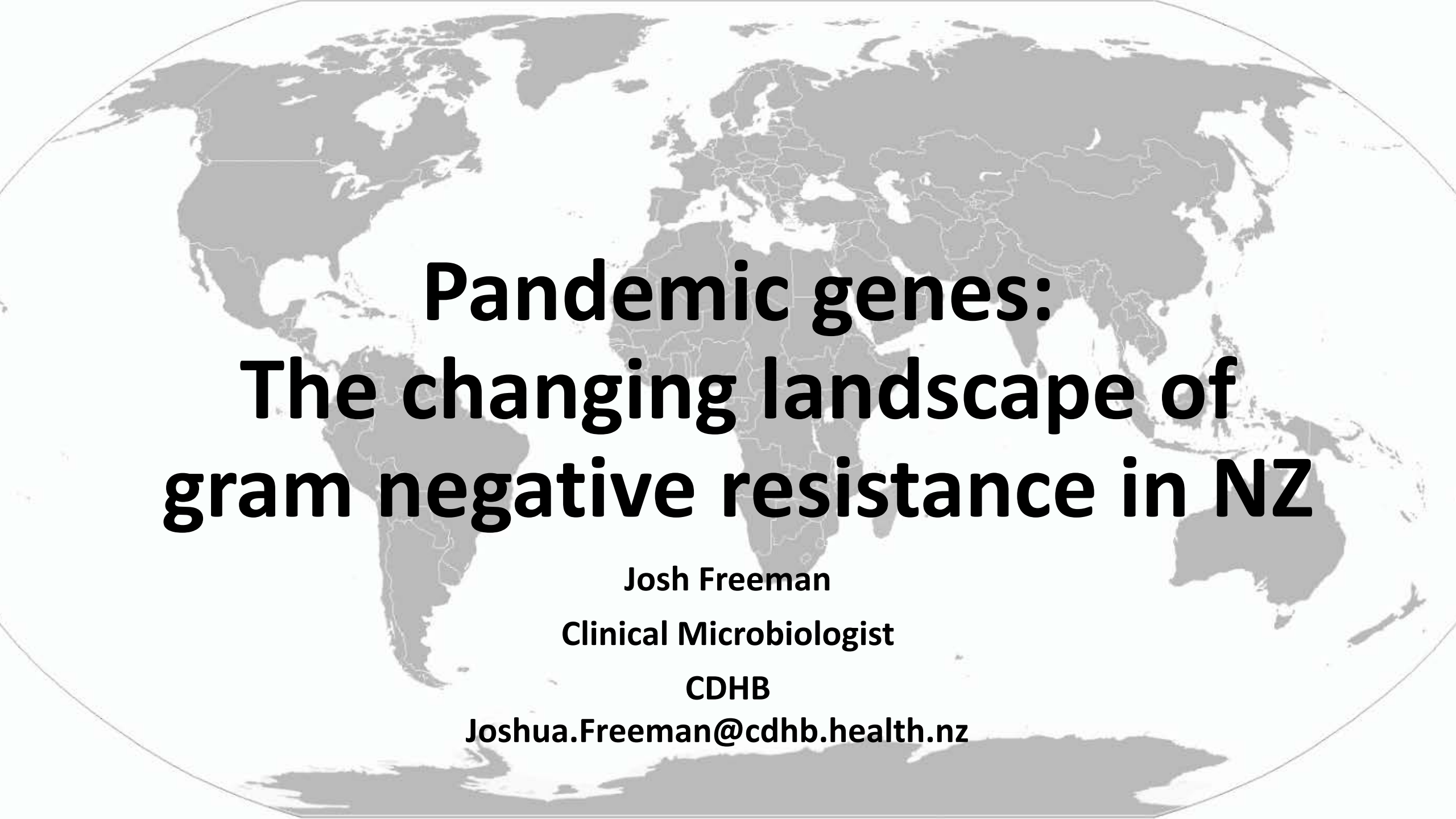

Pandemic genes: The changing landscape of gram negative resistance in NZ

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Outline

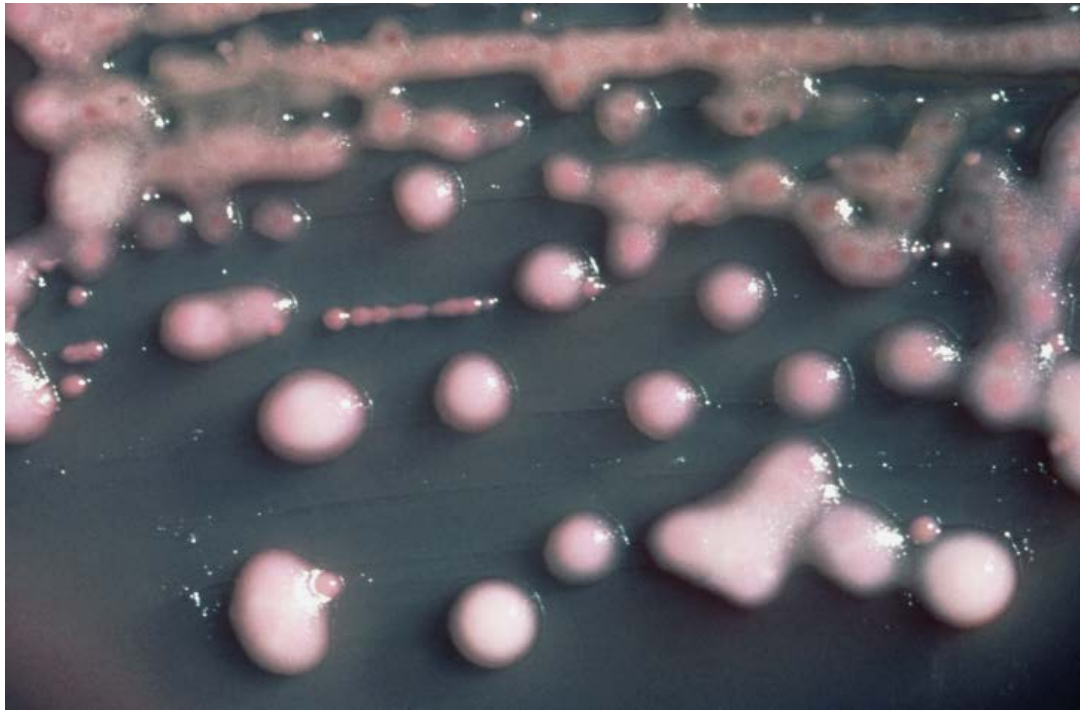
1. Background – Enterobacteriaceae, beta lactam antibiotics, beta-lactamases and mobile genetic elements

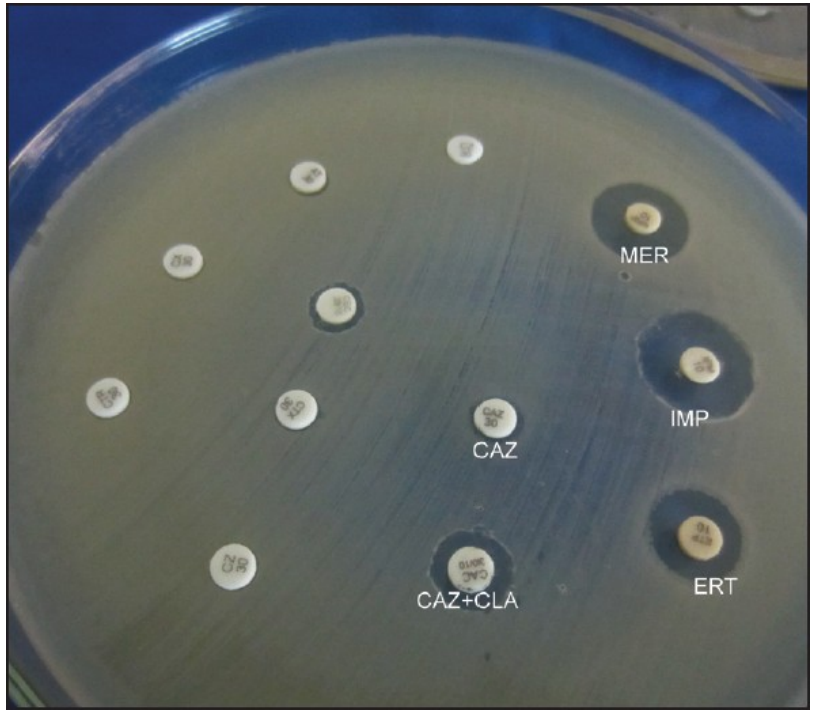
2. Epidemiology of extended-spectrum beta lactamase-producing Enterobacteriaceae (ESBL-E) in NZ
   - CTX-M

3. Evolving epidemiology of carbapenemase-producing Enterobacteriaceae (CPE) in NZ
   - NDM
   - OXA-48-like

4. Strategies to minimise impact of CPE in healthcare settings

5. Questions / comments / discussion

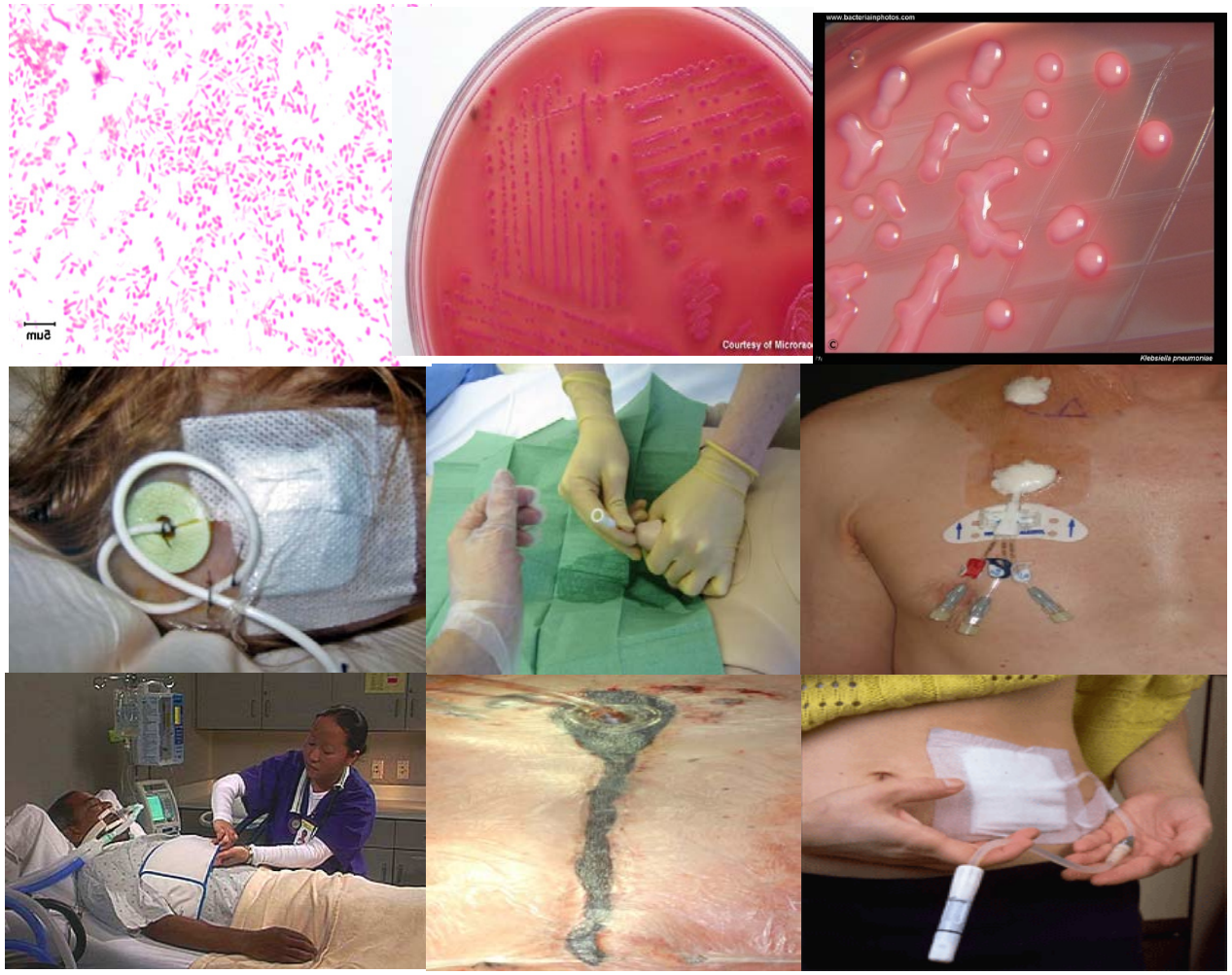




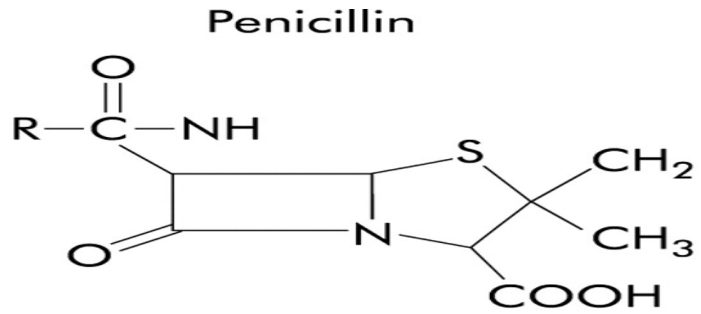
BACKGROUND

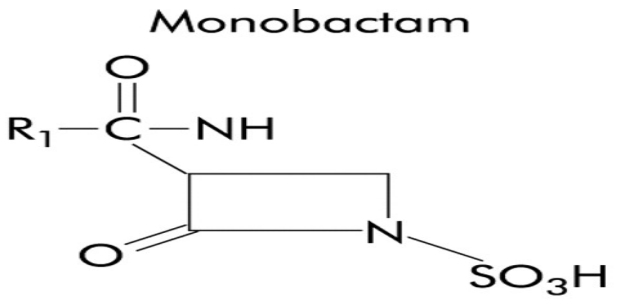
The Enterobacteriaceae family: *E. coli* and *K. pneumoniae*

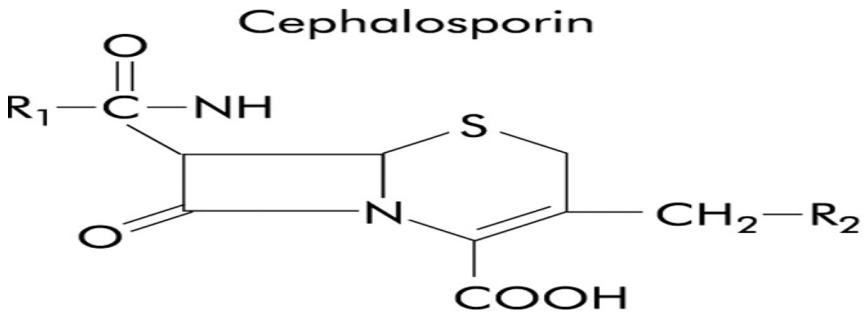
1. **<u>Asymptomatic colonization of GI tract</u>**
2. **<u>Community associated infections</u>**
   - Urinary tract infections (UTI)
   - Biliary tract infections
   - Neonatal meningitis
3. **<u>Healthcare associated infections</u>**
   - Surgical site infections
   - Various device related infections
     - Central lines
     - Drains into CSF
     - Peritoneal dialysis catheters
     - Urinary catheters
   - Complicated urinary tract infections
4. **<u>Life threatening sepsis in critically ill and immune-compromised patients</u>**

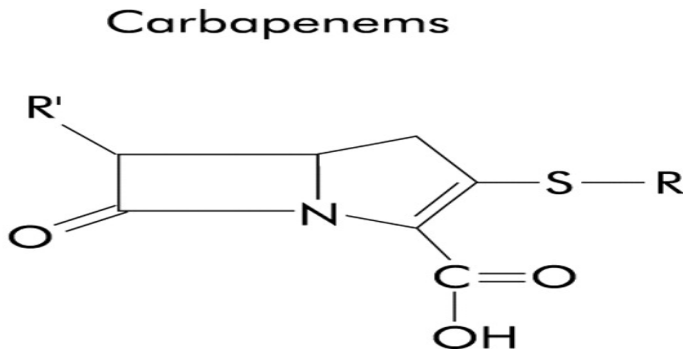


β-Lactam antibiotics









- **Spectrum of activity:**
  - **Amoxycillin < 2nd generation cephalosporins < 3rd generation cephalosporins < 4th generation cephalosporins < carbapenems**
- **Non-toxic, well tolerated, bactericidal, proven efficacy**

β-lactamases – How they work

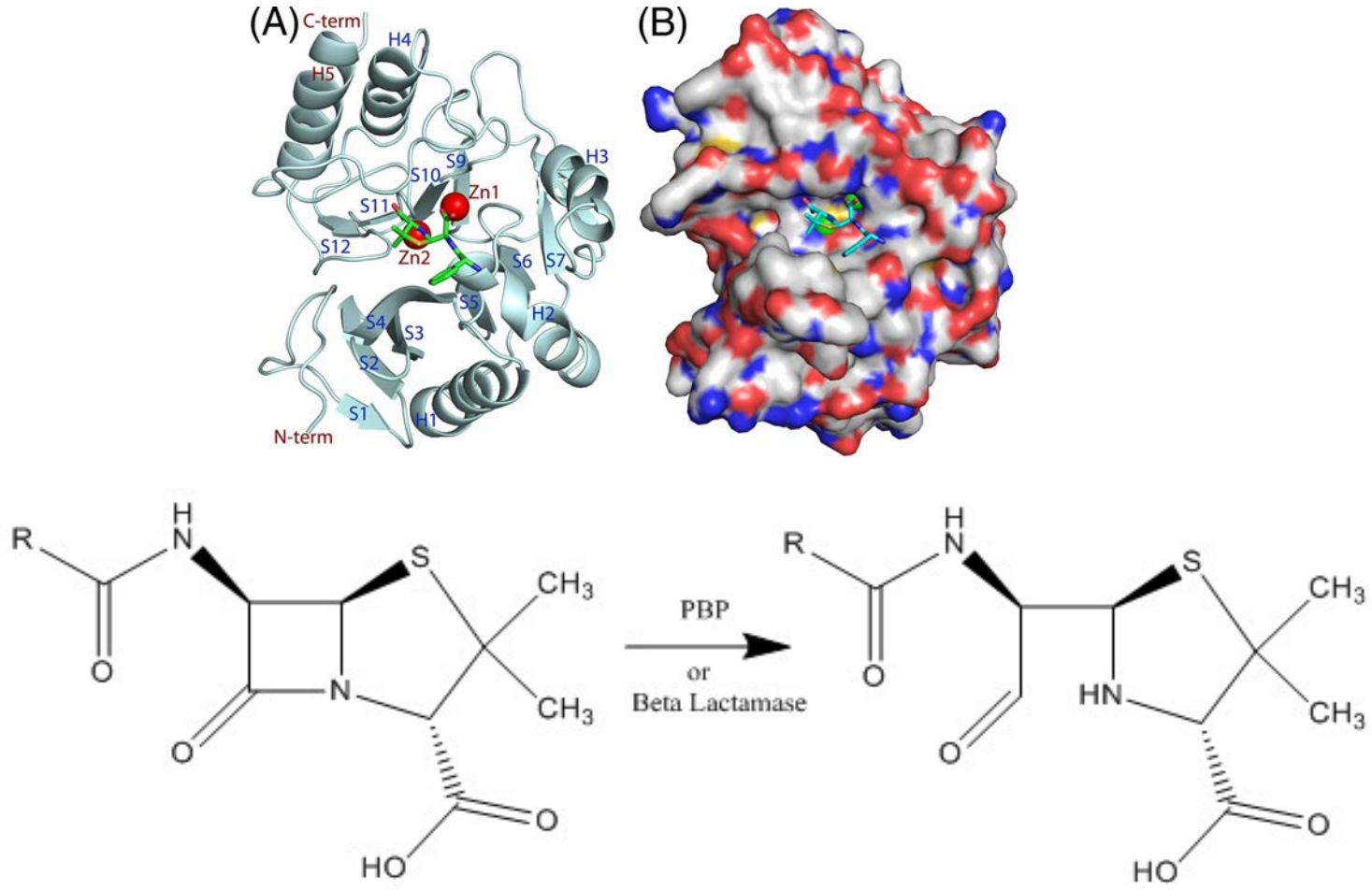
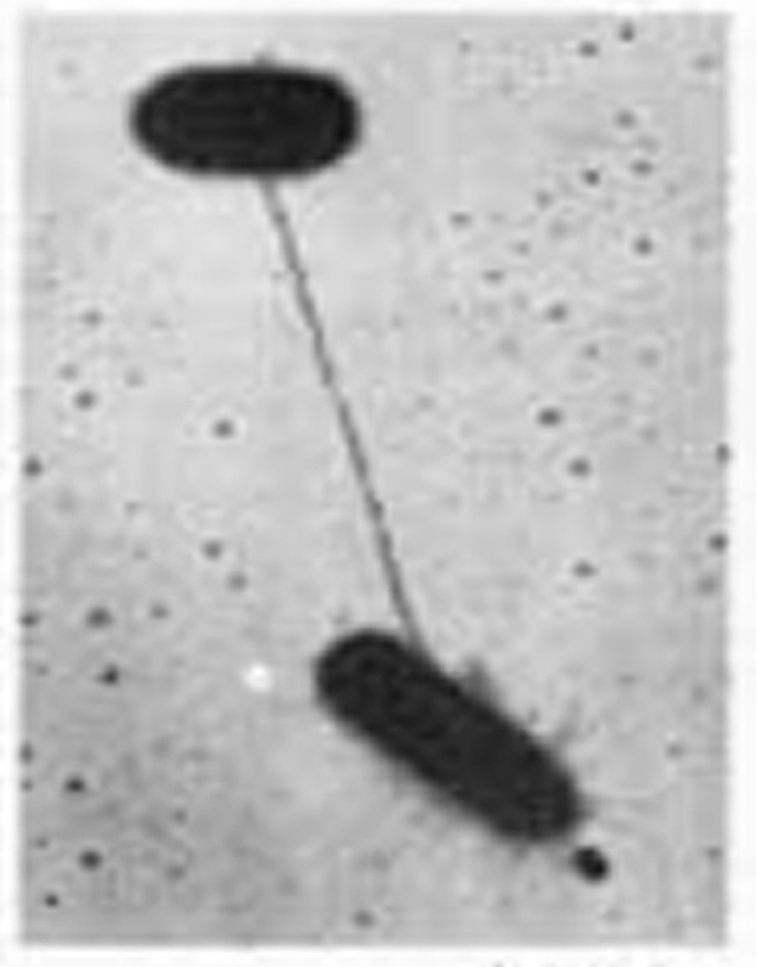


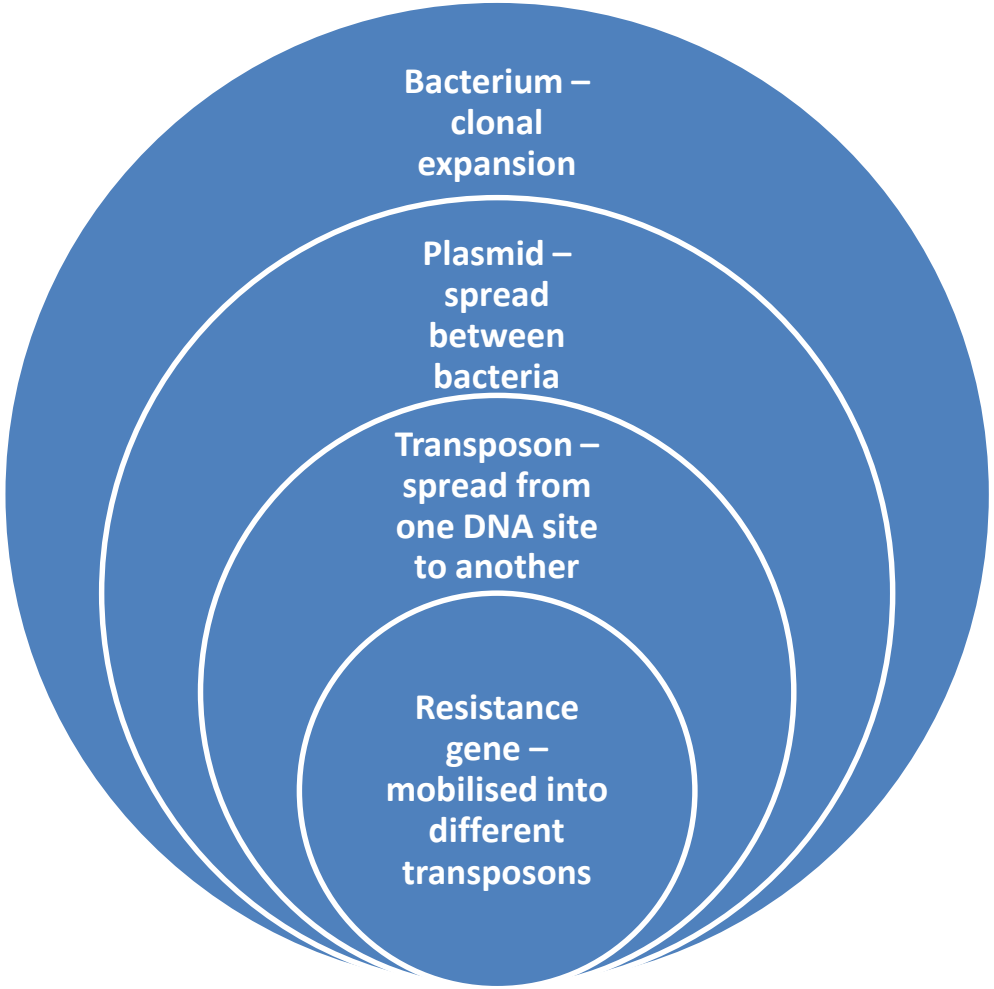
Figure (3) Breaking of the beta lactam ring

β-lactamase genes and mobile genetic elements

- B-lactamase genes are frequently carried on mobile genetic elements
- Plasmids are important mobile genetic elements
  - Self replicating, extra-chromosomal DNA
  - Travel between different bacterial strains and species (horizontal spread)
  - Inherited by daughter cells (vertical spread)
  - Often contain multiple genes encoding antibiotic resistance to different antibiotic classes (associated with ‘integrons’, and ‘transposons’)



Levels at which resistance genes spread



EXTENDED SPECTRUM BETA-LACTAMASE PRODUCING ENTEROBACTERIACEAE (ESBL-PE): CTX-M

Extended Spectrum β-lactamases (ESBL)

- Hydrolyse all β-lactams except the carbapenems

- Frequent co-resistance to non β-lactam drug classes
  - Fluoroquinolones (eg ciprofloxacin)
  - Aminoglycosides (eg gentamicin)
  - Sulphonamides / Trimethoprim (eg cotrimoxazole)

ANTIBIOTIC	
Cotrimoxazole	R
Ticarcillin / clavulanate	R
Amoxycillin	R
Cefuroxime	R
Ciprofloxacin	R
Aztreonam	R
Gentamicin	R
Ceftriaxone	R
Ceftazidime	R
Meropenem	S

Types of ESBL

	SHV/TEM	CTX-M
First described	1980's	1990's
Main associated species	*K. pneumoniae*	*E. coli*
Origins	Derived by point mutation from narrower spectrum β-lactamases of *E. coli* and *K. pneumoniae*	Derived from chromosomal β-lactamases of *Kluyvera* spp mobilised into plasmids.
Pattern of spread	Healthcare settings; outbreaks in specialised units	Healthcare settings; Community settings international dissemination
Profile of affected patients	ICU / haematology / elderly patients	ICU / haematology / elderly patients **Patients with no previous healthcare contact**

Reports of CTX-M in non-hospitalised patients

Current opinion in Microbiology 2006, 9:466-475

2004-2006 – Simultaneous reports from Spain, France, the UK, NZ and Canada of CTX-M-15 producing *E. coli* in non-hospitalised patients

Reports of CTX-M in non-hospitalised patients

Current opinion in Microbiology 2006, 9:466-475

2005 -2010 - Widespread reports of CTX-M (in particular CTX-M-15 AND CTX-M-14) from Europe, Asia, Middle East, Africa, South America

Community-Onset Genitourinary Tract Infection due to CTX-M-15–Producing *Escherichia coli* among Travelers to the Indian Subcontinent in New Zealand

Joshua T. Freeman,[1] Stephen J. McBride,[1] Helen Heffernan,[3] Tracy Bathgate,[1] Chris Pope,[3] and Roderick B. Ellis-Pegler[2]

Table 1. Demographic and clinical characteristics of patients with community-onset urinary tract infection (UTI) due to extended-spectrum β-lactamase producing *Escherichia coli* (ESBL) and Indian subcontinent contact.

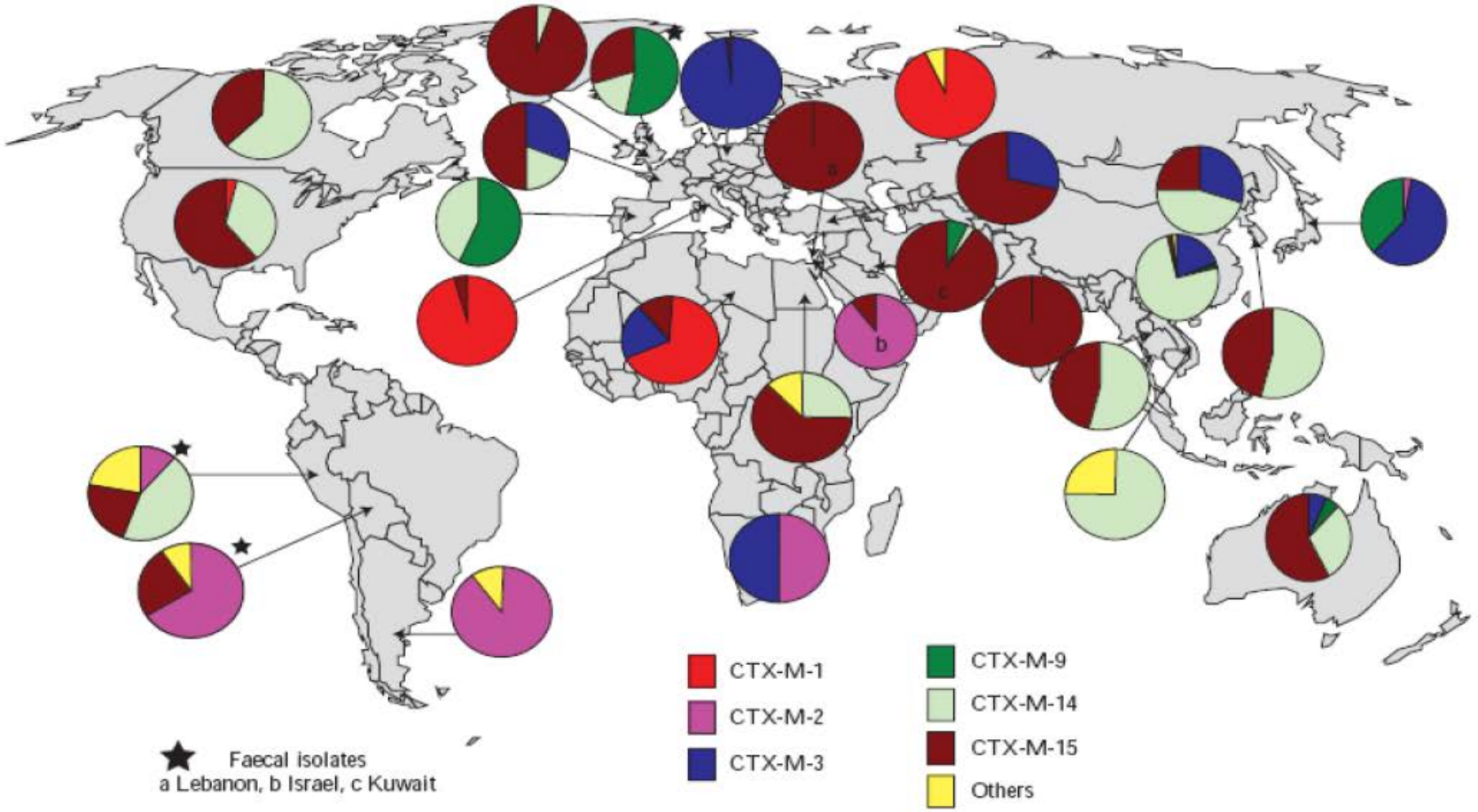
Patient	Date of presentation	Age	Sex	Country of birth	Diagnosis	Comorbidity	Treatment before relapse[a]	Contact type	Travel duration[b]	Time since arrival in New Zealand	Prior hospitalization	ESBL type
1	19 April 2004	25	F	India	Pyelonephritis	None	Oral TMP-SMX	I	NA	6 months	None	CTX-M-15
2	6 September 2004	61	M	India	Catheter-associated UTI	Recurrent UTI	None	I	NA	2 months	None	CTX-M-15
3	26 January 2005	29	M	Italy	Pyelonephritis	None	Oral CIP	V	4 months	4 weeks	None	CTX-M-15
4	8 March 2005	65	F	India	Cystitis	COPD	Oral Amox-Clv	R	6 weeks	2 weeks	New Zealand outpatient clinic within 12 months	CTX-M-15
5	3 March 2006	47	F	India	Cystitis	None	Oral CIP	R	Unknown	10 days	None	CTX-M-15
6	5 April 2006	63	M	India	Epididymo-orchitis	AML	IV MER	V	NA	1 day	Multiple Indian outpatient clinics	CTX-M-15
7	10 June 2006	48	M	India	Epididymo-orchitis	None	Oral DOX	I	NA	<6 months	None	CTX-M-15
8	14 August 2006	33	F	India	Cystitis	Previous UTI	None	I	NA	4 years	None	SHV-12
9	24 September 2006	67	M	Bangladesh	Cystitis	Urethral stricture	IV ERT	I	NA	2 months	None	CTX-M-15
10	30 September 2006	53	F	New Zealand	Cystitis	UTI during childhood	CFC, NOR, and IV ERT	R	5 days	10 days	Health care worker in New Zealand hospital	Isolate unavailable

NOTE. AML, acute myeloid leukemia; Amox-Clv, amoxicillin-clavulanate; CFC, cefaclor; CIP, ciprofloxacin; COPD, chronic obstructive pulmonary disease; DOX, doxycycline; ERT, ertapenem; I, immigrated to New Zealand; IV, intravenous; MER, meropenem; NA, not applicable; NOR, norfloxacin; R, returned New Zealand resident; TMP-SMX, trimethoprim-sulfamethoxazole; V, visiting New Zealand.

[a] Required additional antibiotic treatment after the initial treatment.

[b] Travel duration was NA for some patients, because they were previous permanent residents on the Indian subcontinent rather than having traveled to the Indian subcontinent.

Global Distribution of specific CTX-M genotypes



Global distribution of CTX-M genotypes.[11,13,16,62–84]

CMI 2008

Comparative epidemiology of CTX-M-14 and CTX-M-15 producing *Escherichia coli*: Association with distinct demographic groups in the community in New Zealand

J. T. Freeman · D. A. Williamson · H. Heffernan · M. Smith · J. E. Bower · S. A. Roberts

Characteristics	CTX-M-15-EC (%)	CTX-M-14-EC (%)	P value (Fishers exact test)
Mean age (SD)	52.5 years (24)	59.9 years (23)	0.17
Female gender	37/59 (63)	16/29 (55)	0.6435
Long term care facility domicile	7/59 (12)	2/29 (7)	0.71
Indian ethnicity	20/58 (34)	0/27 (0)	0.0012*
Chinese / Southeast Asian ethnicity	3/58 (5)	13/27 (48)	<0.0001*
Travel	18/57 (32)	1/25 (4)	0.0088*
Travel to Indian subcontinent	12/57 (21)	0/25 (0)	0.0145*
Community acquisition	5/56 (9)	11/25 (44)	0.0006*
Prior hospitalisation	40/59 (68)	15/29 (52)	0.1651

Eur J Clin Microbiol Infect Dis (2012) 31:2057–2060

Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study

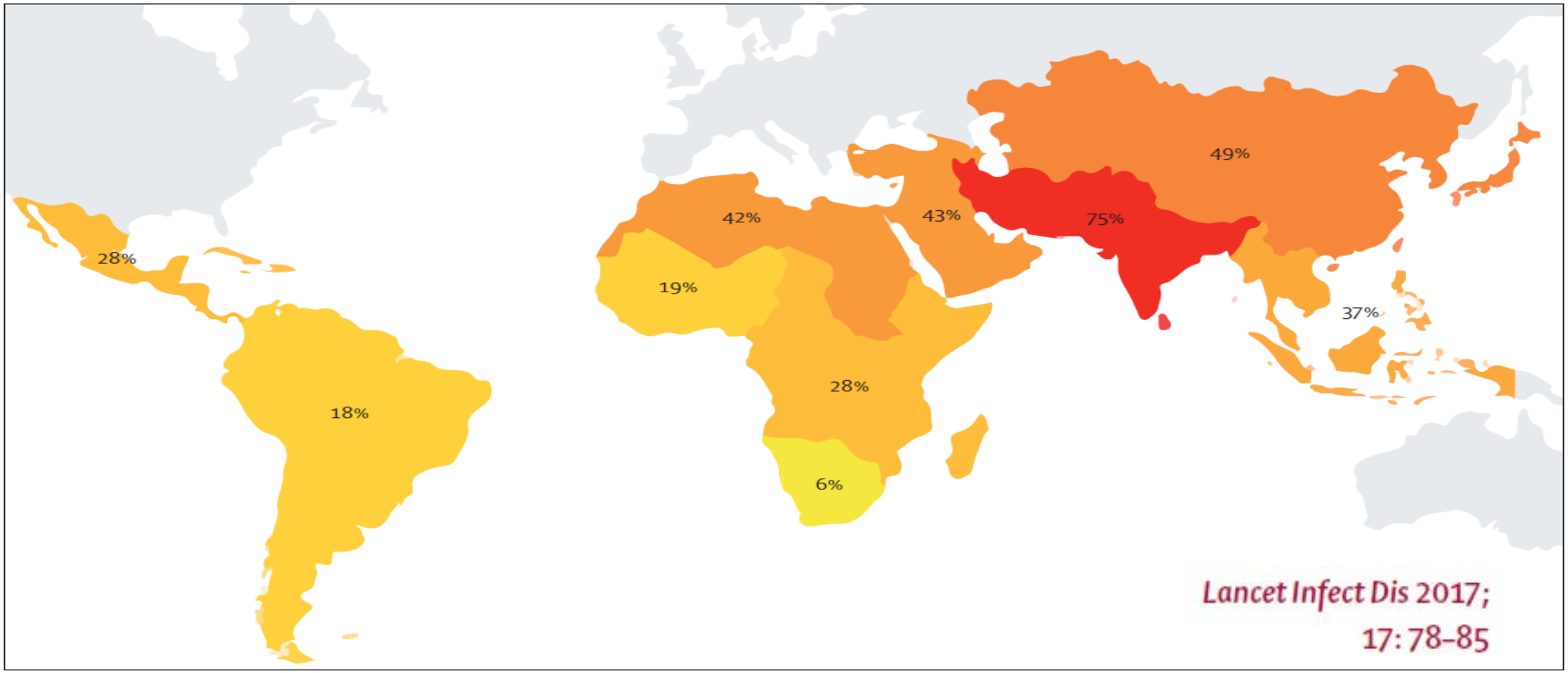
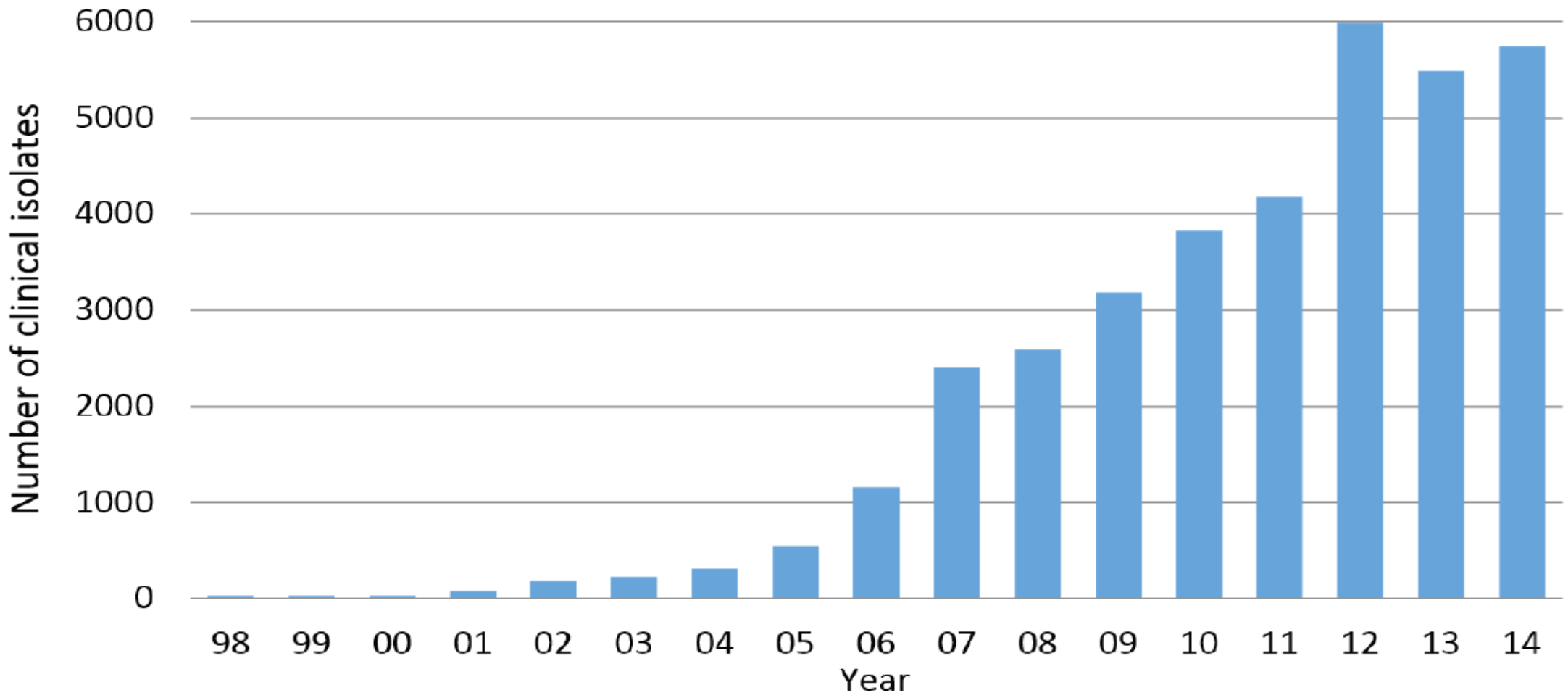


Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

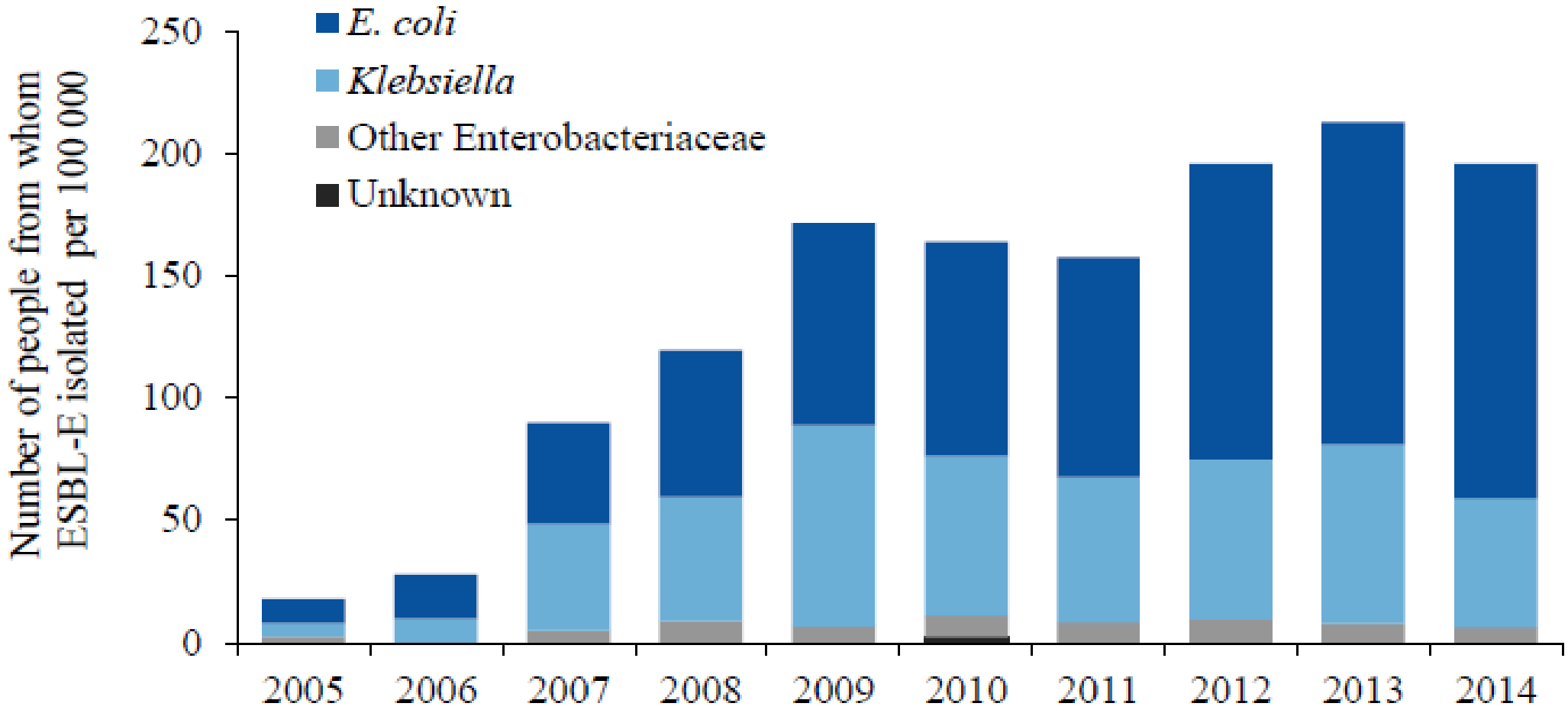
CTX-M prevalence in NZ

Figure 2: ESBL-PE in New Zealand 1998–2014.



ESBL-producing bacterial species in NZ

Figure 1. ESBL-producing Enterobacteriaceae incidence rates, 2005-2014



Differences in risk-factor profiles between patients with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*: a multicentre case-case comparison study

Results: 170 patients and 176 isolates were included in the study (92 patients with ESBL-EC, 78 with ESBL-KP). 92.6% had CTX-Ms. 39% of EC were ST131 while 51% of KP belonged to 3 different STs (i.e. ST20, ST48 & ST1087). Specific sequence types were associated with specific hospitals for ESBL-KP but not ESBL-EC. Variables positively associated with ESBL-EC on multivariate analysis were: community acquired infection (odds ratio [OR] 7.9; 95% CI: 2.6-23.9); chronic pulmonary disease (OR 5.5; 95% CI: 1.5-20.1); and high prevalence country of origin (OR 4.3; 95% CI: 1.6-11.6). Variables negatively associated with ESBL-EC were previous transplant (OR 0.06; 95% CI: 0.007-0.6); Hospital 2 (OR 0.3; 95% CI: 0.1-0.7) and recent ICU admission (OR 0.3; 95% CI: 0.07-0.9).

Conclusions: Differences in risk profiles between patients with ESBL-EC and ESBL-KP suggest fundamental differences in transmission dynamics. Understanding the biological basis for these differences could have implications for infection control practice. Tailoring of infection control measures according to ESBL species may be indicated in some instances.

Freeman *et al. Antimicrobial Resistance and Infection Control* 2014, **3**:27
http://www.aricjournal.com/content/3/1/27

Extended-spectrum β-lactamase (ESBL)-producing enterobacteria: factors associated with infection in the community setting, Auckland, New Zealand

C.T. Moor [a], S.A. Roberts [b], G. Simmons [a,*], S. Briggs [c], A.J. Morris [d], J. Smith [d], H. Heffernan [e]

Journal of Hospital Infection (2008) **68**, 355—362

Table II Multivariate analysis of statistically significant associations with extended-spectrum β-lactamase-producing enterobacterial infection

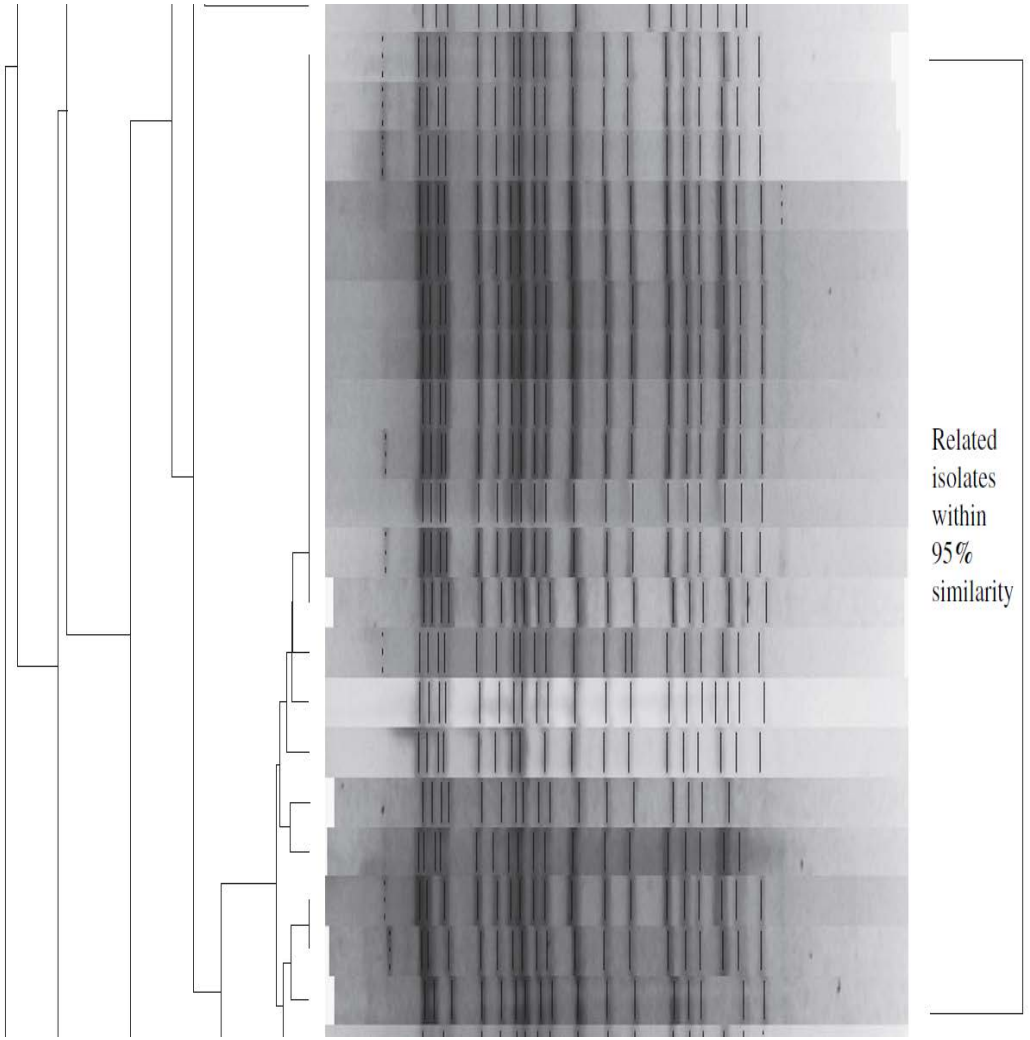
Variable	No. of cases (%)	Odds ratio	95% CI	*P*-value
Residential care facility[a]	42 (45)	6.1	1.6, 23.2	0.008
COPD	13 (14)	10.6	1.04, 107.7	0.046
Age (years)[b]				
20—39	13 (14)	1.7	0.3, 8.5	0.5
40—74 years	31 (33)	1.8	0.4, 7.8	0.5
≥75 years	46 (49)	1.7	0.3, 8.6	0.5
Antibiotics used in the 3 months preceding isolate identification	50 (53)	2.0	0.9, 4.5	0.1
CVD	42 (45)	0.9	0.3, 2.4	0.8
Hospital admission[c]	52 (55)	1.2	0.4, 3.4	0.7
Admission to hospital M[c]	33 (35)	3.6	0.9, 14.3	0.07
Neurological disease	23 (25)	0.6	0.2, 2.5	0.5
Recurrent UTIs	35 (37)	0.8	0.3, 2.0	0.6
Urinary catheter	25 (33)	1.5	0.5, 4.6	0.5

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; UTIs, urinary tract infections.

[a] Place of residence at the time of infection.

[b] Dummy age-group variables have been created with 0—19-year-olds as the reference group.

[c] In the preceding year.



CTX-M ESBL: Summary

- *E. coli* and *K. pneumoniae* are colonisers of the human GI tract but are also important causes of serious healthcare associated infections and sepsis
- Extended spectrum beta-lactamase-producing E. coli and K. pneumoniae are frequently resistant to all commonly used antibiotics except the carbapenems
- CTX-M ESBL genes appear to have spread globally within less than a decade
- Travel and immigration have played a key role in dissemination of CTX-M
- The Indian Subcontinent (and to a lesser extent China and SE Asia) appear to have played an important role in the global spread of CTX-M
- In NZ, CTX-M-producing *E. coli* is now endemic in the community while CTX-M-producing *K. pneumoniae* has become established in hospital settings
- Long term care facilities appear to have played a role in the spread of CTX-M in NZ

CARBAPENEMASE PRODUCING ENTEROBACTERIACEAE (CPE)

Carbapenemases

- Beta-lactamases that hydrolyse the carbapenems
- Range of different genes
  - Metallo-β-lactamases (zinc at active site)
    - IMP
    - VIM
    - NDM
  - Serine carbapenemases (serine at active site)
    - KPC
    - OXA

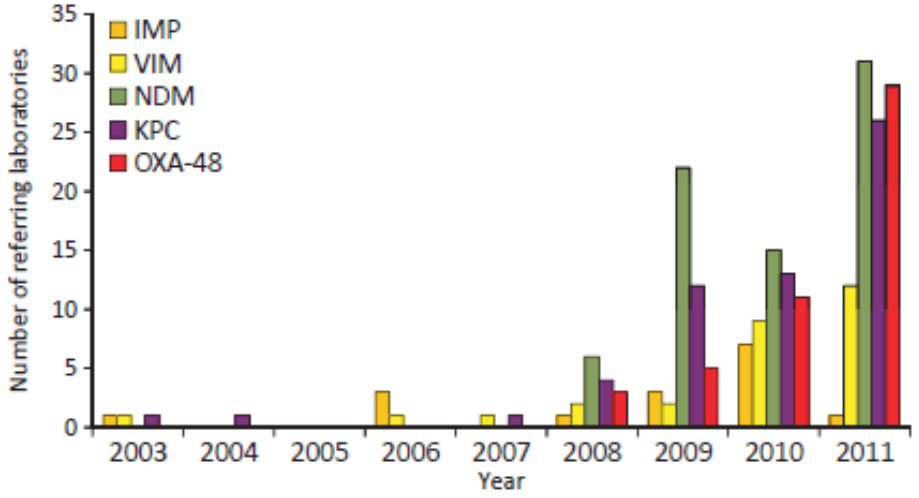


FIG. 4. Numbers of UK laboratories referring at least one carbapenemase-producing *Enterobacteriaceae* (CPE) isolate to the Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) (Health Protection Agency). Additionally, in 2010 and 2011, two and one laboratories, respectively, referred IMI-producing CPE isolates, respectively. In 2011, one laboratory referred at least one CPE isolate producing both KPC and VIM enzymes.

Clin Microbiol Infect 2012; **18:** 413–431

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

Lancet Infect Dis 2011; 11: 355–62

- 147 isolates (UK-37, India and Pakistan-110); 2003-2009
- Isolates from India and Pakistan associated with community-acquired UTI, pneumonia and bloodstream infections

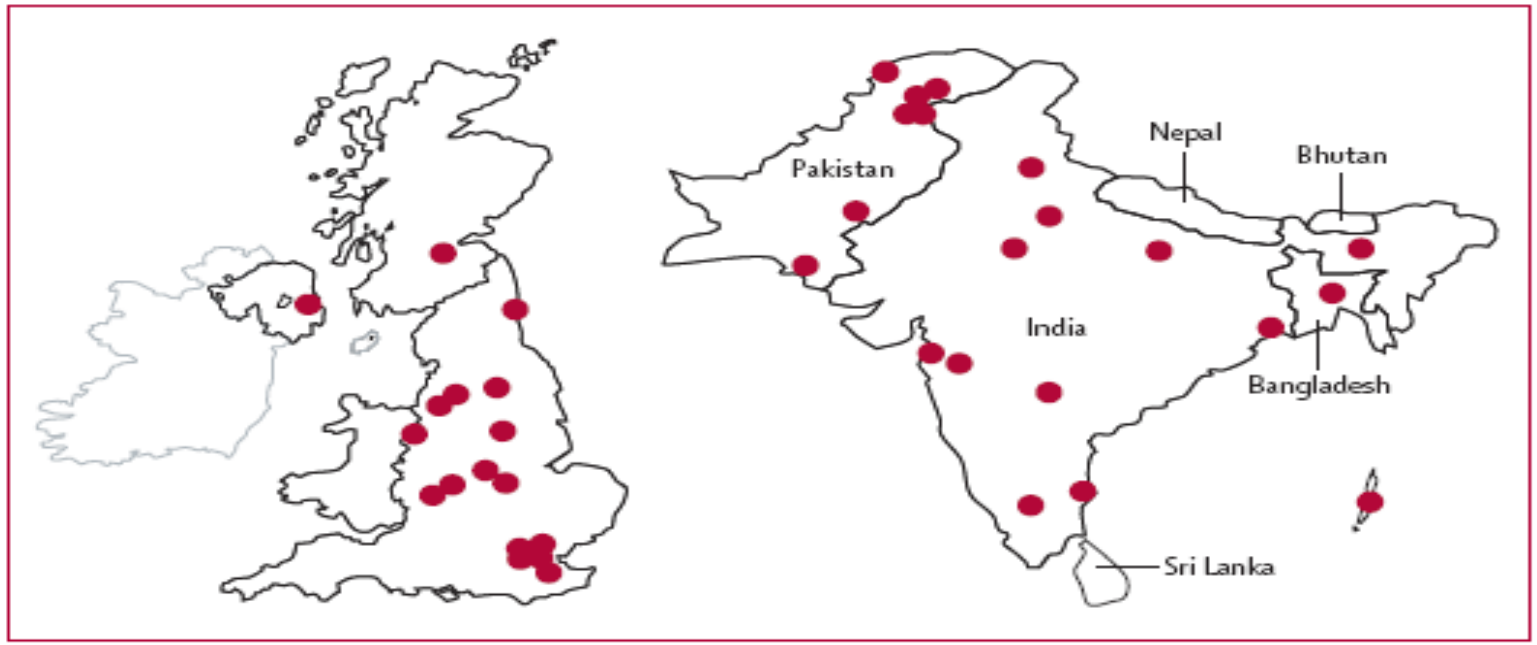


Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

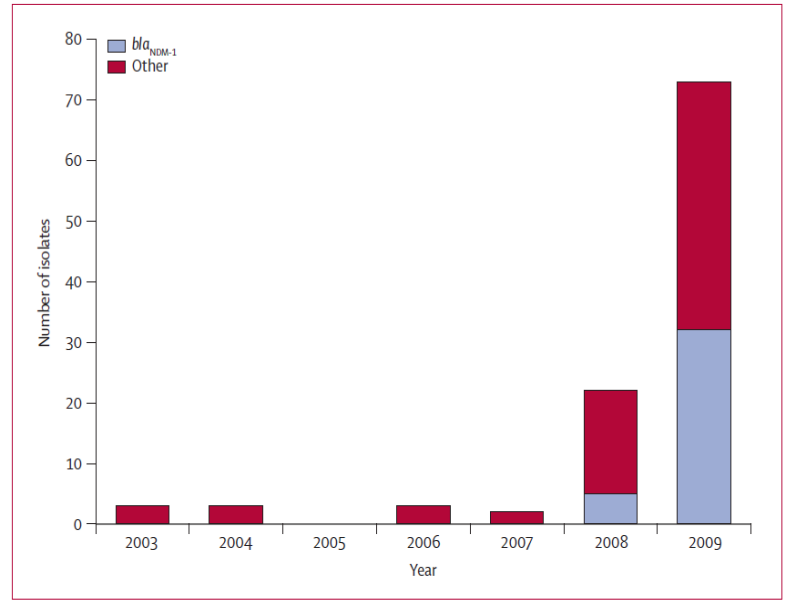


***Figure 1*: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009**
The predominant gene is bla_{NDM-1}, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Lancet Infect Dis 2011; 11: 355–62

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

- **Sep-Oct 2010: environmental water samples within 12km radius of New Delhi**
  - **Seepage samples - 51/171 (29.8%) positive for NDM-1**
  - **Drinking water - 2/50 (4%) positive for NDM-1**
  - **14 different species**

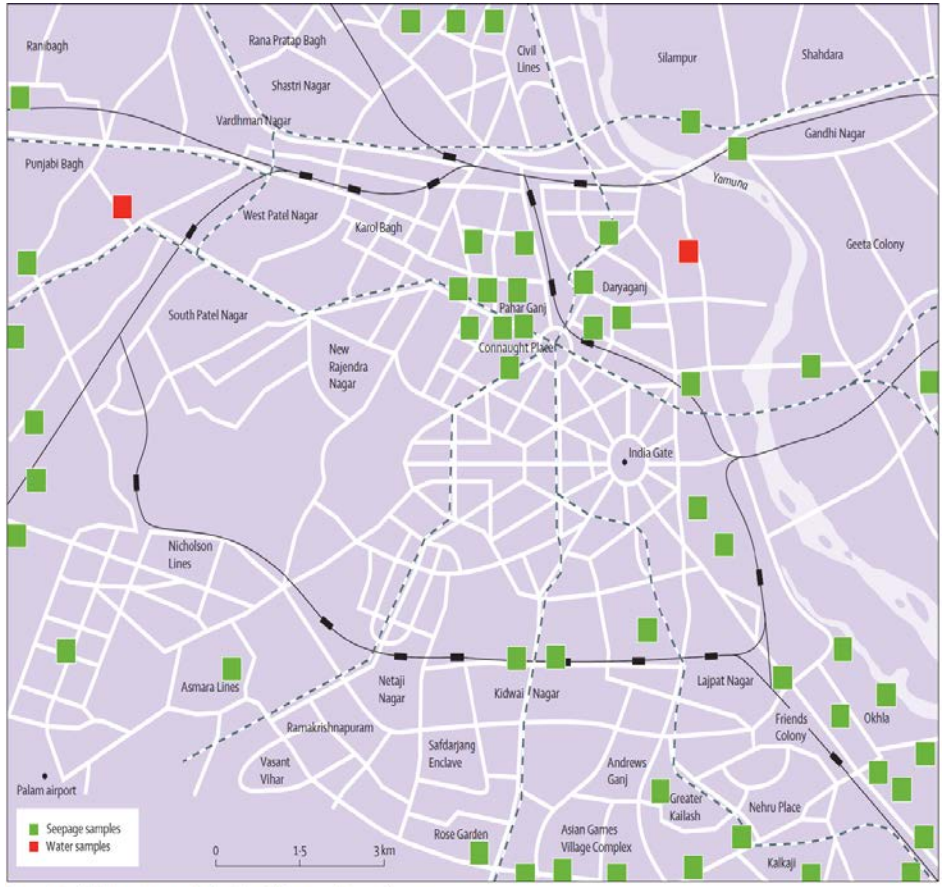


Figure 1: Map of NDM-1-positive samples from New Delhi centre and surrounding areas

Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance

Alan P. Johnson[1] and Neil Woodford[2]

Fig. 1. Countries from which NDM-positive bacteria have been reported. Triangles indicate an epidemiological link to the Indian subcontinent.

Short communication

Identification and molecular characterisation of New Delhi metallo-β-lactamase-1 (NDM-1)- and NDM-6-producing Enterobacteriaceae from New Zealand hospitals

Table 2
Antimicrobial susceptibility profile of five NDM-producing Enterobacteriaceae isolates from four patients in New Zealand.

	Escherichia coli ARL09/232	*Proteus mirabilis* ARL10/166[a]	*E. coli* ARL10/167[a]	*E. coli* ARL10/1398	*Klebsiella pneumoniae* ARL10/1720
Minimum inhibitory concentration (mg/L)[b]					
Imipenem	**≥32**	**≥32**	**≥32**	**≥32**	**4**
Meropenem	**16**	1	**≥32**	**≥32**	**4**
Ertapenem	**≥32**	**≥32**	**≥32**	**≥32**	**≥32**
Doripenem	**≥32**	**≥32**	**≥32**	**≥32**	**≥32**
Aztreonam	**≥256**	4	**≥256**	**32**	**64**
Ceftriaxone	**≥256**	**64**	**≥256**	**≥256**	**≥256**
Cefepime	**≥256**	**64**	**≥256**	**≥256**	**64**
TZP	**≥256**	**≥256**	**≥256**	**≥256**	**≥256**
TIM	**≥256**	**≥256**	**≥256**	**≥256**	**≥256**
Ciprofloxacin	**≥32**	**≥32**	**≥32**	**≥32**	**≥32**
Colistin	0.5	**≥256**[c]	0.5	0.5	0.25
SXT	**≥32**	**≥32**	**≥32**	**≥32**	**≥32**
Amikacin	**≥256**	**≥256**	**≥256**	**≥256**	**≥256**
Gentamicin	**≥256**	**≥256**	**≥256**	**≥256**	**≥256**
Tigecycline	0.5	**8**[c]	0.5	0.5	**2**
Fosfomycin	2	16	4	4	4
Phenotypic tests for carbapenemase					
MHT	+	Indeterminate	Weak+	+	Indeterminate
EDTA DDST	–	–	–	–	–
MPA/TE DDST	+	+	+	–	+

TZP, piperacillin/tazobactam; TIM, ticarcillin/clavulanic acid; SXT, trimethoprim/sulfamethoxazole; MHT, modified Hodge test; EDTA, ethylene diamine tetra-acetic acid; DDST, double-disk synergy test; MPA/TE, 2-mercaptopropionic acid in Tris–EDTA.

[a] ARL10/166 and ARL10/167 were isolated from the same patient.

[b] MICs in bold are in the resistant range.

[c] Intrinsically resistant to colistin and tigecycline.

Intercontinental transfer of OXA-181-producing *Klebsiella pneumoniae* into New Zealand

J Antimicrob Chemother 2011
doi:10.1093/jac/dkr396
Advance Access publication 19 September 2011

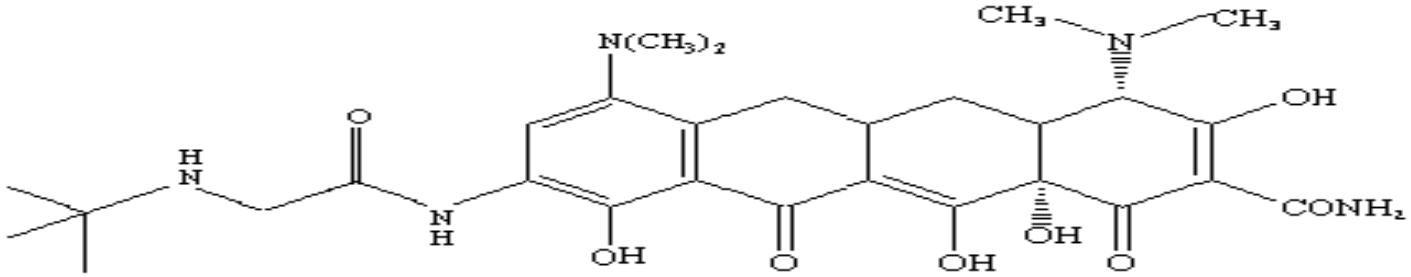
Table 1. Antimicrobial susceptibility of OXA-181-producing *K. pneumoniae*

Antimicrobial	MIC (mg/L)[a]
Ampicillin	≥256
Ceftriaxone	≥256
Ceftazidime	≥256
Cefepime	≥256
Aztreonam	≥256
Piperacillin/tazobactam	≥256
Ticarcillin/clavulanate	≥256
Imipenem	8
Meropenem	≥32
Ertapenem	≥32
Doripenem	≥32
Ciprofloxacin	>32
Gentamicin	128
Amikacin	16
Tigecycline	4
Colistin	0.25
Fosfomycin	128

[a]MICs determined by Etest.

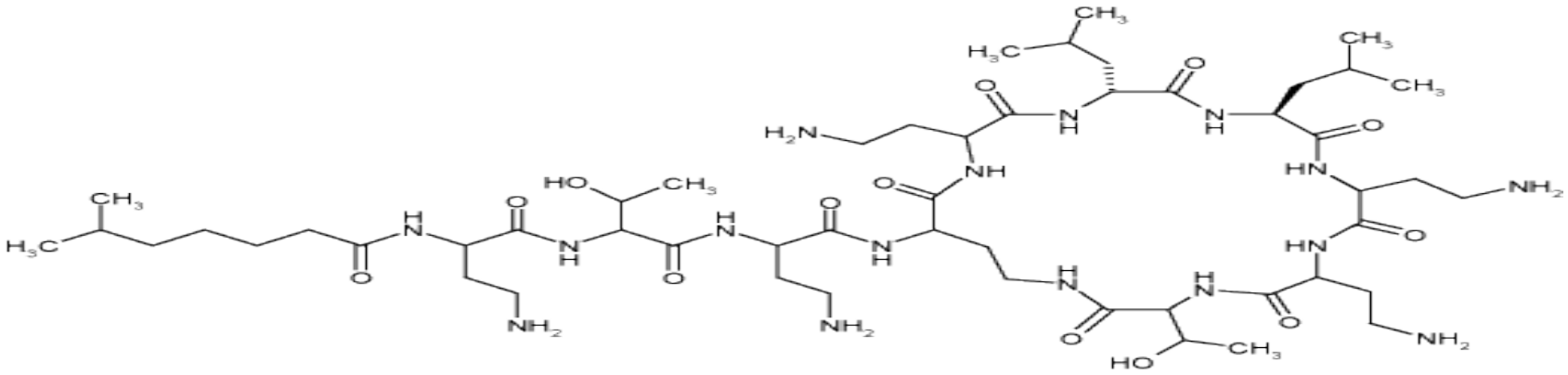
Treatment options: Tigecycline

- “Glycylcycline” – novel antibiotic class derived from tetracyclines
- Inhibits bacterial translation
- No activity against *Pseudomonas aeruginosa* or *Proteus* spp.
- Not suitable for meningitis, UTI, septic shock. Questionable suitability for intravascular infections
- Resistance increasing
- Expensive



Treatment options: Colistin (polymyxin E)

- Fell out of use in the 1970s (replaced by the aminoglycosides) due to **<u>neurotoxicity</u>** and **<u>nephrotoxicity</u>**
- Disrupts bacterial cell membrane
- No activity against *Proteus* spp., *Serratia* spp., *Stenotrophomonas maltophilia*, *Burkholderia* spp.
- Plasmid mediated resistance recently discovered and found to be widespread



Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

	Year	Positive isolates (%)/number of isolates
Escherichia coli		
Pigs at slaughter	All	166 (20·6%)/804
Pigs at slaughter	2012	31 (14·4%)/216
Pigs at slaughter	2013	68 (25·4%)/268
Pigs at slaughter	2014	67 (20·9%)/320
Retail meat	All	78 (14·9%)/523
Chicken	2011	10 (4·9%)/206
Pork	2011	3 (6·3%)/48
Chicken	2013	4 (25·0%)/16
Pork	2013	11 (22·9%)/48
Chicken	2014	21 (28·0%)/75
Pork	2014	29 (22·3%)/130
Inpatient	2014	13 (1·4%)/902
Klebsiella pneumoniae		
Inpatient	2014	3 (0·7%)/420

Table 2: Prevalence of colistin resistance gene *mcr-1* by origin

Lancet Infect Dis 2016; 16: 161–68

Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals

www.thelancet.com/infection Vol 16 March 2016

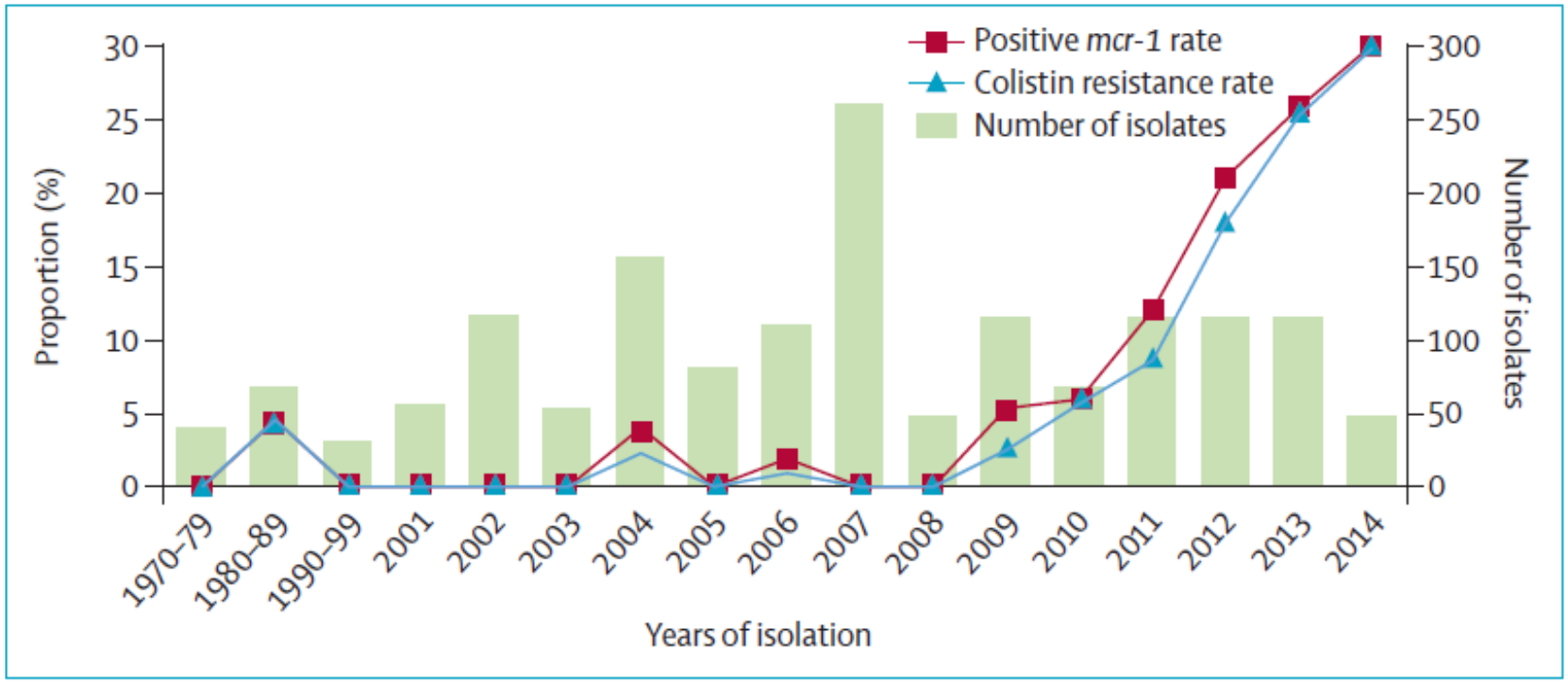


Figure: **Presence of *mcr-1* and colistin resistance in *Escherichia coli* of chicken origin during 1970–2014**
Susceptibility testing of colistin was done by agar dilution and interpreted according to European Committee on Antimicrobial Susceptibility Testing clinical breakpoints (version 6.0). Strains with a minimum inhibitory concentrations >2 mg/L are reported as resistant *E coli*.

Detection of the *mcr-1* Colistin Resistance Gene in Carbapenem-Resistant *Enterobacteriaceae* from Different Hospitals in China

Antimicrob Agents Chemother 60:5033–5035. 2016

TABLE 1 Characteristics of MCR-1-producing *E. coli* strains and their *E. coli* J53 transconjugants[a]

E. coli strain	ST	β-Lactamase(s)	Plasmid	MIC (μg/ml)[b]					
				SAM	AMC	CFZ	CAZ	CTX	FEP
CDA6	167	NDM-5, CMY-2, TEM-1	ND	>16/8	>16/8	>16	>16	>32	>16
BJ10	156	NDM-5, TEM-1	ND	>16/8	>16/8	>16	>16	>32	>16
BJ13	457	CTX-M-14, CMY-2, TEM-1	ND	>16/8	>16/8	>16	>16	>32	>16
CDA6-mcr-T	ND	—	IncX4	≤4/2	≤8/4	≤4	≤1	≤1	≤2
BJ13-mcr-T	ND	—	IncI2	≤4/2	≤8/4	≤4	≤1	≤1	≤2
CDA6-NDM-T	ND	NDM-5	IncX3	>16/8	>16/8	>16	>16	>32	>16
BJ10-NDM-T	ND	NDM-5	IncX3	>16/8	>16/8	>16	>16	>32	>16

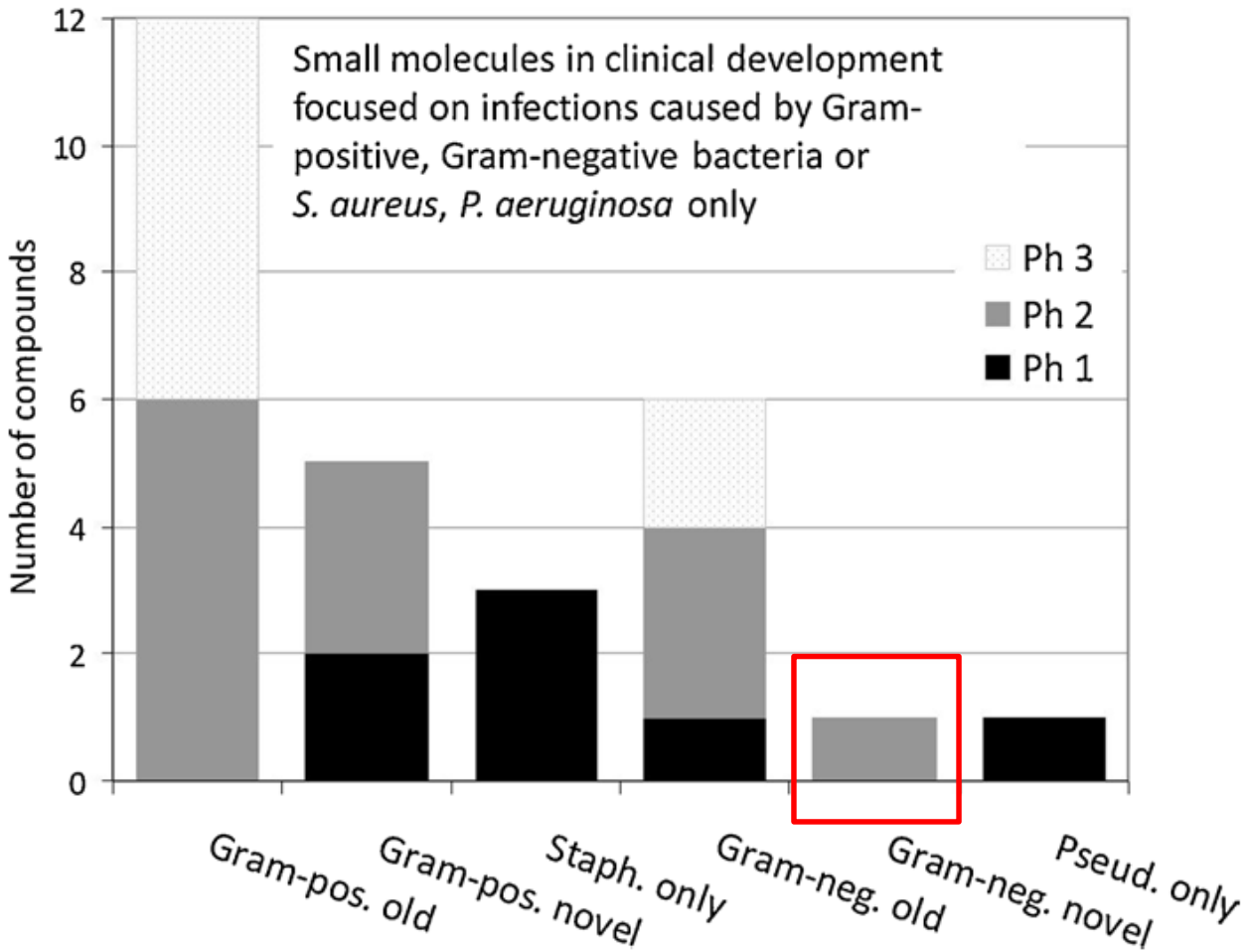
New Antibiotics?

- Not forthcoming because less profitable than other drug types
  - Short courses only
  - Often alternatives to patented agents
  - Risk of resistance development
  - Kept “in reserve”

Review

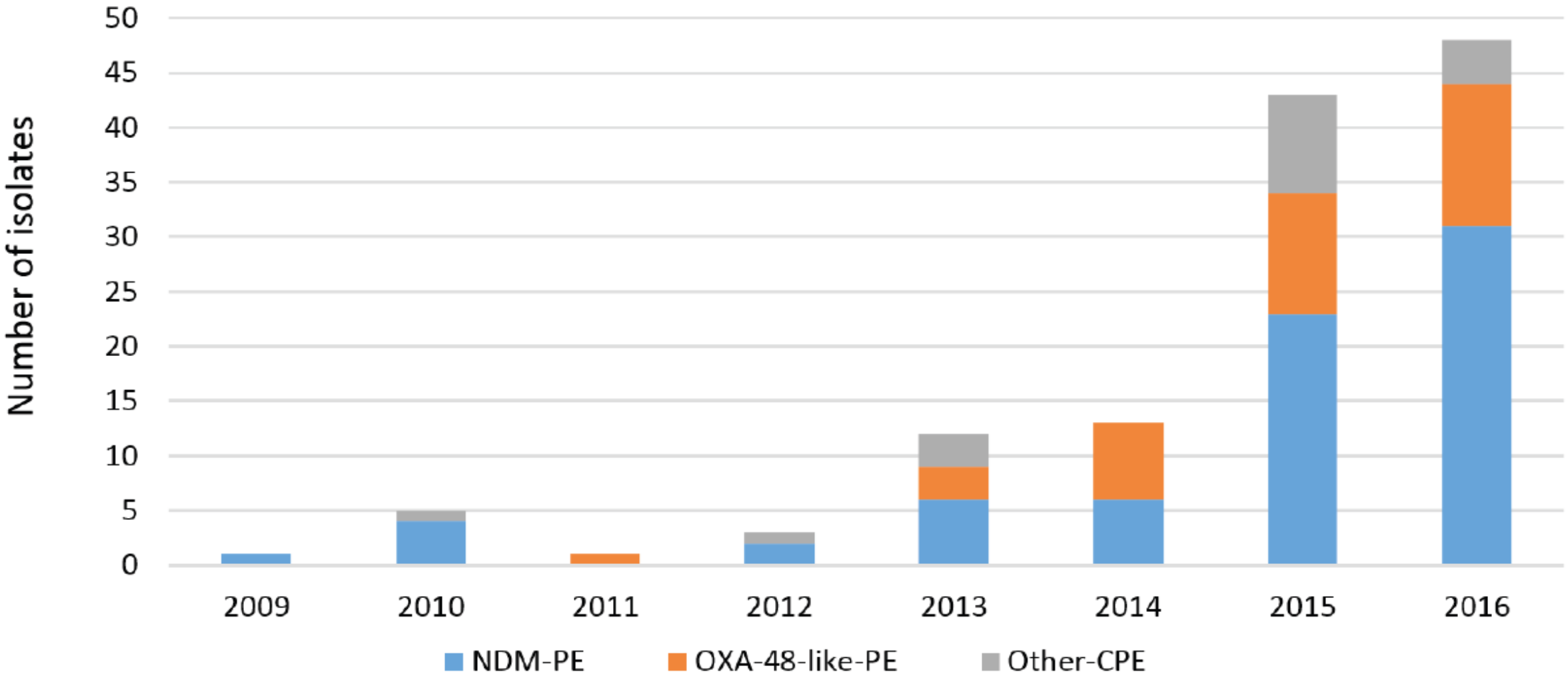
Accelerating resistance, inadequate antibacterial drug pipelines and international responses

Ursula Theuretzbacher*



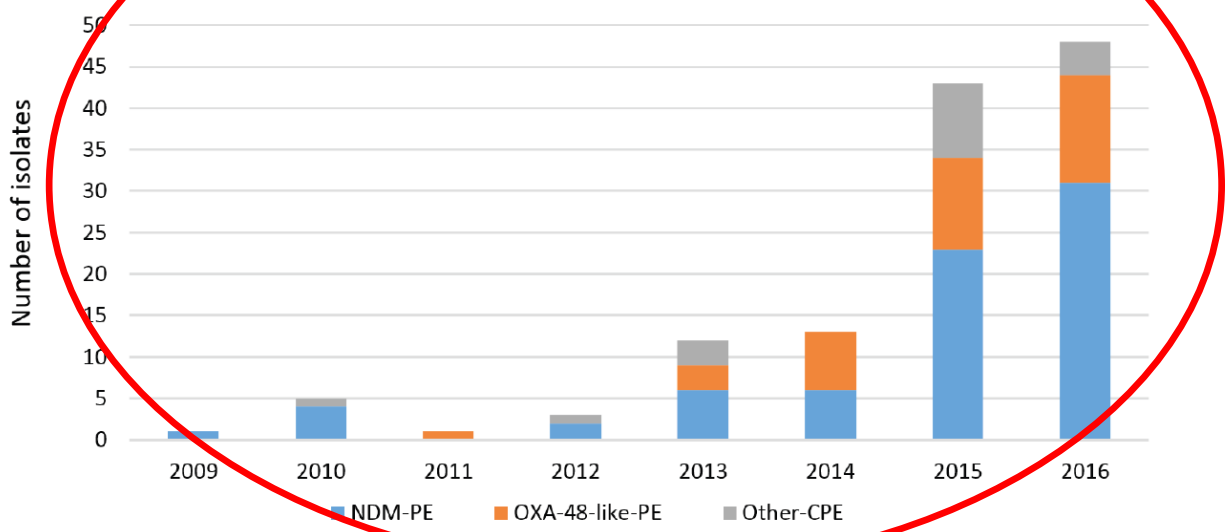
The “Perfect Storm”: Increasing Gram negative resistance and decreasing new drug development

Figure 1: CPE in New Zealand, 2009–2016.



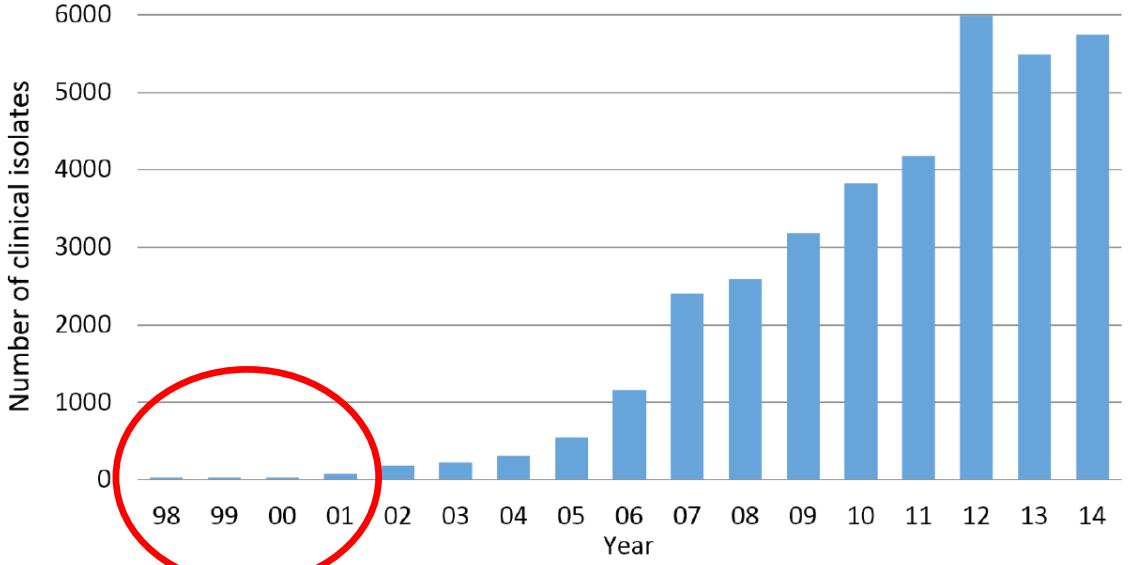
CPE in NZ

Figure 1: CPE in New Zealand, 2009–2016.



ESBL-PE in NZ

Figure 2: ESBL-PE in New Zealand 1998–2014.



STRATEGIES TO MINIMISE IMPACT

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

World Health Organization

- to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- to strengthen the knowledge and evidence base through surveillance and research;
- to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- to optimize the use of antimicrobial medicines in human and animal health;
- to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The clear and present danger of carbapenemase-producing *Enterobacteriaceae* (CPE) in New Zealand: time for a national response plan

Matthew Blakiston, Helen Heffernan, Sally Roberts, Joshua Freeman

ABSTRACT

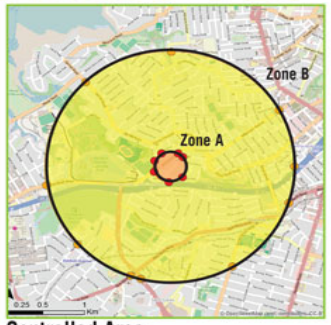
Antimicrobial resistance (AMR) in general poses a threat to the sustainability of modern healthcare, but a particularly urgent and serious threat is posed by a specific group of antibiotic-resistant bacteria known as carbapenemase-producing *Enterobacteriaceae* (CPE). CPE are resistant to nearly all antibiotics and include common pathogens such as *Escherichia coli* and *Klebsiella pneumoniae*. In New Zealand, the incidence of CPE has increased from three isolates in 2012 to 45 in 2016. The current epidemiology of CPE in New Zealand has similarities with the extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) epidemic in the early 2000s (just before ESBL-PE underwent a non-linear increase in incidence). Although to date in New Zealand, nearly all CPE have been imported from overseas, this situation appears to be changing, with evidence of secondary spread in both households and healthcare facilities over the last year. In this article, we argue that CPE should be regarded as the foremost AMR threat currently facing New Zealand, and highlight the need for a comprehensive national response plan, analogous to plans for other emerging transmissible infections, such as pandemic influenza and Ebola. We also make recommendations about the components of such a plan and advocate that CPE should be recognised as a key priority in New Zealand's national AMR strategy, due to be published in May 2017.

“Healthcare biosecurity” – principles of surveillance and quarantine

QUEENSLAND FRUIT FLY

A single male Queensland fruit fly has been found in the Auckland Suburb of Grey Lynn. If established this insect could have serious consequences for New Zealand's horticultural growers.

A Controlled Area has been placed around the location of the find, taking in parts of Grey Lynn, Western Springs, Mt Albert, Ponsonby and Kingsland.



Controlled Area

YES can leave zone


Root vegetables and leafy vegetables

NO cannot leave zone


Whole fruit and some vegetables

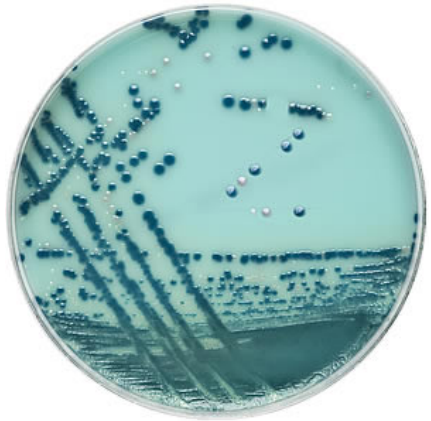
For more information visit www.mpi.govt.nz or call 0800 80 99 66

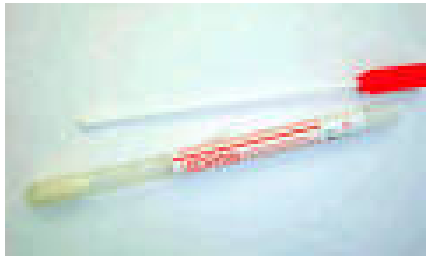
New Zealand Government

Ministry for Primary Industries
Manatū Ahu Matua

Active surveillance and contact precautions

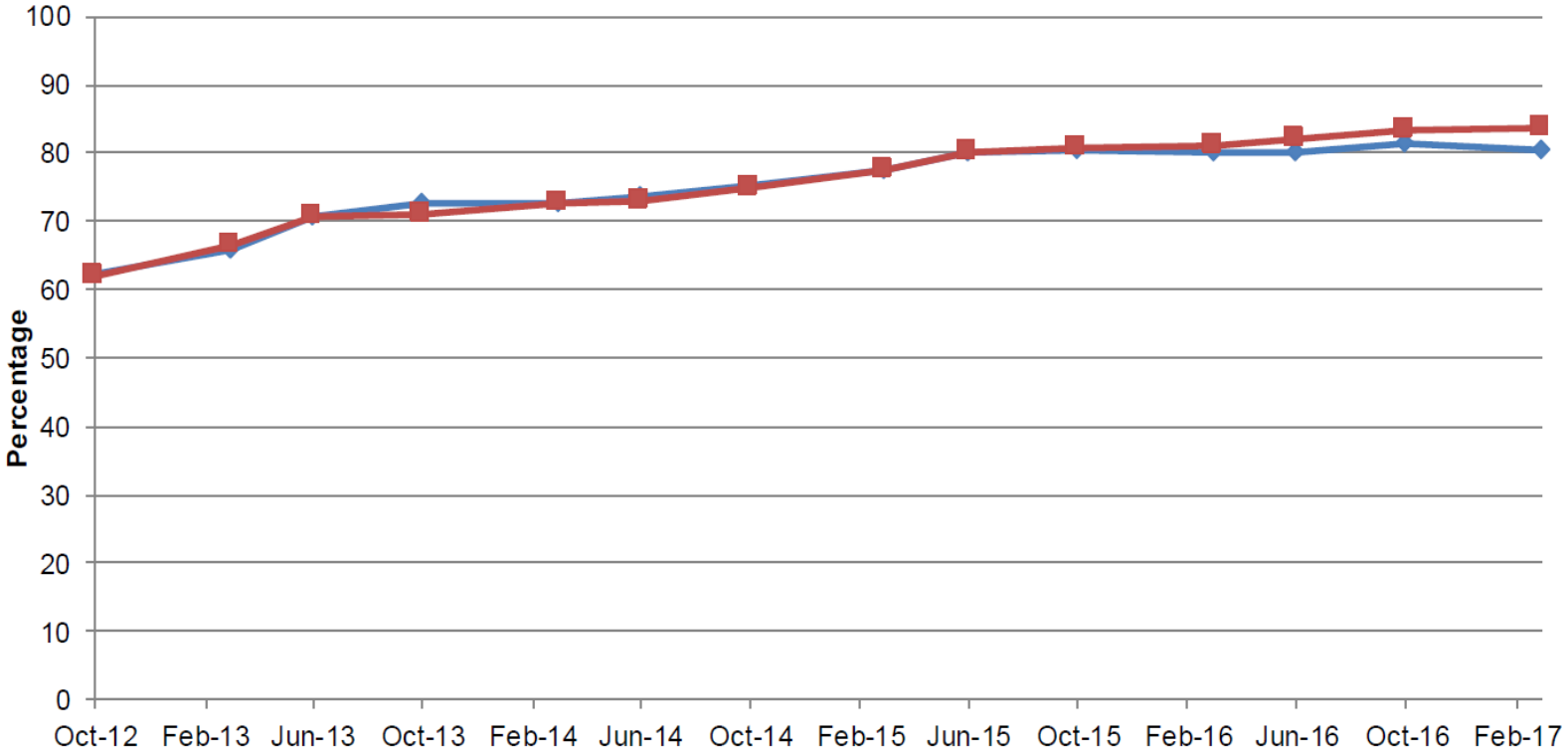
- "Active surveillance" = screening patients for asymptomatic colonization with CPE
- Involves taking rectal swab and plating on selective media
- Criteria for screening for asymptomatic colonization with CPE??
  - ? Needs to include patients who have recently travelled to high risk areas (even without healthcare exposure)
- Need minimum standards for CPE active surveillance nationally

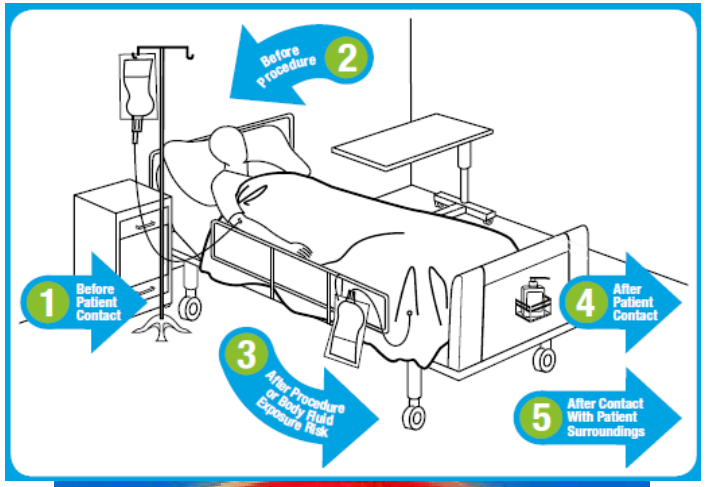


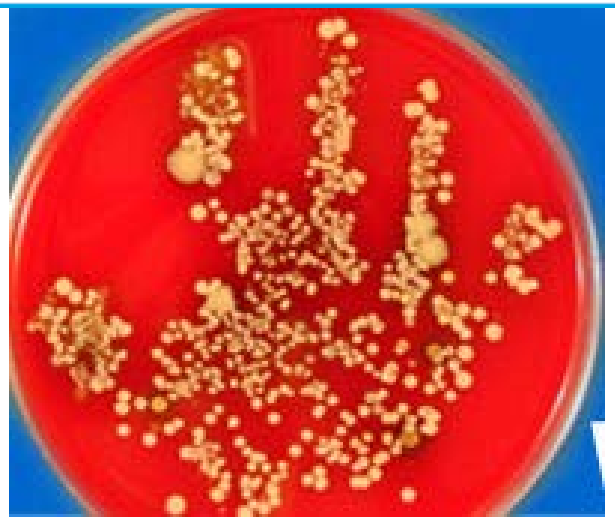


Maintaining high hand hygiene standards

Figure 1: Trends in national aggregate and average hand hygiene compliance, October 2012 to March 2017

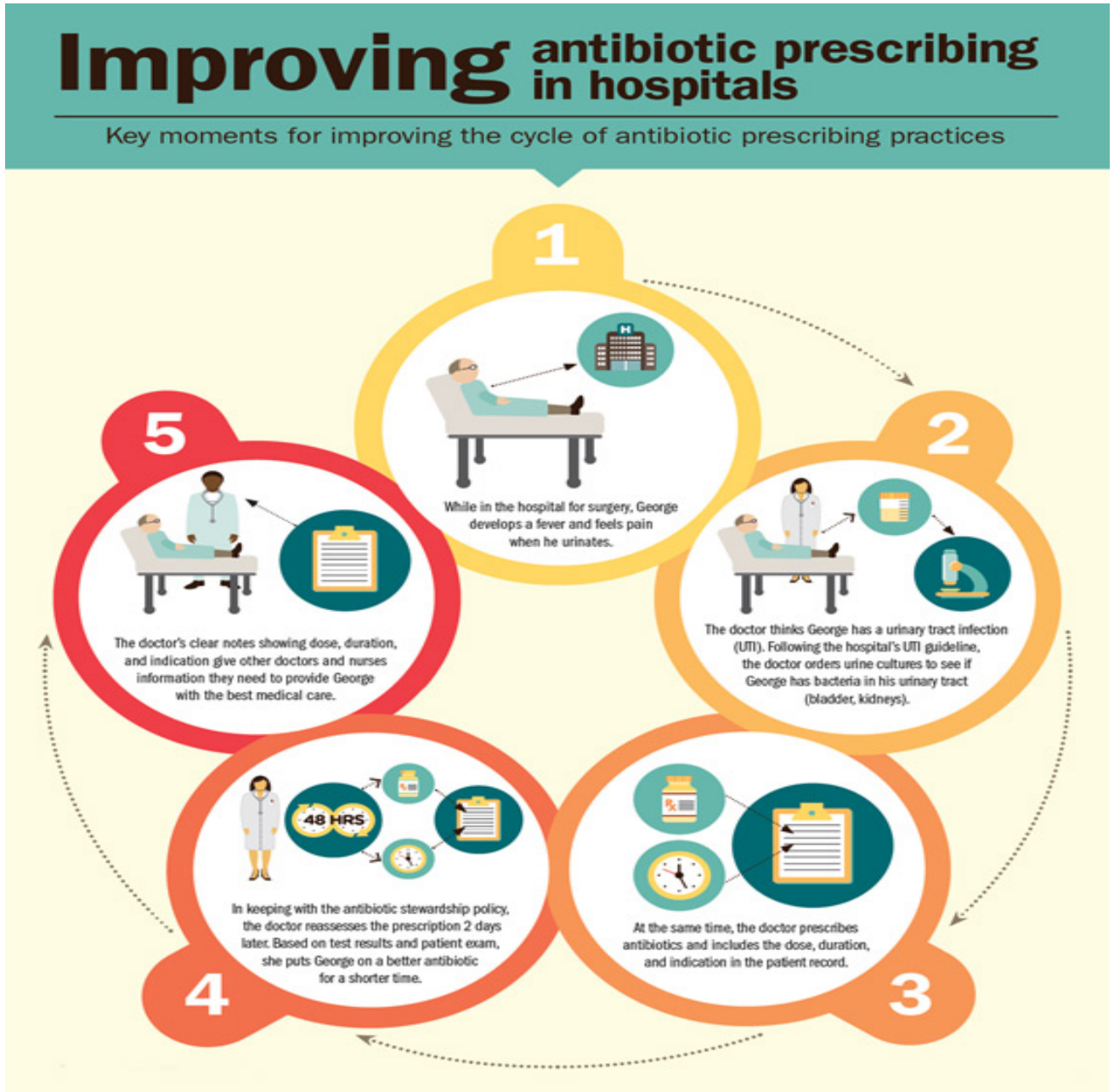






Improving antibiotic prescribing in hospitals

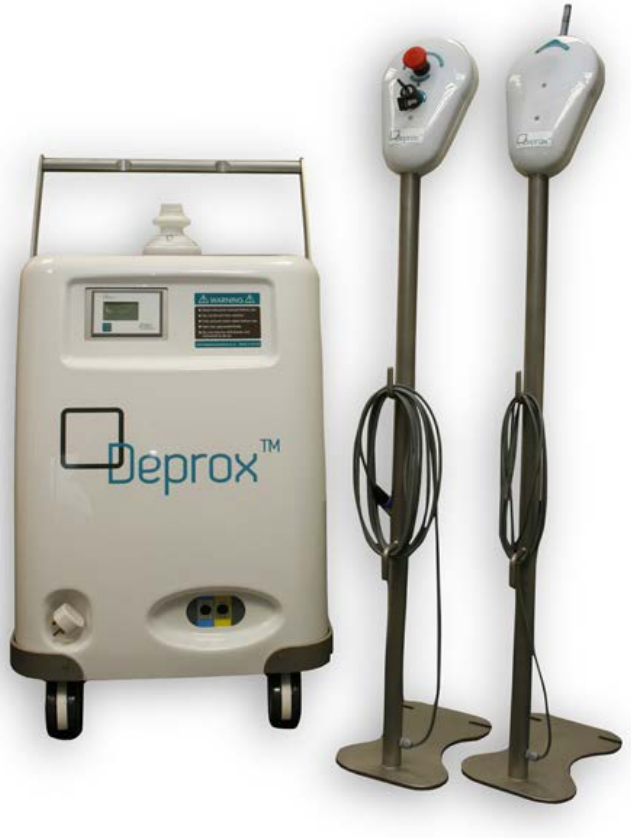
Key moments for improving the cycle of antibiotic prescribing practices



An Evaluation of Environmental Decontamination With Hydrogen Peroxide Vapor for Reducing the Risk of Patient Acquisition of Multidrug-Resistant Organisms

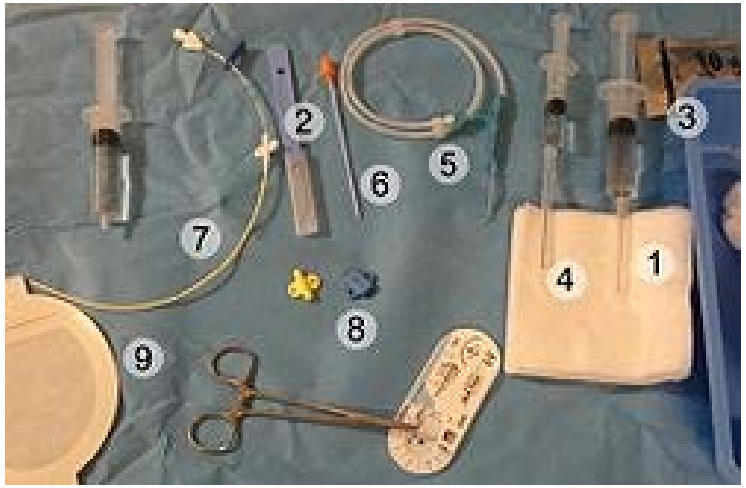
- Increasing evidence that environment plays an important role in transmission of multi-resistant organisms in hospitals

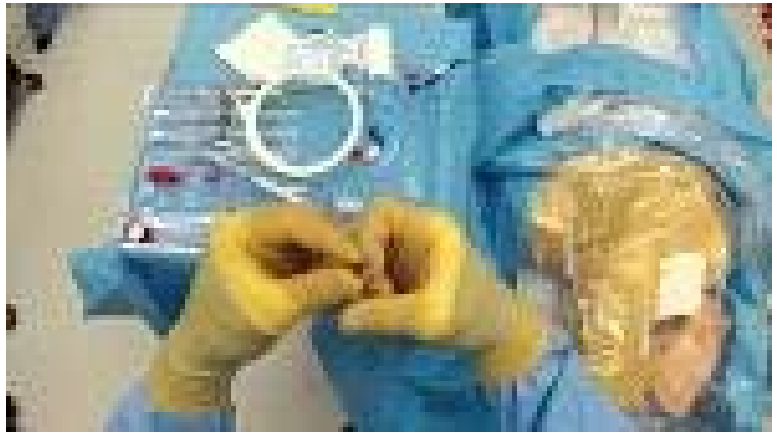
- Patients in rooms decontaminated with vaporised hydrogen peroxide 64% less likely to acquire a multi-resistant organism ($p<0.001$)



Clinical Infectious Diseases 2013;56(1):27–35

Other tools: procedural checklists and antiseptics





Systematic Review and Meta-Analysis: Reminder Systems to Reduce Catheter-Associated Urinary Tract Infections and Urinary Catheter Use in Hospitalized Patients

- **Urinary catheters frequently placed unnecessarily and not removed promptly when no longer required**
- **Simple system changes such as stop orders and reminder systems can reduce mean duration of catheterisation by 37% and reduce rate of CA-UTI by 52% ($p<0.001$)**
- **? A role for antimicrobial impregnated catheters in patients known to be colonized with CPE**

Clinical Infectious Diseases 2010;51(5):550–560

Long term care facilities

- Establish national standards for managing patients colonised with CPE in long term care facilities
- Ensure LTCF are adequately prepared and equipped to adhere to those standards
- Implement targeted antimicrobial stewardship programmes for LTCF
- Address structural factors such as inadequate staffing that may increase the risk of transmission of CPE in LTCF

Summary

- Extended spectrum beta-lactamase-producing Enterobacteriaceae are typically resistant to (nearly) all antibiotics except the carbapenems.
- The predominant ESBL type in NZ is CTX-M, CTX-M producing E. coli and K. pneumoniae are endemic in NZ, causing community onset urinary tract infections and healthcare-associated infections
- Spread of ESBL and CPE genes can occur at many levels with clonal expansion, horizontal spread of plasmids, movement of transposons containing ESBL and CPE genes between different plasmids
- Carbapenemase-producing Enterobacteriaceae are resistant to carbapenems and can typically only be treated with colistin but resistance to this is increasing rapidly, leaving no treatment options
- CPE in NZ currently appears to be following the path of CTX-M ESBL, with sharply increasing incidence as occurred for CTX-M in the early 2000's

Summary

- Like CTX-M-15, NDM and OXA-48 like carbapenemases are associated with travel to and emigration from the Indian Subcontinent
- Acquisition of NDM and OXA-48 like carbapenemases during travel to the Indian Subcontinent is increasingly occurring in the absence of healthcare exposure
- Long term care facilities in NZ appear to have played some role in dissemination of CTX-M and in the absence of action are likely to play a similar role in the spread of CPE
- A specific targeted national action plan is needed to prepare and respond to the unfolding CPE epidemic in NZ

Take home messages

- Antibiotic resistance in gram negative organisms is all about “pandemic genes” that spread globally due to travel and emigration from high prevalence areas
- CPE pose an imminent and serious threat to healthcare in NZ
- Specific, targeted infection control measures are needed to mitigate the clinical impact of CPE in NZ

Emergence of Extended-Spectrum β-Lactamase–Producing *Escherichia coli* in Community Hospitals throughout North Carolina: A Harbinger of a Wider Problem in the United States?

Joshua T. Freeman, Daniel J. Sexton, and Deverick J. Anderson

Duke Infection Control Outreach Network, Duke University Medical Center, Durham, North Carolina

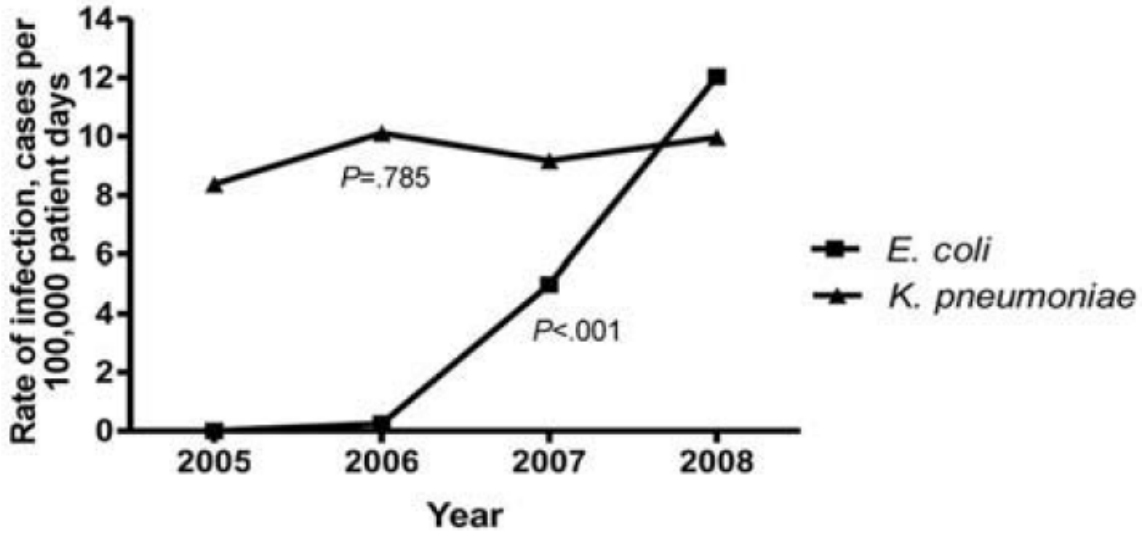


Figure 1. Aggregated rates of extended-spectrum β-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae* infection among 16 community hospitals in North Carolina (*P* values for trend were determined by Poisson regression).

Clinical Infectious Diseases 2009; 49:e30–2

Predictors of hospital surface contamination with Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: patient and organism factors

Results: 24 patients (11 with ESBL-KP, 11 ESBL-EC and 2 with both organisms) had 1104 swabs collected during 138 visits. The overall contamination rate was 3.4% (38/1104) and was significantly higher for ESBL-KP than ESBL-EC (5.4% versus 0.4%; $p < 0.0001$). After multivariate analysis, environmental contamination was found to be negatively associated with carbapenem exposure (OR 0.06 [95% CI 0.01-0.61]; $p = 0.017$) and positively associated with the presence of an indwelling urinary catheter (OR 6.12 [95% CI 1.23-30.37]; $p = 0.027$) and ESBL-KP in the source patient (OR 26.23 [95% CI 2.70-254.67]; $p = 0.005$).

Conclusions: Contamination of the hospital environment with ESBL-producing Enterobacteriaceae (ESBL-E) is inversely associated with carbapenem exposure. Predictors of hospital contamination with ESBL-E include: indwelling urinary catheters and ESBL-KP. Rooms of patients with ESBL-KP have substantially higher contamination rates than those with ESBL-EC. This finding may help explain the apparently higher transmissibility of ESBL-KP in the hospital setting.