,3% good outcome	Konti, Annals Clin Micro and Antimicrob, 2013
27 children / 30 courses	5-8mg/kg/day	53,3% improved	Dimitriades, Arch Dis Child, 2014
50 patients	50 – 75 000 U/kg/day	72% good outcome	Kapour, Ped Crit Care Med, 2013
79 children / 87 courses	5,4mg/kg/day	83,9% good outcome	Paksu, Int J Antimicrob Agents, 2012

Survey of clinicians
No loading dose used
Commonest dose 2,5mg/kg/BD
84% used additional antibiotics

Colistin dosing

- Loading dose recommended in adults
  - 9mU loading (up to 12mU…)
  - 4,5 mU BD
- Limited data in children
  - 75 - 85 000 U/kg/dose BD (2.5mg base/kg/dose)
  - Loading dose suggested 160-170 000 U/kg (5mg base/kg)
    - No evidence!

Fosfomycin

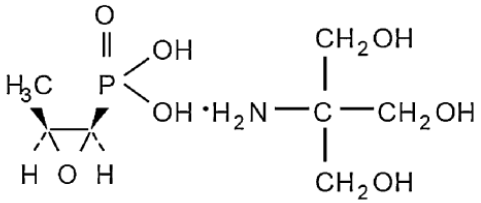
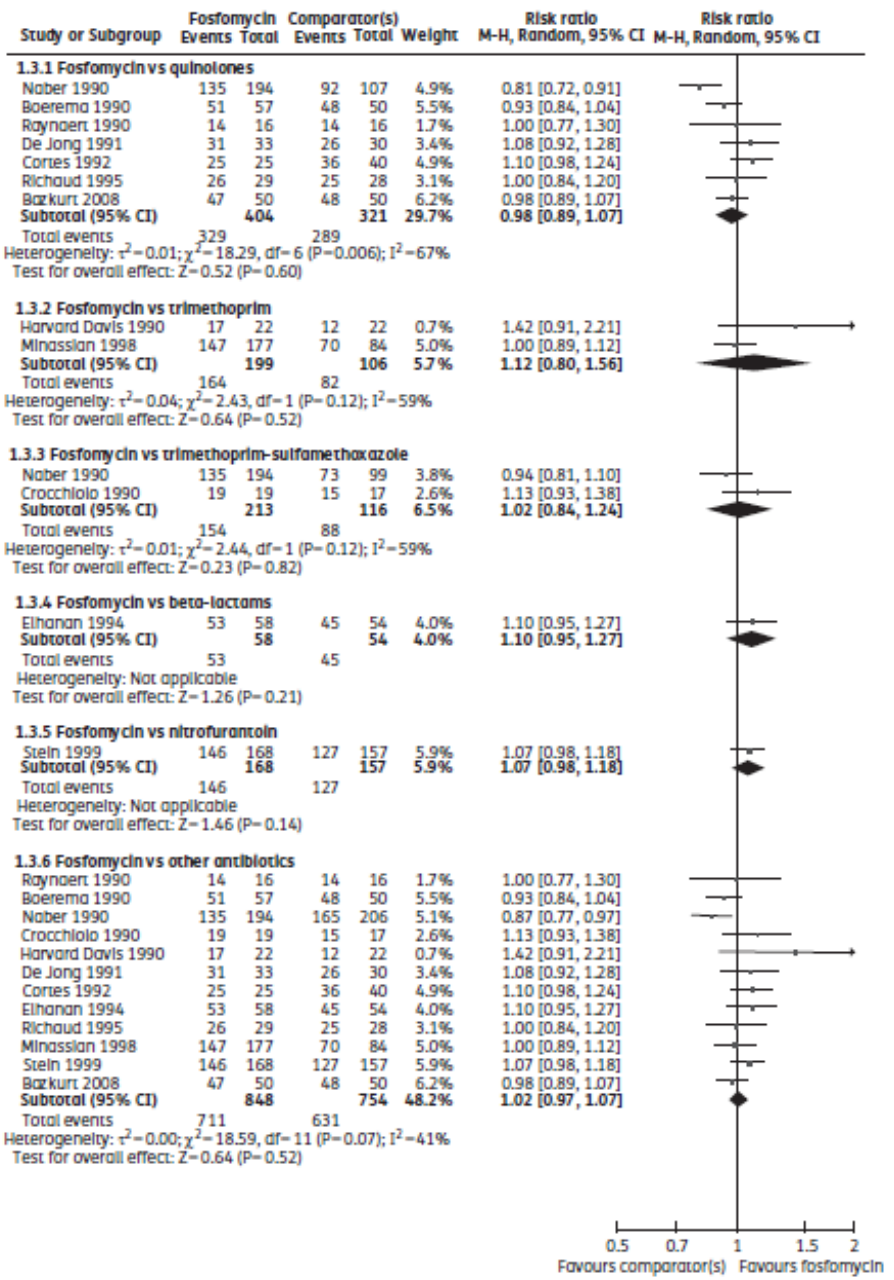


Figure 1. Chemical structure of fosfomycin.

- Inhibits cell wall synthesis
- Broad spectrum
  - >95% E. coli susceptible
  - Less so for other GNB
- Clinical success / cure in >90% patients with ESBL E. coli UTI
- Dose in children >5yrs – 2g stat



Falagas. J Antimicrob Chemo 2010, 65: 1862

2 paed RCTs; RR 0.98 (0.92-1.05)

Fosfomycin

- IV form potential option for serious infections
- Good in vitro activity against MDR GNB (incl Pseudomonas)
  - Best lab testing methodology still unclear
  - Acinetobacter – resistance is common
- Limited published experience using IV; even less in children…
- Possibly needs to be used in combination

Michalopolous. Clin Micro Infect 2010; 16: 184
Pontikis. Int J Antimicrob Agents 2014; 43: 52
Perdigao-Neto. Antimicrob Agents Chemother 2014 (epub)

IV Fosfomycin in children

- Appears safe
- Limited efficacy studies
- Dosing in children unclear

	1-12y	1-12 mo	Preterm, neonates 0-1mo
Austria	4-8g; 2-3x daily	100-200mg/kg/d (max 400); 2-3x daily	100-200mg/kg/d (max 400); 2-3x daily
Germany	100-200mg/kg/d (max 300); 3x daily	200-250mg/kg/d, 3x daily	100mg/kg/d 2x daily
Spain	200-400mg/kg/d, 2-3x daily		
France	100-200mg/kg/d		

Traunmuller. Clin Pharmacokinetics 2011; 50: 493

Table III. T>MIC32 values for different fosfomycin dosing regimens

Age group	T>MIC32 value (%)									
	50 mg bid	100 mg bid	200 mg bid	50 mg tid	70 mg tid	100 mg tid	25 mg qid	50 mg qid	70 mg qid	100 mg qid
Children aged 3–12 y[31]	20	30	40	30	37	45	20	40	50	61
Children aged 5–6 y[32]	24	39	54	38	49	60	29	53	67	82
Full-term and pre-term neonates[32]a	41	67	87	69	85	105	54	102	124	146
Pre-term neonates aged 1–3 d[33]	100	159	219	181	224	271	156	276	334	396
Pre-term neonates aged 20–34 d[33]	60	101	142	107	137	169	80	163	203	245

a Merged into a single study group.

bid = twice daily; **qid** = four times daily; **tid** = three times daily; **T>MIC32** = time above a minimum inhibitory concentration of 32 mg/L.

- T>MIC important parameter

- Suggest higher dose of 100mg/kg/dose 6 hourly (ie total 400mg/kg/day)
  - Need clinical and safety data to back this up…

Traunmuller. Clin Pharmacokinetics 2011; 50: 493

Role of carbapenems

Table 4. Outcomes of the 36 Bloodstream Infections Treated With Combination Therapy Including Meropenem Stratified by Meropenem Minimum Inhibitory Concentration

		No. (%)	
Meropenem MIC (mg/L)	Total	Nonsurvivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Abbreviation: MIC, minimum inhibitory concentration.

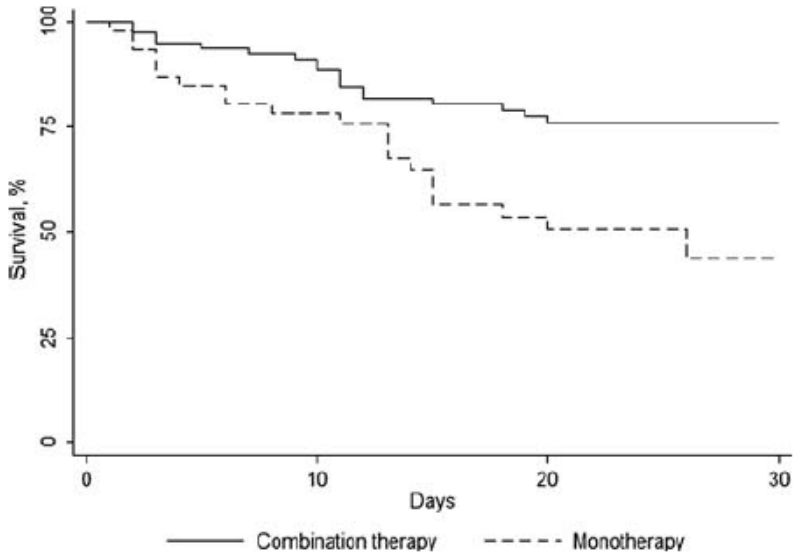
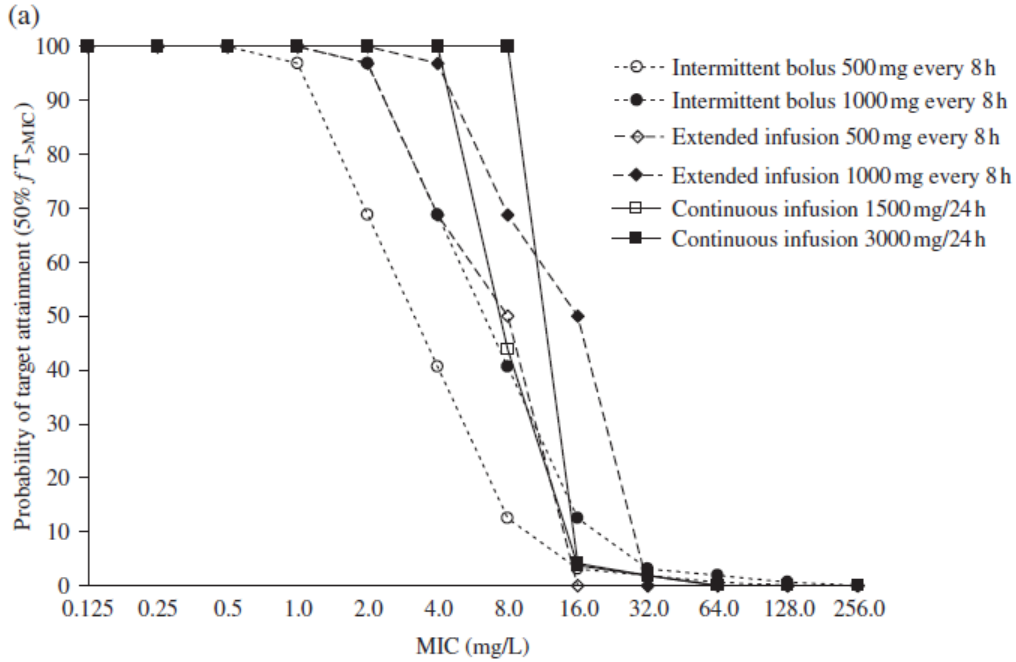
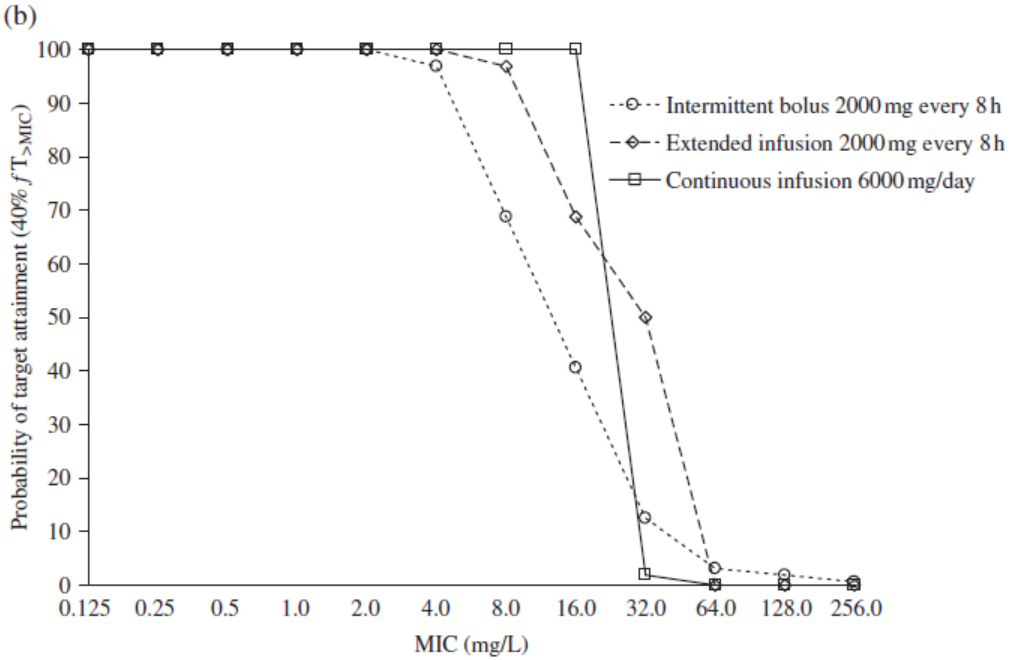


Figure 2. Kaplan-Meier curves showing the impact of combination therapy (solid line) versus monotherapy (dotted line) on 30-day mortality of patients with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* isolate bloodstream infections ($P = .002$).

Therapy with tigecycline + meropenem + colistin :
Mortality OR 0.11 (0.02-0.69)

Tumbarello. Clin Infect Dis 2012; 55: 943





Roberts. J Antimicrob Chemother 2009; 64: 142

So what do I do with my carbapenem resistant Klebsiella?

- Look at available MICs
  - Current criteria may not be best predictors of outcome
  - Combination therapy
  - Which combination???
    - Probably include a carbapenem unless MICs very high (>16ug/mL)
    - Carbapenem plus colistin plus tigecycline
    - Optimise dosing of carbapenem – extended infusion

Mortality

	Carbapenemase producing Klebsiella	Carbapenem resistant Klebsiella
Tigecyclin - colistin	0-30%	25 & 31%
Tigecycline - gentamicin	0-50%	
Carbapenem - colistin	0-67%	
Colistin - gentamicin	40-61%	
Carbapenem	9-50%	50%
Tigecycline	0-53%	73%
Colistin	33-57%	50%

Numerous other combinations (fosfomycin, carbapenem, FQ, tigecycline, colistin, amikacin, piptazobactam, gentamicin, linezolid, vancomycin, doxycycline)

Falagas. Antimicrob Agents Chemother 2014; 58: 654

Infections – Acinetobacter…

Table 2. Sources of bloodstream infection (BSI) caused by either *Acinetobacter baumannii, Acinetobacter* species other than *A. baumannii,* or other gram-negative pathogens.

	No. (%) of patients with BSI caused by						
	Acinetobacter			Other gram-negative pathogens (n = 2952)[a]			
Source of entry	All (n = 129)	*A.* non-*baumannii* (n = 18)	*A. baumannii* (n = 111)		P	OR	95% CI
Intravenous device	26 (20.2)	2 (11.1)	24 (21.6)	470 (15.9)	NS	—	—
Respiratory tract	21 (16.3)	1 (5.6)	20 (18.0)	324 (11.0)	NS	—	—
Urinary tract	2 (1.6)	—	2 (1.8)	462 (15.6)	.0001	10.1	2.5–31.5
Gastrointestinal tract	3 (2.3)	1 (5.6)	2 (1.8)	190 (6.4)	NS	—	—
Wound infection	7 (5.4)	2 (11.1)	5 (4.5)	152 (5.2)	NS	—	—
Other	6 (4.6)	2 (11.1)	4 (3.6)	114 (3.9)	NS	—	—
Unknown	64 (49.6)	10 (55.6)	54 (48.6)	240 (42.0)	NS	—	—

Wisplinghoff. CID 2000; 31: 90

4 year study, multicentre, US, adult and paeds

and Pseudomonas

Table 3
Primary diagnoses of bacteremic *P. aeruginosa* infections.

Primary diagnosis (n = 249)	Total number (%[a])	Nosocomial	Healthcare-associated	Community-acquired
Primary bacteremia	52 (20.8)	26	17	9
Skin and soft tissue [a]	21 (8.4)	10	7	4
Respiratory	81 (32.5)	48	22	11
Endovascular	8 (3.2)	3	5	0
Intrabdominal/pelvic	19 (7.6)	10	4	5
Urinary	50 (20.1)	19	23	8
Hepatobiliary	14 (5.6)	5	4	5
Other [b]	4 (1.6)	3	1	0

[a] Including three episodes secondary to burn infections; [b] others include one bone and joint infection, two CNS infections, one transfusion-associated infection

6 years, multicentre, Canada,, adult and paeds

Parkins. Infection 2010; 38:25

Outcome

- Very variable
  - Colonisation vs infection
  - Different control groups and definitions
  - *A. baumannii* complex vs *A. baumannii*
  - Affected by start of appropriate therapy
- Review of case-control / cohort studies
  - Attributable Mort in hosp – 8-23%
  - Attributable Mort in ICU - 10-43%
  - Longer LOS in infected / colonised

Falagas. Crit Care 2006; 10

Outcome

Table 1. Incidence rates and distribution of pathogens most commonly isolated from monomicrobial nosocomial bloodstream infections (BSIs) and associated crude mortality rates for all patients, patients in intensive care units (ICU), and patients in non-ICU wards.

Pathogen	BSIs per 10,000 admissions	Percentage of BSIs (rank)			Crude mortality, %		
		Total (n = 20,978)	ICU (n = 10,515)	Non-ICU ward (n = 10,442)	Total	ICU	Non-ICU ward
CoNS	15.8	31.3 (1)	35.9 (1)[a]	26.6 (1)	20.7	25.7	13.8
Staphylococcus aureus[b]	10.3	20.2 (2)	16.8 (2)[a]	23.7 (2)	25.4	34.4	18.9
Enterococcus species[c]	4.8	9.4 (3)	9.8 (4)	9.0 (3)	33.9	43.0	24.0
Candida species[c]	4.6	9.0 (4)	10.1 (3)	7.9 (4)	39.2	47.1	29.0
E scherichia coli	2.8	5.6 (5)	3.7 (8)[a]	7.6 (5)	22.4	33.9	16.9
Klebsiella species	2.4	4.8 (6)	4.0 (7)[a]	5.5 (6)	27.6	37.4	20.3
Pseudomonas aeruginosa	2.1	4.3 (7)	4.7 (5)	3.8 (7)	38.7	47.9	27.6
Enterobacter species	1.9	3.9 (8)	4.7 (6)[a]	3.1 (8)	26.7	32.5	18.0
Serratia species[b]	0.9	1.7 (9)	2.1 (9)[a]	1.3 (10)	27.4	33.9	17.1
Acinetobacter baumannii	0.6	1.3 (10)	1.6 (10)[a]	0.9 (11)	34.0	43.4	16.3

Wisplinghoff. CID 2004; 39: 309

Treatment

- Colistin
- Tigecycline (not for P. aeruginosa)
- Combination therapy

Tigecycline

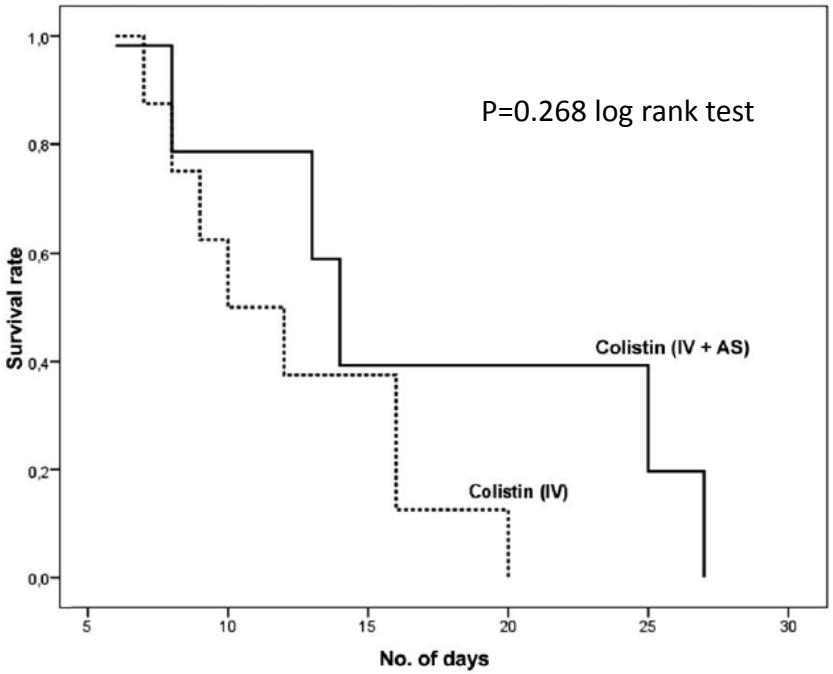
Table 3 Summary of treatments and outcomes among patients with MDRAB in the TG and non-TG treatment groups

	Total (n=386)	Group		p-Value[a]
		Non-TG (n=120)	TG (n=266)	
Treatment				
Duration of antibiotic use[b] (days)	10.0 (7.0, 14.0)	12.0 (9.0, 18.5)	8.0 (6.0, 13.0)	**<0.001**
Switch to other antibiotics[c]	178 (46.1 %)	35 (29.2 %)	143 (53.8 %)	**<0.001**
Death				
No[c]	211 (54.7 %)	64 (53.3 %)	147 (55.3 %)	0.930
Death related to MDRAB infection[c]	142 (36.8 %)	46 (38.3 %)	96 (36.1 %)	
Death not related to MDRAB infection[c]	33 (8.5 %)	10 (8.3 %)	23 (8.6 %)	
Length of hospital stay[b] (days)	40.0 (26.0, 62.0)	37.5 (25.5, 62.0)	43.0 (26.0, 62.0)	0.526
Length of ICU stay[b] (days)	21.0 (10.0, 41.0)	23.5 (10.0, 46.0)	20.0 (10.0, 40.0)	0.338
Microbiological and clinical outcomes				
Microbiological eradication[c]	17 (4.4 %)	14 (11.7 %)	3 (1.1 %)	**<0.001**
Favorable (cure or improvement) [c]	244 (63.2 %)	60 (50.0 %)	184 (69.2 %)	**<0.001**
Unfavorable (stationary or deterioration) [c]	142 (36.8 %)	60 (50.0 %)	82 (30.8 %)	

Retrospective study, 386 patients (adults)
MDR A. baumannii
Non TG – all imipenem and sulbactam
TG – alone or combination

Lee. Eur J Clin Micro Inf Dis 2013; 32: 1211

Nebulised colistin



Ventilator-associated pneumonia–related mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.

- Retrospective case control study
- 43 pts each arm
- Not only *A. baumannii*
- All cause mortality – also no difference

Kofteridis. CID 2010; 51: 1238

- 12/15 VAP patients on colistin only died
- 1/8 VAP patients on colistin plus neb colistin died

Livermore. Int J Antimicrob Agents 2010; 35: 19

Table 3 Summary of available studies on colistin administered by inhalation versus administered parenterally

Study name	Route of administration	% of success
Falagas [15]	inhalation	80% (4 of 5)
Michalopoulos [16]	inhalation + parenteral parenteral	88% (7 of 8) 67% (30 of 45)
Hamer [17]	inhalation + parenteral beta-lactam therapy	100% (3 of 3)
Pereira [18]	inhalation after failing parenteral therapy	93% (13 of 14)
Korbila [19]	inhalation + parenteral parenteral	80% (62 of 78) 61% (26 of 43)
Michalopoulos [20]	inhalation + parenteral (57 of 60 patients) inhalation (3 patients)	83% (50 of 60)

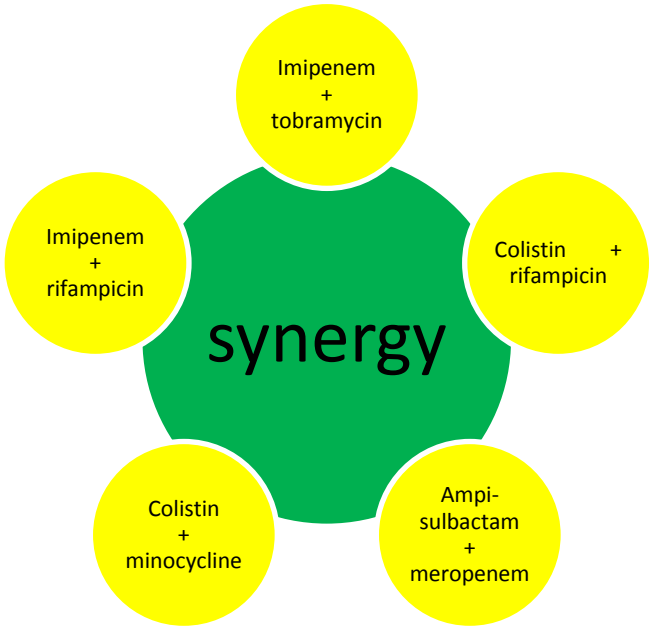
Naesens, BMC Infec Dis. 2012; 11:317

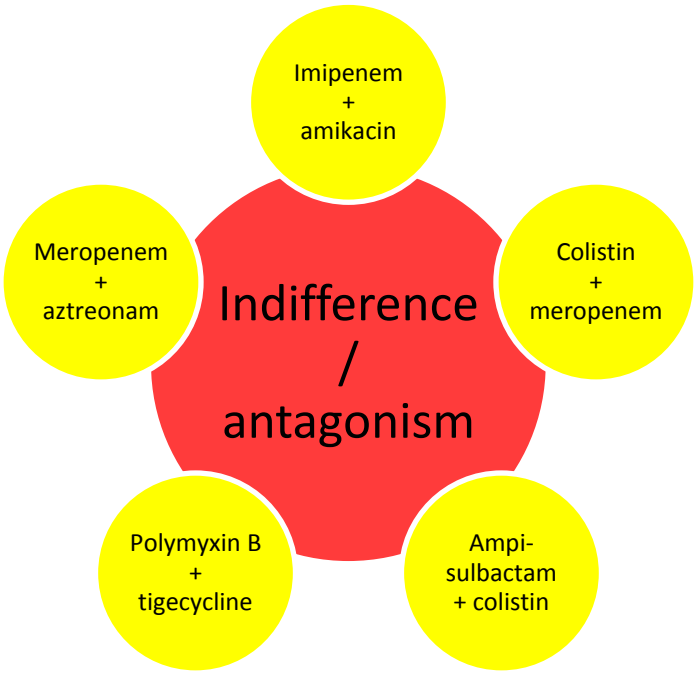
- Nebulised colistin may eradicate carriage
- Need more data - ?infection control implications

Kuo, Clin Micro and Infect. 2012; 18:870

Combination therapy

- Every possible combination seems to have been tried for Acinetobacter
- Colistin / rifampicin seems most popular





Combination therapy - clinical

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	*P* Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	. . .

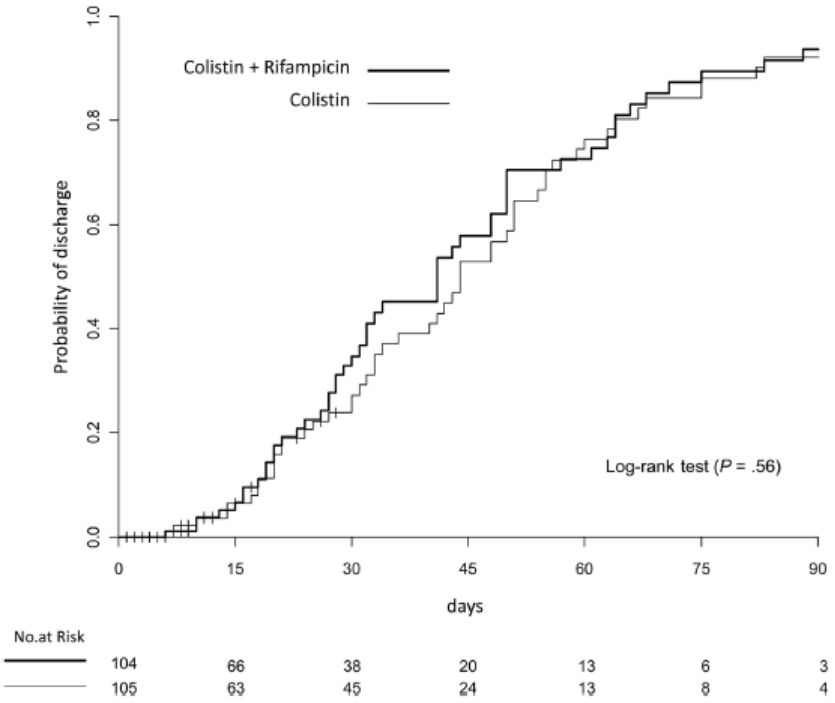


Figure 3. Probability of discharge from hospital by treatment arm (Kaplan-Meier curve).

Durante-Mangoni. Clin Infect Dis 2013; 57: 349

Combination therapy - clinical

Available clinical evidence doesn't seem to show an advantage of combination therapy for Acinetobacter

Fishbain. CID 2010; 51: 79
Garnaco-Montero. Cur Opin Infect Dis 2010; 23: 332
Karageorgopoulos. Lancet Inf Dis 2008; 8: 751
Towner. J Hosp Infec 2009; 73:355
Petrosillo. Clin Micro Infec 2008; 14: 816

Table 2
Outcome of infection due to different pathogens, according to the specific therapeutic regimen received.

Pathogen	Infection outcome	Regimen					
		COL monotherapy[a]	COL + MER[b]	COL + PIP/TAZ	COL + SAM	COL + other agents[c]	All regimens
Acinetobacter baumannii	Cure [*n*/*N* (%)]	20/23 (87.0)*	99/118 (83.9)†	4/6 (67.7)	8/11 (72.7)	7/12 (58.3)	138/170 (81.2)
	Deterioration [*n*/*N* (%)]	3/23 (13.0)*	19/118 (16.1)†	2/6 (33.3)	3/11 (27.3)	5/12 (41.7)	32/170 (18.8)
Pseudomonas aeruginosa	Cure [*n*/*N* (%)]	9/12 (75.0)	24/28 (85.7)	6/10 (60)	1/1	11/17 (64.7)	51/68 (75.0)
	Deterioration [*n*/*N* (%)]	3/12 (25.0)	4/28 (14.3)	4/10 (40)	0/1	6/17 (25.3)	17/68 (25.0)
Klebsiella pneumoniae	Cure [*n*/*N* (%)]	0	11/15 (73.3)	1/1	–	1/2	15/18 (83.3)
	Deterioration [*n*/*N* (%)]	0	4/15 (26.7)	0/1	–	1/2	5/18 (27.8)
All pathogens	Cure [*n*/*N* (%)]	30/36 (83.3)**	135/162 (83.3)††	11/17 (64.7)	9/12 (75.0)	19/31 (61.3)	204/258 (79.1)
	Deterioration [*n*/*N* (%)]	6/36 (16.7)**	27/162 (16.7)††	6/17 (35.3)	3/12 (25.0)	12/31 (38.7)	54/258 (20.9)

COL, colistin; MER, meropenem; PIP/TAZ, piperacillin/tazobactam; SAM, ampicillin/sulbactam.
Relative comparisons for infections caused by *P. aeruginosa* and *K. pneumoniae* were not meaningful because of the small number of cases.
[a] Statistically significant differences between groups of patients—COL monotherapy vs. COL + PIP/TAZ or COL + SAM or COL + other agents: *$P = 0.076$ (not significant) for infections caused by *A. baumannii*; **$P = 0.05$ for infections caused by all pathogens.
[b] Statistically significant differences between groups of patients—COL + MER vs. COL + PIP/TAZ or COL + SAM or COL + other agents: †$P = 0.026$ for infections caused by *A. baumannii*; ††$P = 0.003$ for infections caused by all pathogens.
[c] Other agents included aminoglycosides (11 patients), imipenem (10 patients), cephalosporins (7 patients), aztreonam (2 patients) and ciprofloxacin (1 patient).

Falagas. Int J Antimicrob Agents, 2010; 35: 194

Combination therapy - Pseudomonas

- Susceptible isolates – probably limited benefit (beta lactam vs beta lactam plus other)
  - Data is limited, studies heterogenous.
- Resistant isolates
  - Unknown, but combination based on in-vitro susceptibility seems appropriate

Table 2. 24 hour bacteria burden (log_{10} CFU/ml) after exposure to two-drug & three-drug combinations.

		Baseline	Amikacin-Rifampicin-Polymyxin B	Amikacin-Meropenem - Polymyxin B	Meropenem - Polymyxin B	Amikacin-Meropenem	Amikacin-Rifampicin	Amikacin-Polymyxin B
Clonal Group	**Isolates**	**inoculum**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**
6	PA 403	5.10	**0.89**	2.86	3.20	6.86	8.68	6.27
7	PA 154	5.33	-	-	**0.65**	**1.75**	3.27	**1.60**
5	PA 386	5.20	**0.00**	**0.80**	9.00	6.12	8.80	4.49
8	PA 5	5.16	**2.15**	3.39	3.71	3.71	8.09	2.59
9	PA 6	5.76	-	-	3.00	3.16	3.72	**1.24**
10	PA 15	5.47	-	-	4.22	3.86	8.94	**2.12**
3	PA 30	5.19	**1.30**	**0.65**	4.44	4.37	5.13	2.84
4	PA 35	5.55	-	-	**2.26**	8.08	8.76	**1.30**
5	PA 28	4.97	-	-	**1.69**	3.38	8.16	3.55
2	PA 47	5.04	**0.00**	2.83	4.05	5.15	6.54	3.14
1	PA 48	5.08	4.58	**1.45**	2.38	3.28	6.96	7.50
2	PA 14	5.22	**0.00**	**1.00**	5.90	4.11	4.54	3.15
11	PA 14004	5.14	**1.94**	**0.00**	4.49	3.42	8.50	6.50
12	PA 425	5.39	4.19	4.02	4.11	3.70	7.28	4.35
4	PA 426	5.33	-	-	**1.60**	4.96	9.12	6.27
5	PA 377	5.14	2.89	**0.00**	4.80	6.23	8.78	4.84
3	PA 3355	5.25	-	-	**1.89**	4.09	4.82	4.35
13	PA 31165	5.00	-	-	3.37	**1.65**	7.27	**0.80**
1	PA 2854	5.58	-	-	**0.00**	6.15	5.19	5.36
5	PA 37428	5.56	-	-	**1.95**	8.90	7.47	3.36
5	PA 19224	5.00	-	-	**0.00**	4.43	8.08	6.21
5	PA 50116	5.08	-	-	2.89	**0.00**	**0.00**	**0.00**

Bactericidal combinations denoted in bold.

Tze-Ping, PLoS One 2011, 12:28177

So what do I do with my resistant Pseudomonas / Acinetobacter?

- Look at available MICs
  - Try combination therapy, esp for Pseudomonas
- Options under investigation
  - Phage therapy, immunomodulation, cathelicidins, radio-immunotherapy, nanoparticles
    - All early, no human data
  - Few / no new antibiotics

- SOURCE CONTROL


LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED

The bottom line?

- Very few new antibiotics appearing on the market
- Resistance in community acquired pathogens occurs, poses some challenges
- Hospitals may serve as reservoirs of resistant organisms for the community
- Resistance in hospitals becoming unmanageable…
  - Increased morbidity and mortality
  - Longer hospital stays
  - Increased hospital costs
- Optimal management for many is still unclear

What can we do to prevent this? The biggest challenge

- Antibiotic stewardship

- Infection Control

Imported *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* Clones in a Greek Hospital: Impact of Infection Control Measures for Restraining Their Dissemination

Aggeliki Poulou,[a,b] Evangelia Voulgari,[b] Georgia Vrioni,[b] Grigorios Xidopoulos,[c] Aris Pliagkos,[b] Vassiliki Chatzipantazi,[c] Fani Markou,[a] and Athanassios Tsakris[b]

Intensified IPC

Screening and isolation carriers

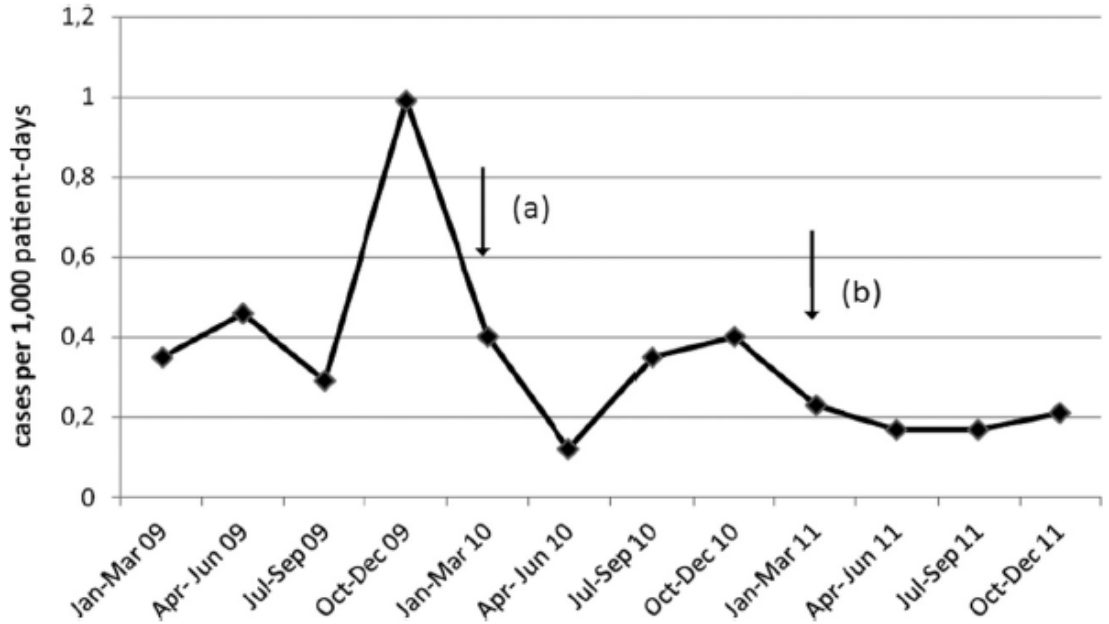


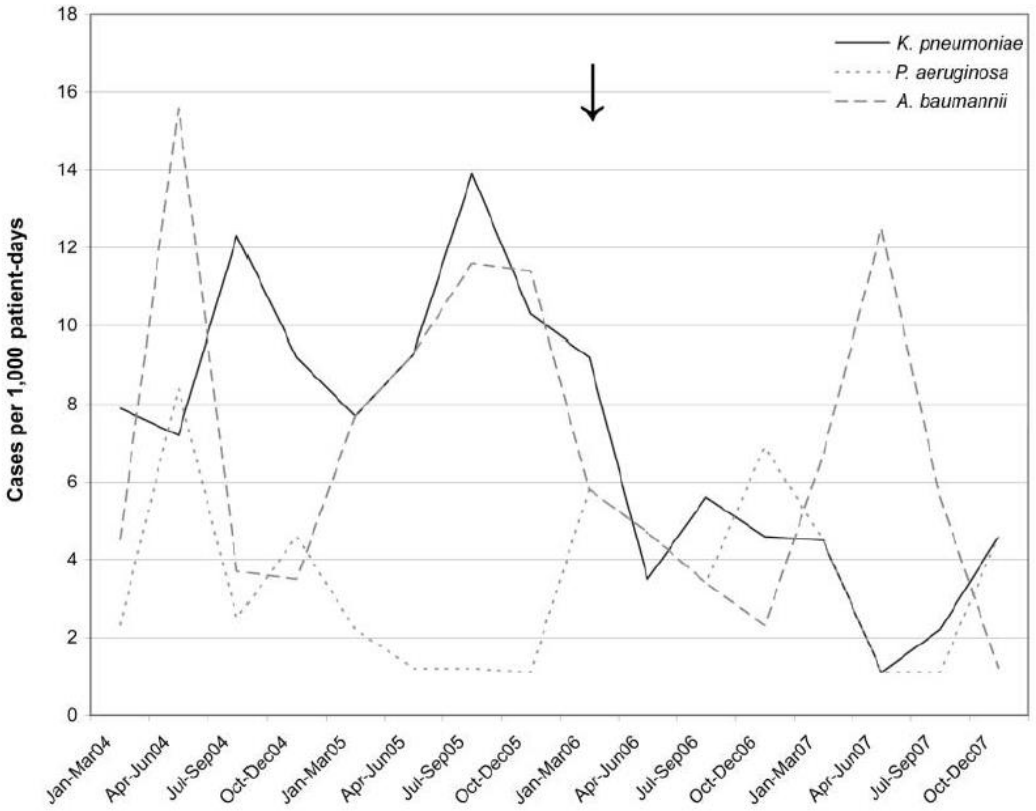
FIG 3 Incidence of new clinical cases due to carbapenemase-producing *K. pneumoniae* per 1,000 patient days per quarter during the 3 years of this study. Arrows a and b indicate the starting points of the additional infection control intervention measures undertaken in January 2010 and January 2011, respectively.

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MAY 2009, VOL. 30, NO. 5

ORIGINAL ARTICLE

Success of an Infection Control Program to Reduce the Spread of Carbapenem-Resistant *Klebsiella pneumoniae*

Sandeep Kochar, MD; Timothy Sheard, MA; Roopali Sharma, PharmD; Alan Hui, PharmD; Elaine Tolentino, MS; George Allen, PhD; David Landman, MD; Simona Bratu, MD; Michael Augenbraun, MD; John Quale, MD



Number of clinical cultures positive for carbapenem-resistant gram-negative bacilli per 1,000 patient-days per quarter. *Arrow,* start of intervention.

J Antimicrob Chemother 2012; **67**: 1427–1431
doi:10.1093/jac/dks063 Advance Access publication 29 February 2012

Journal of Antimicrobial Chemotherapy

Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration

David Landman, Elizabeth Babu, Neha Shah, Paul Kelly, Olafisoye Olawole, Martin Bäcker, Simona Bratu and John Quale*

Table 2. Changes in carbapenem resistance rates in the years 2006 and 2009, and infection control policies at nine hospitals

Hospital	Patients with *K. pneumoniae* with bla_{KPC} per 10000 patient-days		Patients with meropenem-resistant *A. baumannii* per 10000 patient-days		Patients with imipenem-resistant *P. aeruginosa* per 10000 patient-days		Educational programmes for Gram-negative resistance	Rectal surveillance cultures performed for carbapenem-resistant organisms	Cohort patients with resistant pathogens	Cohort staff caring for patients with resistant pathogens	Change in number of infection control staff 2006–09
	2006	2009	2006	2009	2006	2009					
Hospitals with a decline in KPC-possessing *K. pneumoniae*											
1	15.89	1.69	10.59	5.08	4.89	2.37	yes	yes[a]	no	no	increased
2	4.62	2.39	4.84	4.14	1.10	1.09	no	no	no	no	increased
3	5.81	3.2	0.39	5.95	1.55	3.66	no	no	no	no	unchanged
4	13.06	6.71	11.19	7.22	7.09	6.19	no	no	no	no	unchanged
5	9.73	5.94	6.63	6.16	5.75	6.58	yes	no	yes[b]	no	increased
6	5.23	2.43	7.32	2.44	3.83	5.57	yes	no	no	no	decreased
Hospitals without a decline in KPC-possessing *K. pneumoniae*											
7	5.87	7.21	7.27	19.20	5.03	11.42	yes	no	yes[b]	no	decreased
8	14.00	24.94	18.07	22.06	9.94	24.46	yes	no	yes[b]	no	unchanged
9	5.50	13.80	9.85	9.10	1.74	4.11	no	no	no	no	increased

Better understand the burden of AMR in children

More experience / evidence to guide treatment options

Practice antimicrobial stewardship

Focus on infection control


THE END
THANK YOU