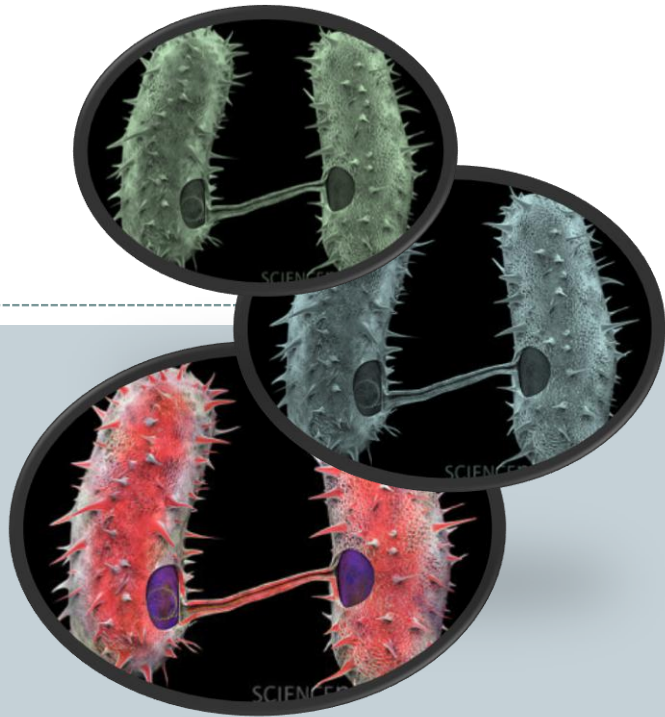


# Carbapenem Resistance in *Enterobacteriaceae* in SA



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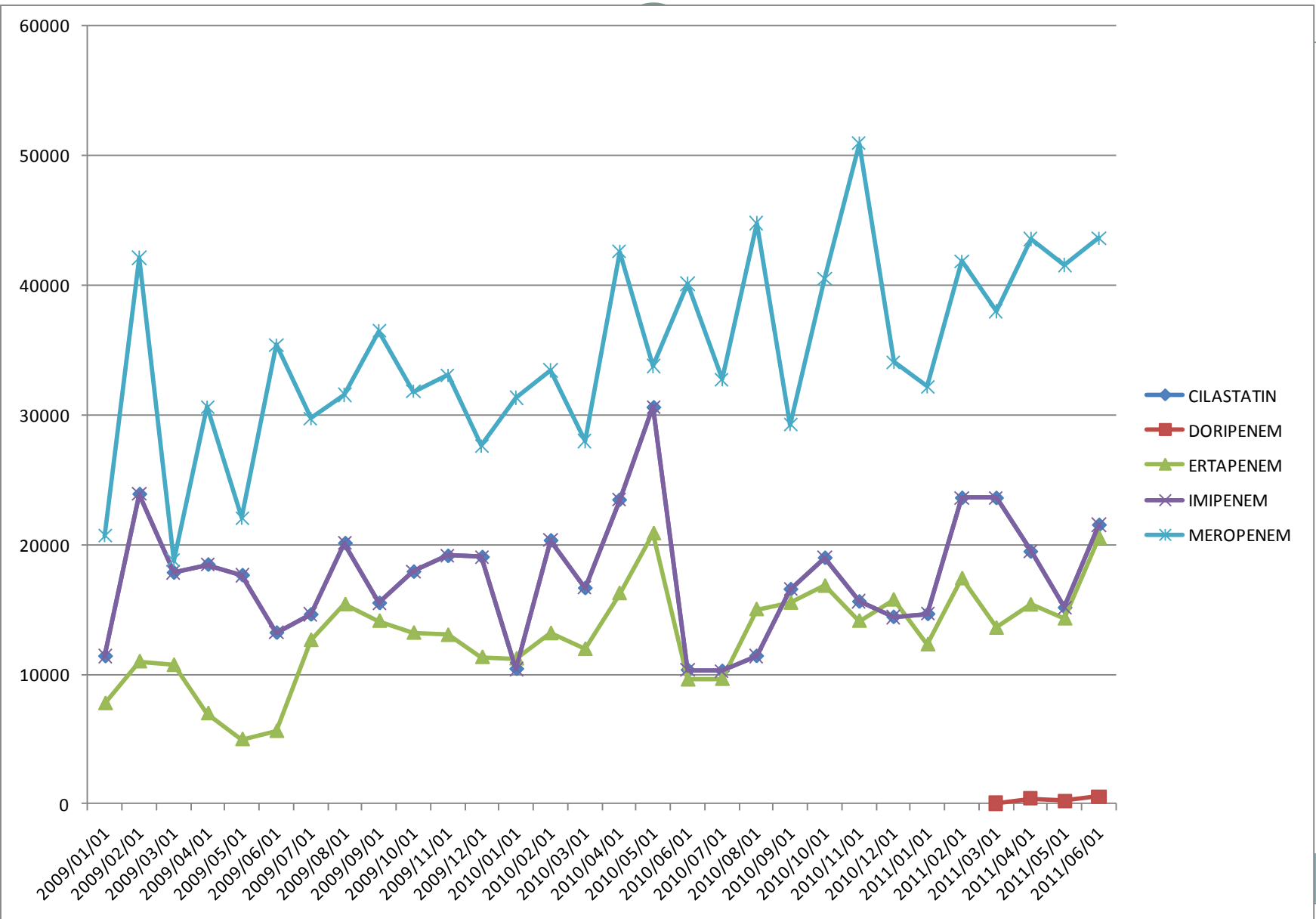
# Introduction



- Resistance to antibiotics among *Enterobacteriaceae* is a reality in SA

	Percentage Susceptible						
(Number of laboratories)	Jhb (3)	Pta (3)	Dbn (2)	CT (2)	PE (1)	EL (1)	Bfn (1)
<b>n = Total of isolates</b>	<b>316</b>	<b>203</b>	<b>166</b>	<b>73</b>	<b>14</b>	<b>9</b>	<b>10</b>
Ampicillin	0	0	0	0	0	0	0
Cefuroxime	34	26	38	37	31	22	50
Ceftriaxone/cefotaxime	36	27	39	38	43	22	50
Cefepime	36	27	39	38	43	22	50
Amox / clavulanate	32	27	40	37	43	22	40
Piperacillin/tazobactam	41	27	54	45	43	22	80
Gentamicin	44	37	61	67	50	44	67
Amikacin	77	74	80	82	93	90	80
Ertapenem	97	94	99	97	100	100	100
Imipenem/meropenem	98	98.5	100	100	100	100	100
Ciprofloxacin	74	70	52	48	57	70	90
% ESBL	60	57	55	55	57	78	50

# Monthly Unit Chart for Carbapenem Use in SA



# Mechanisms of Resistance to Carbapenems in *Enterobacteriaceae*



- AmpC or ESBL overproduction with porin loss
- Carbapenemase production:
  - **Class A carbapenemases** (Bush group 2f) e.g. KPC, IMI, SME, NMC-A and some GES enzymes
  - **Class B enzymes** (Bush group 3) e.g. VIM, IMP and SPM-1, NDM
  - **Class D enzymes** belonging to the OXA family

# What is happening in SA?



- We're not sure
- It has previously been shown that the CTX-M ESBLs in conjunction with porin loss in *K pneumoniae* influenced carbapenem susceptibility in SA

Elliott E et al. CID 2006:42(1 June) e95-98

Segal H et al. South Afr J Epidemiol Infect 2006; vol 21(2):41-44

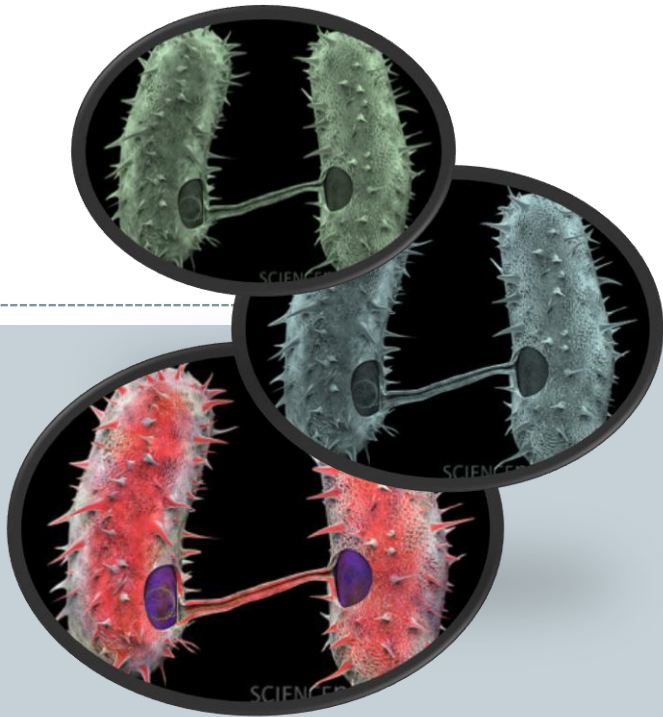
# What is happening in SA?



- Started screening carbapenem resistant *Enterobacteriaceae* with multiplex PCR for Class A carbapenemases in March 2010
- Started with 38 stored isolates, 16 of which was modified Hodge test positive
- All negative
- Very disappointed!
- A year and 143 isolates later...

“Multiplex PCR for Rapid Detection of Genes Encoding Class A Carbapenemases”  
Hong S.G. et al. 20th ECCMID Poster session 93

# Case report of the 1<sup>st</sup> described KPC in SA



# Case Study



- 37 year old female patient
- Admitted with severe DVT of left leg
- Underlying condition of ulcerative colitis
- Had wound on right ankle
- Admitted to high care, subsequently ICU
- Admission blood culture grew CNS, sensitive to vancomycin, teicoplanin and linezolid
- Teicoplanin initiated on day 1 (22 days)

# Case Study



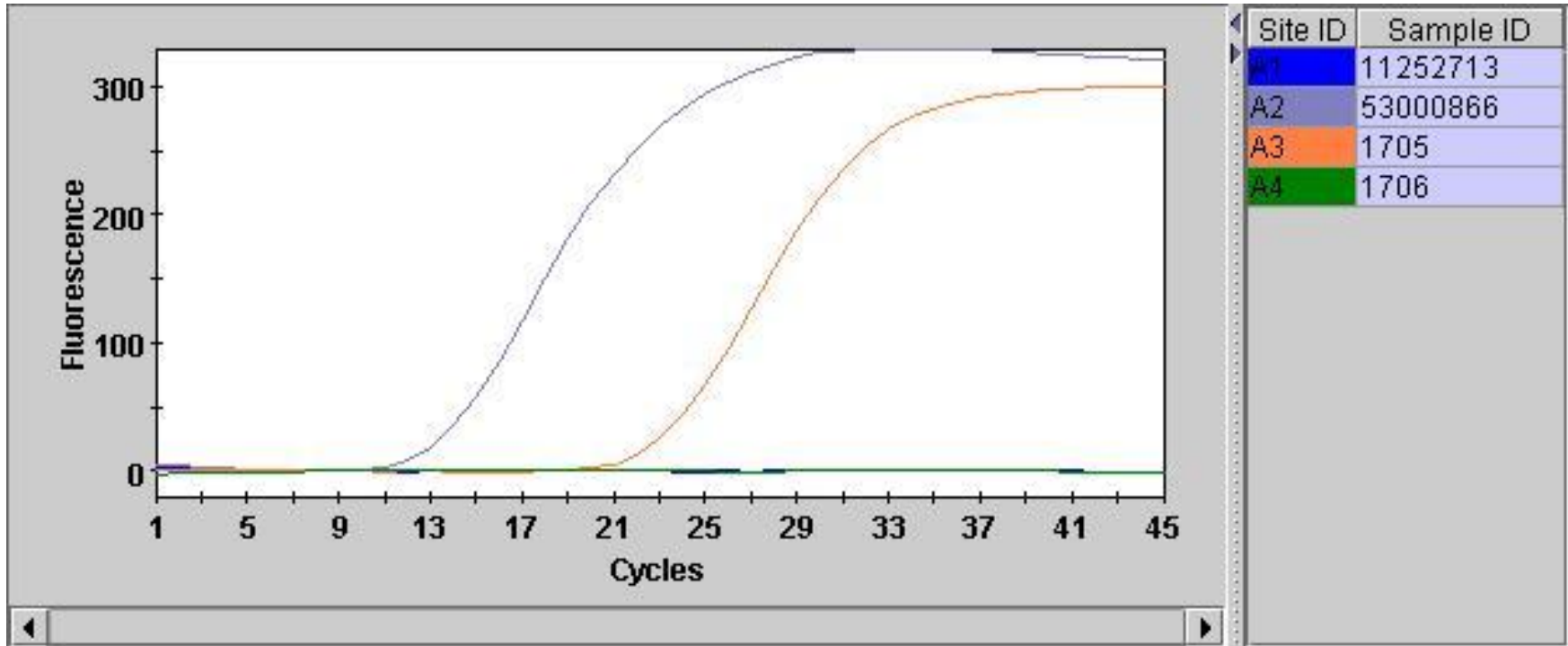
- Day 3 pus swab of wound on right ankle grew *P aeruginosa*, sensitive to all “antipseudomonal agents”
- Day 4 surgery for insertion of IVC filter
- Daily episodes of bloody stools shortly thereafter, Diflucan 400mg daily commenced
- Day 9 doripenem 500mg 8-hly started, continued for 10 days
- Day 11 patient requires resuscitation and intubation

# Case Study



- Day 13 Flagyl 500mg IVI 8-hly for 7 days, blood cultures drawn negative
- Sputum sent for MC&S on day 13, grew *Enterobacter cloacae*: sensitive to amikacin, gentamicin, tobramycin, ciprofloxacin and tigecycline
- MIC's for carbapenems: ertapenem, imipenem and doripenem = 4 $\mu$ g/ml, meropenem = 8 $\mu$ /ml
- Molecular surveillance confirmed *bla*<sub>KPC</sub>
- Doripenem continued

# Real-Time PCR for KPC



Hindiye M et al. J Clin Microbiol 2008;46(9):2879-2883

Positive control: ATCC BAA 1705

# Case Study



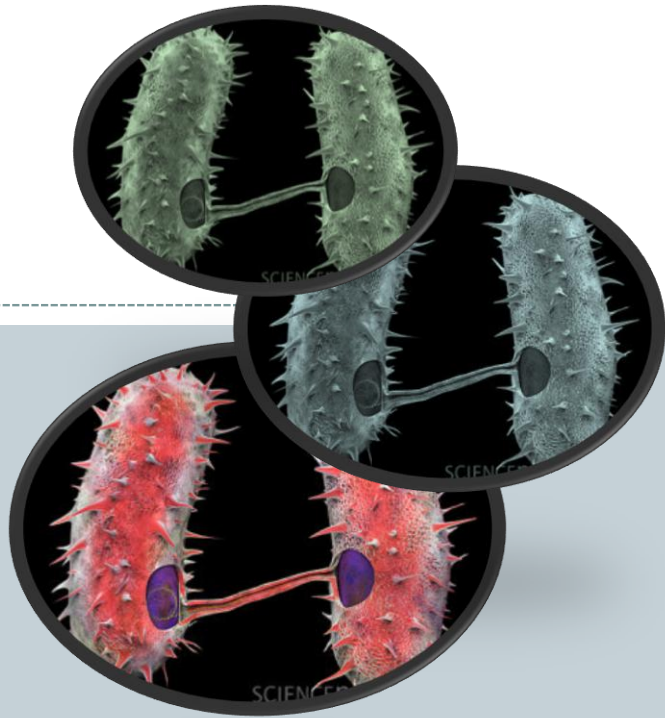
- Day 17 extubated, sputum sent for MC&S cultured *Klebsiella pneumoniae* only resistant to ampicillin
- CVP removed on day 23, sent for culture
- Day 24 hypotensive, Tygacil 100 mg stat then BD and Ciprobay 400mg stat then 8-hly commenced
- Blood cultures and sputum sent for MC&S
- Patient passed away 16h00 afternoon
- CVP tip, blood cultures and sputum grew *K pneumoniae*,  $bla_{KPC}$  confirmed on multiplex and realtime PCR

# Limitations of Molecular Surveillance



- Multiplex for CACs detected 3 GES positive isolates as well
- With PCR methods you only find what you are looking for
- Need to test for Class B enzymes (MBLs) as well
- Isolates tested mainly from Gauteng region
- Started looking for NDM recently

# Case report of 1<sup>st</sup> detected NDM in SA

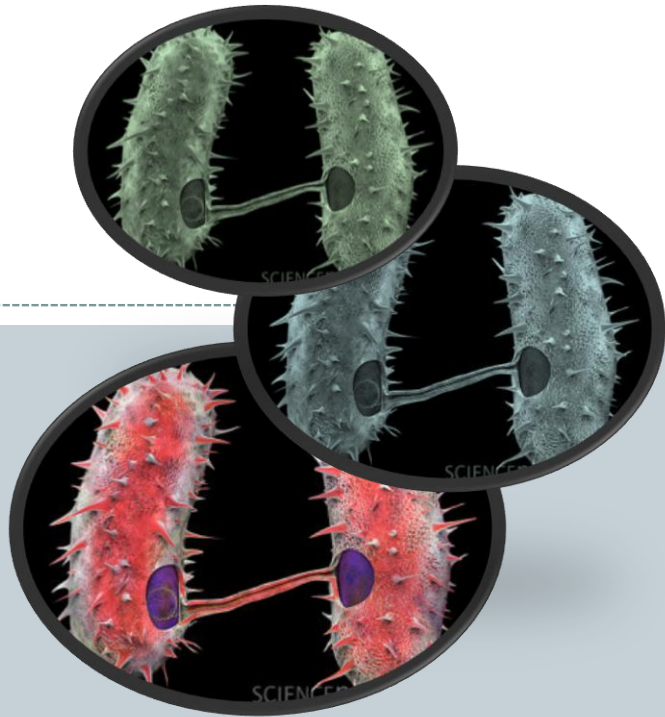


# NDM Has Arrived in SA...



- *Enterobacter cloacae* sent by dr Warren Lowman from Infection Control, NHLS, Wits medical school
- Patient that was admitted with empyema to Charlotte Maxeke hospital
- MIC as determined by E-test for carbapenems were 1µg/ml for doripenem and meropenem, and 8µg/ml for imipenem and ertapenem
- Isolate was susceptible to amikacin, ciprofloxacin, tigecycline and colistin

# Detection of Carbapenem Resistance Mechanisms in SA



**DOES IT MATTER?**

# Treatment Options for Carbapenem Resistant Enterobacteriaceae



- Depends on the mechanisms of resistance and MIC levels
- If AmpC overproduction / porin loss, and carbapenem MIC  $\leq 4\mu\text{g/ml}$ , then can use carbapenem
- Carbapenemase production (KPC, MBL or whatever) then two active drugs, can't use carbapenems?

# The Clinical Microbiologists' Dilemma



- Private sector uses Vitek 2 system for AST
- Vitek 2 system is problematic for detecting carbapenemase production in *Enterobacteriaceae*
- Detection tests are still evolving
- Heterogeneity of both enzymes and hosts complicate matters
- We need to establish a molecular antibiotic surveillance unit in SA

Kenneth Thomson. J Clin Microbiol 2010;48(4):1019-1025

Woodford N et al. J Clin Microbiol 2010;48(8):2999-3002

Thomson K et al. J Clin Microbiol 2011;49(9):3386-3387

# Acknowledgements



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- The microbiology peer group at Ampath who keep sending us isolates to be screened