Contemporary epidemiology of Gram-negative resistance in New Zealand

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Specialist Science Solutions

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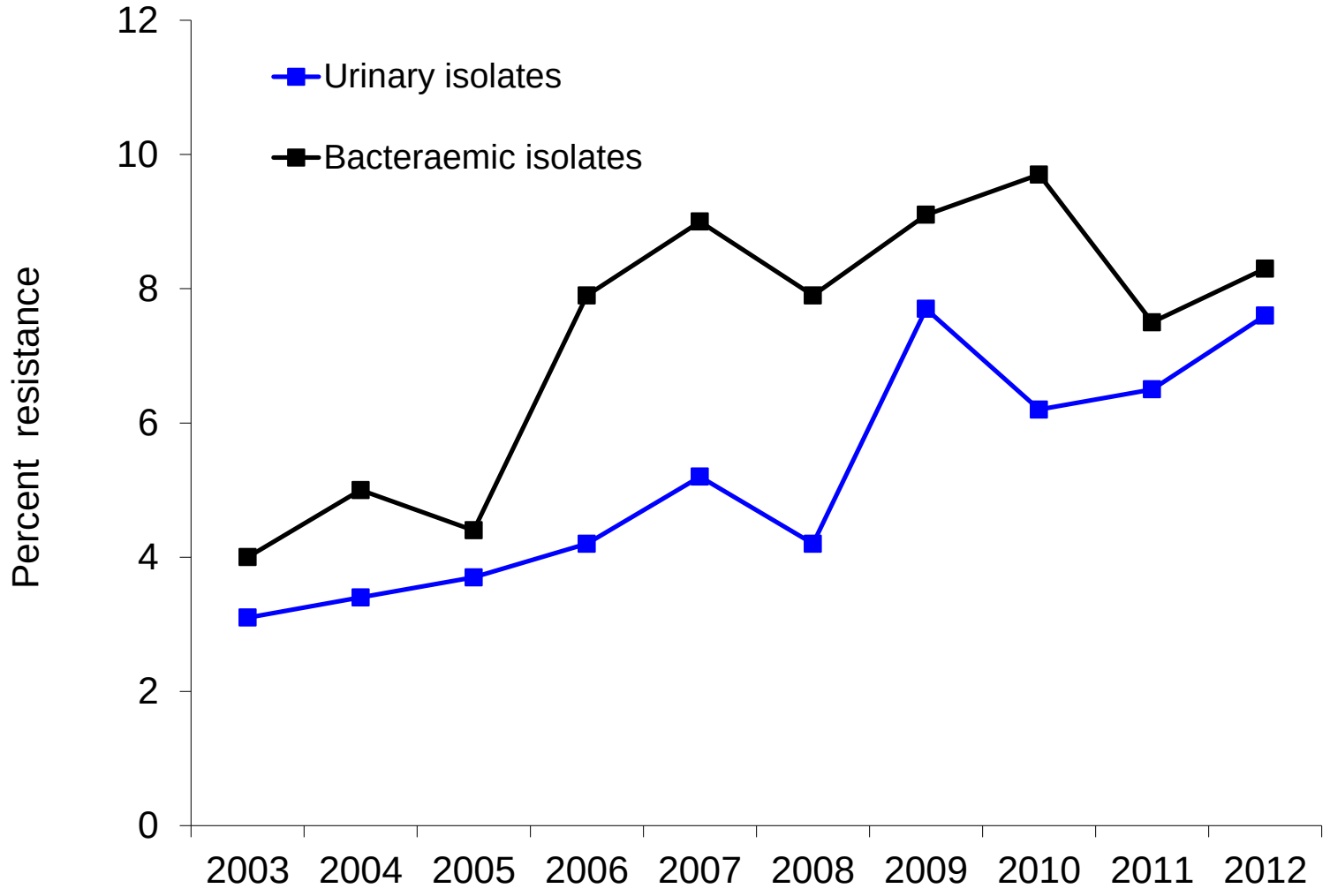
Outline

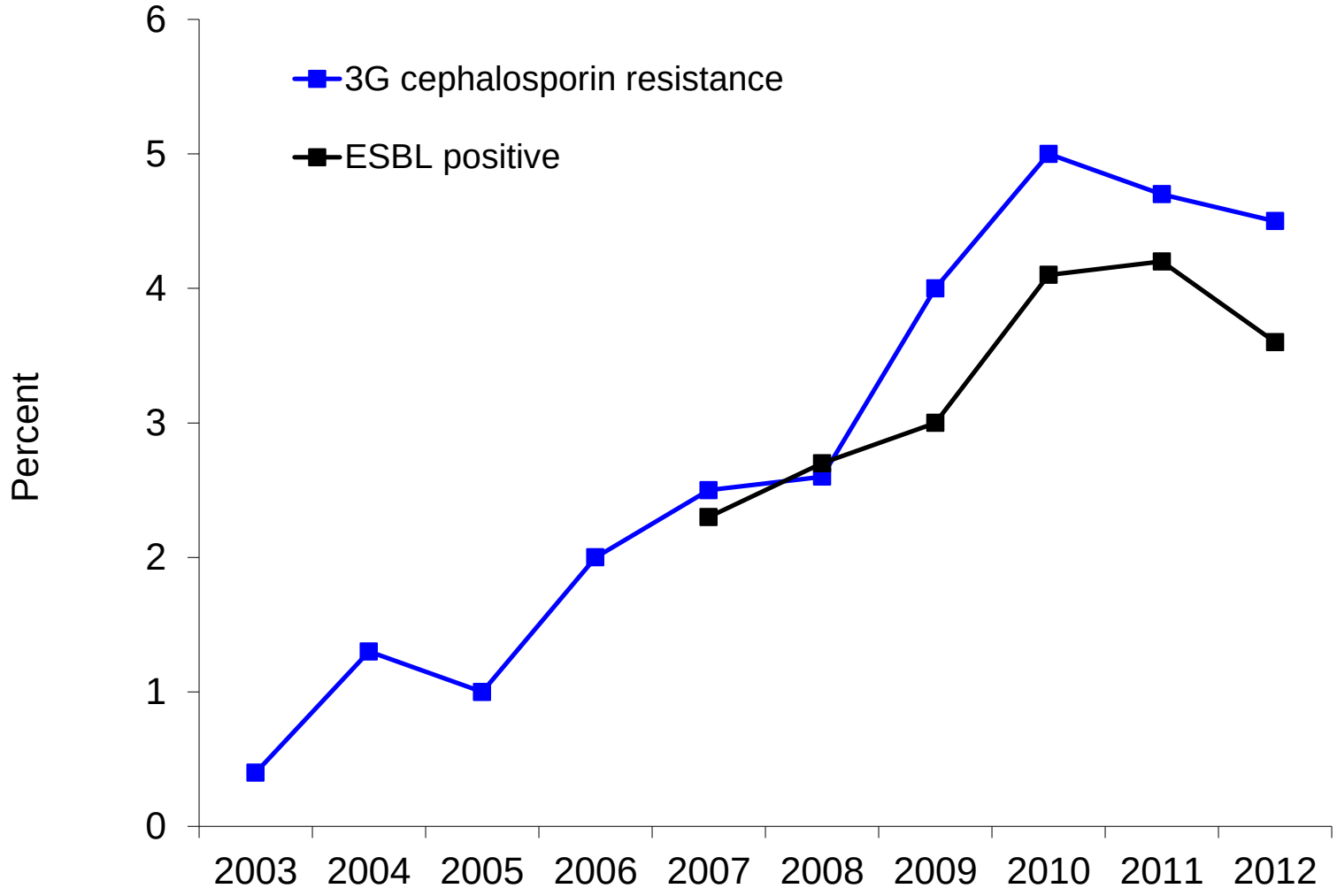
- Selected resistance trends in Gram-negatives
- Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae
- Acquired carbapenemases in Enterobacteriaceae and Pseudomonas
- Resistance among Gram-negatives from food-producing animals

Fluoroquinolone resistance in *E. coli*



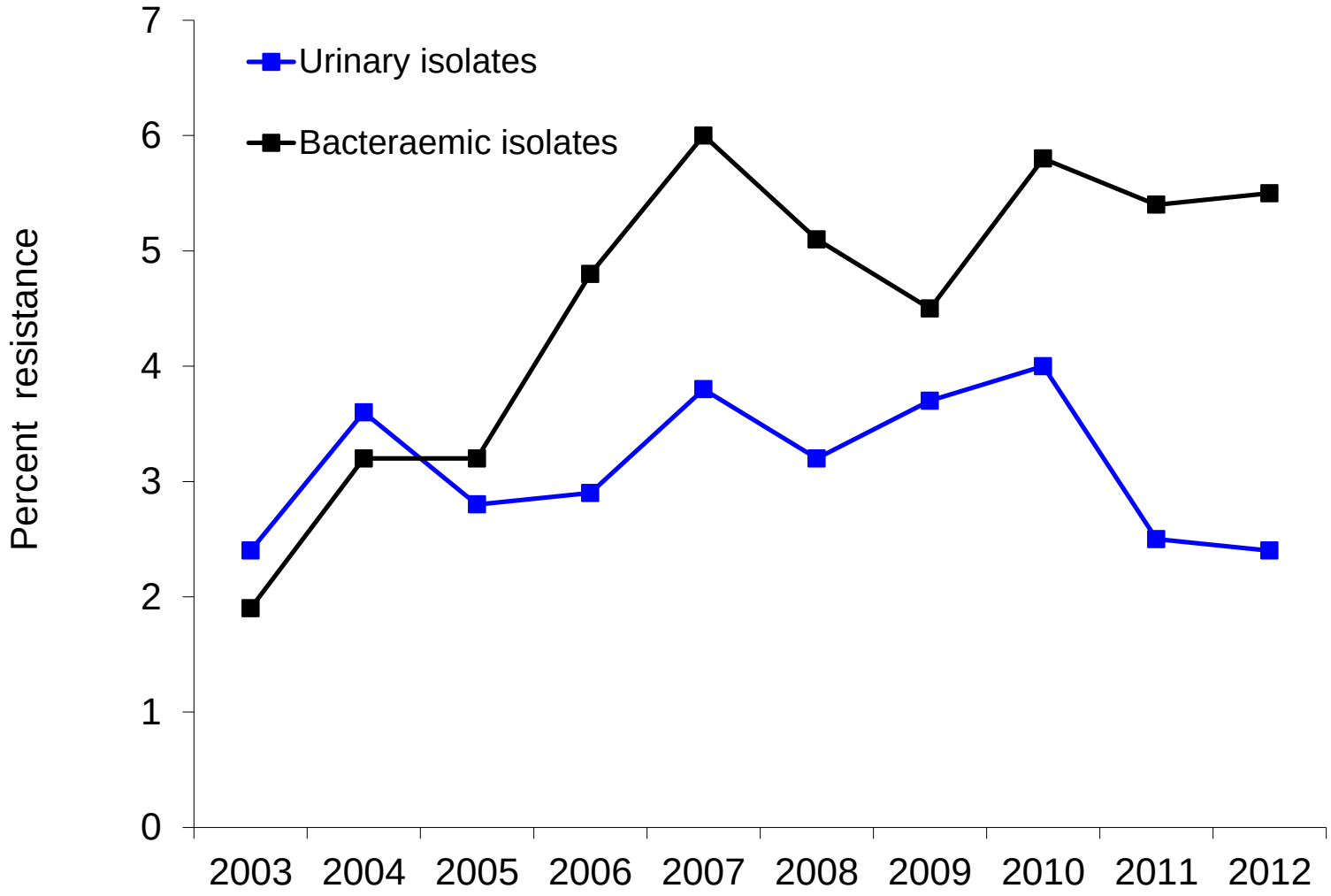
Source: Diagnostic lab data collected annually

3rd gen cephalosporin resistance in bacteraemic *E. coli*



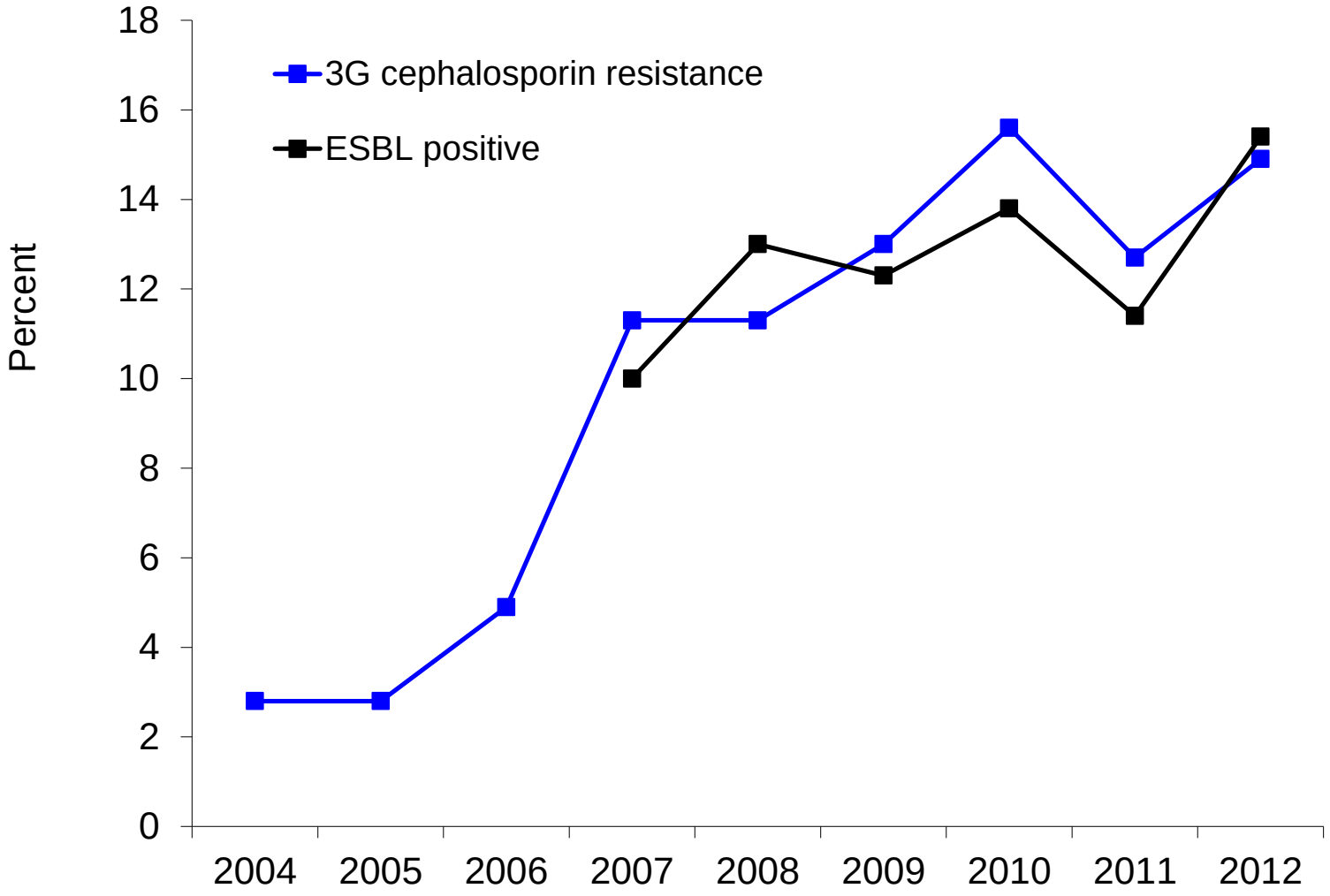
Source: Diagnostic lab data collected annually

Gentamicin resistance in *E. coli*



Source: Diagnostic lab data collected annually

3rd gen cephalosporin resistance in bacteraemic *Klebsiella*



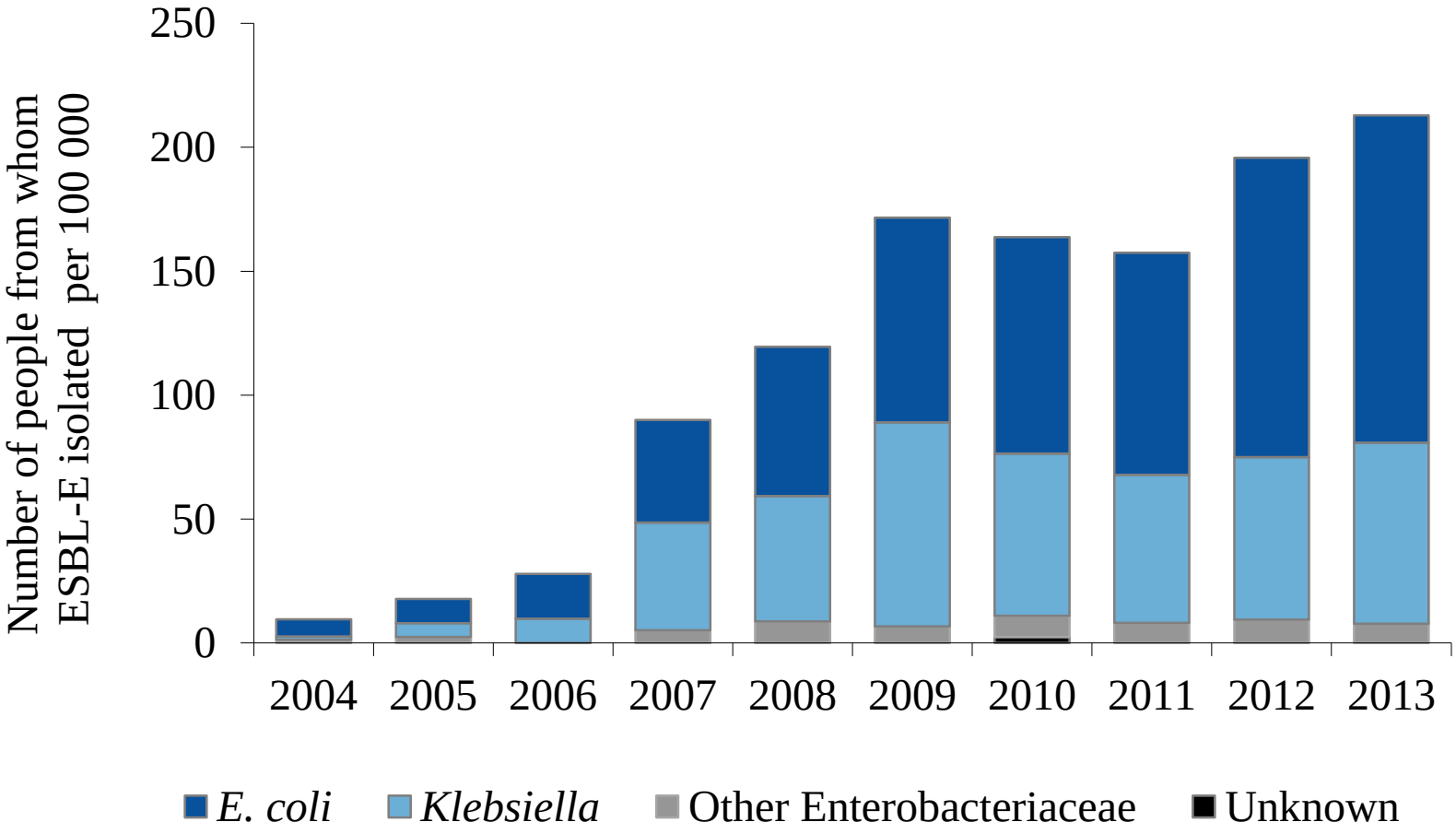
Source: Diagnostic lab data collected annually

NZ vs other countries

	Percent resistance		
	E. coli		*Klebsiella*
	3G cephalosporin	fluoroquinolone	3G cephalosporin
New Zealand	4.5	8.3	14.9
Australia	9.6	10.6	12.1
United Kingdom	9.6	17.5	5.3
United States	14.6	33.3	23.0
China	→70.0	→50.0	→50.0
India	→90.0	→80.0	→100.0

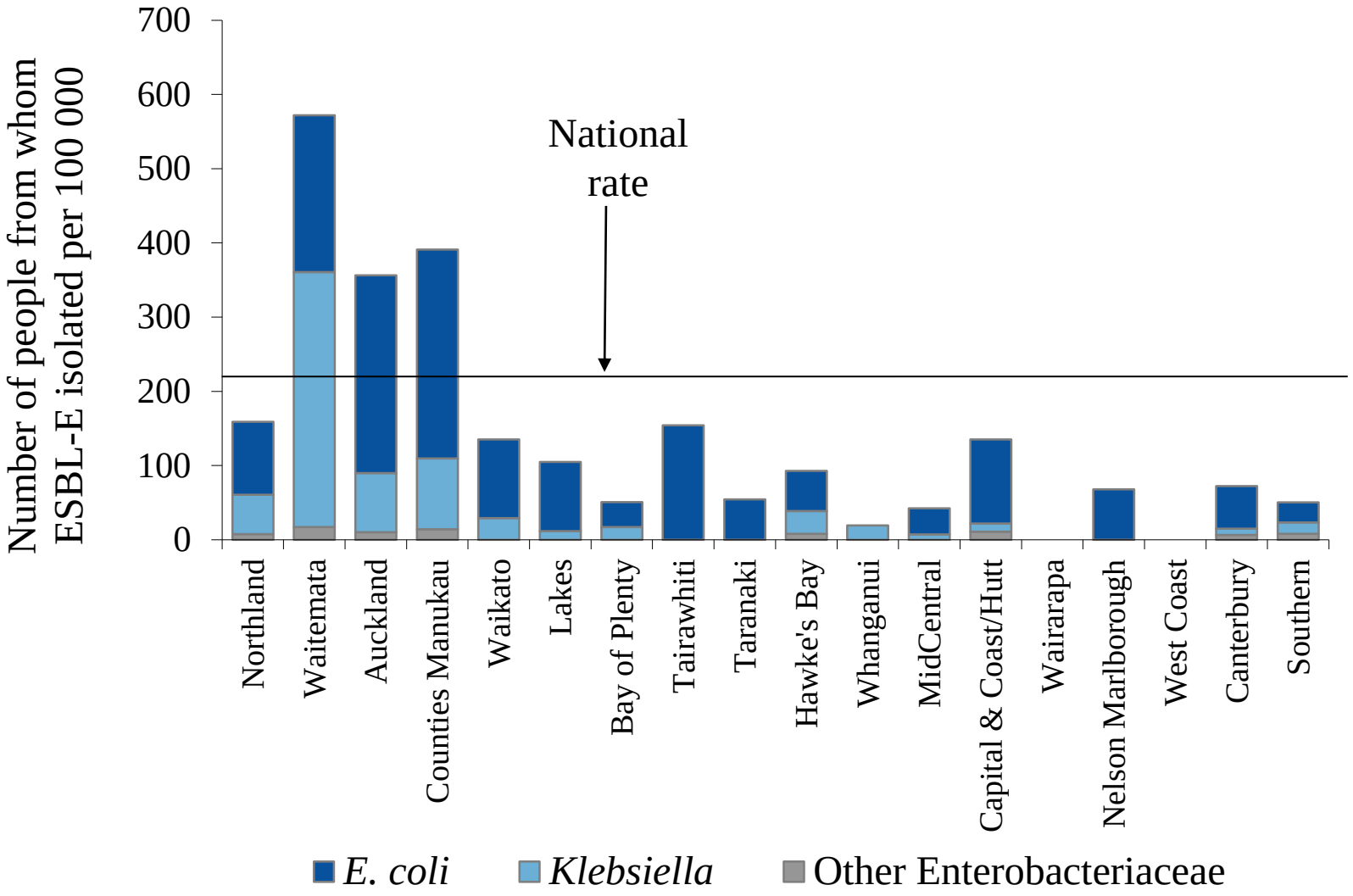
Source: Antimicrobial resistance: global report on surveillance. WHO; 2014

ESBL-producing Enterobacteriaceae incidence rates, New Zealand, 2004-2013



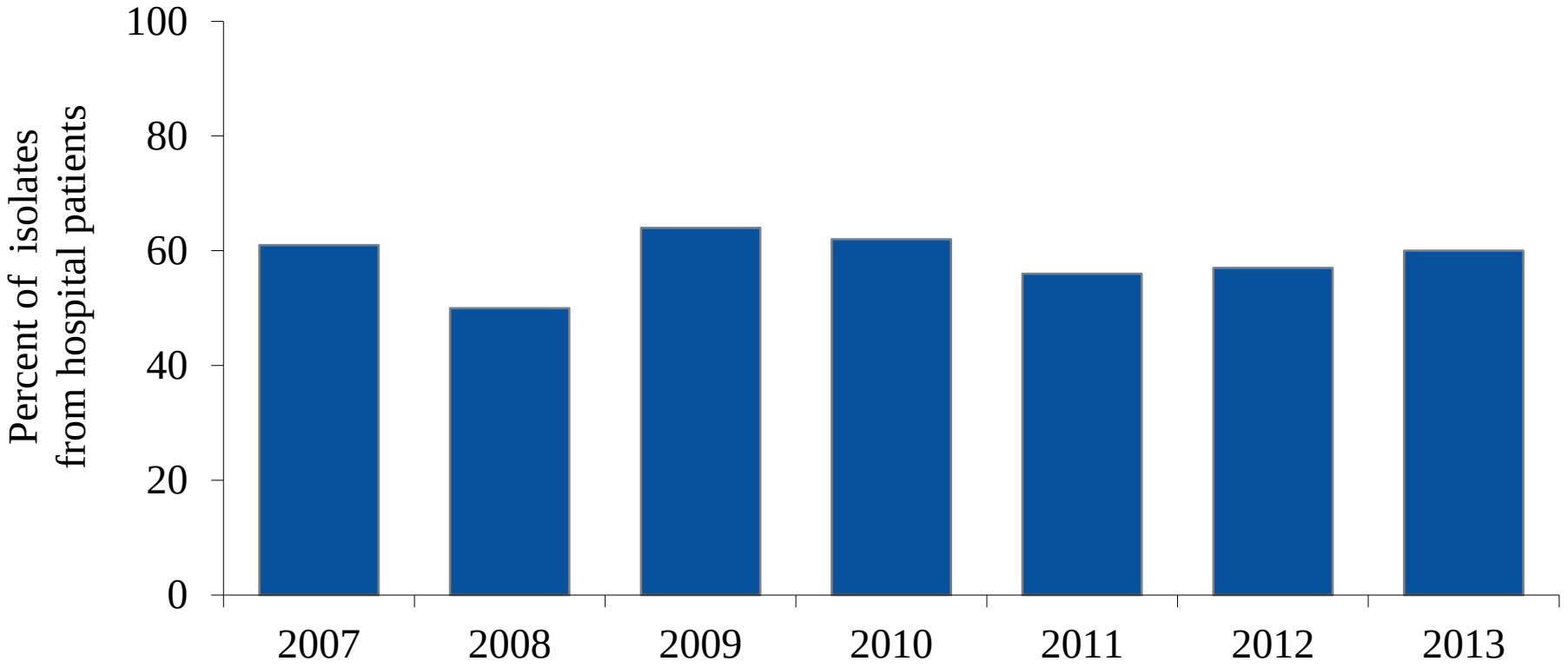
Sources ≤2005: continuous surveillance
2006: annual survey of urinary isolates
≥2007: annual surveys

Annualised incidence of ESBL-producing Enterobacteriaceae by district health board, 2013



Source: 2013 annual survey

ESBL-producing Enterobacteriaceae (infections only): proportion from hospital patients, 2007-2013



Definition: a 'hospital' patient was in a HCF (including LTCF) when their ESBL-producing organism isolated or had been in a HCF in ≤3 months

Source: annual surveys

Resistance among ESBL-producing Enterobacteriaceae, 2013*

	Percent resistance		
	E. coli	*Klebsiella*	All (No. tested)
co-amoxiclav	26.1	47.5	33.7 (484)
piperacillin-tazobactam	4.2	6.5	6.6 (166)
cefoxitin	5.5	2.7	7.4 (499)
ertapenem	0.4	0.9	0.8 (397)
imipenem	0.0	0.0	0.0 (193)
meropenem	0.6	1.7	0.8 (240)
ciprofloxacin	58.7	29.9	49.2 (370)
norfloxacin	66.0	25.6	52.7 (421)
gentamicin	44.2	57.1	48.6 (636)
co-trimoxazole	69.9	86.3	74.8 (413)
trimethoprim	69.9	91.6	76.1 (493)
fosfomycin	2.5	6.3	4.2 (190)

Source: 2013 annual survey; susceptibility as reported by referring diagnostic labs

ESBL-producing Enterobacteriaceae in NZ

- **Prevalence of ESBLs (data from diagnostic labs):**
  - **<2% among urinary *E. coli***
  - **<5% among *E. coli* blood isolates**
  - **10-15% among *Klebsiella* blood isolates**
- **Risk factors (NZ studies):**
  - **COPD**
  - **LTCF residency**
  - **colonisation with ESBL**
- **Patient demographics (2013 survey)**
  - **61% patients ≥65 years (76% with *Klebsiella* and 53% with *E. coli*)**
  - **83% from urinary tract infections**
- **ESBL types (2006 survey):**
  - **78% CTX-M-15**
  - **14% CTX-M-14**

Further investigation of 350 clinical ESBL-producing isolates from the 2013 annual survey to determine:

- **Susceptibility to a range of antibiotics (including fosfomycin, mecillinam and tigecycline) and multidrug resistance**
- **Prevalence of ESBL types: CTX-M, SHV, TEM or VEB**

  [in 2006 study, 78% CTX-M-15 and 14% CTX-M-14]
- **Clonality among ESBL-producing *E. coli* and *Klebsiella pneumoniae***
- **Prevalence of multilocus sequence typing (ST)131 *E. coli***

Acquired carbapenemases

Belong to three molecular (Ambler) β-lactamases classes:

1 **Class A: *Klebsiella pneumoniae* carbapenemases (KPCs)**

2 **Class B: metallo-β-lactamases (MBLs)**

- **IMP**
- **VIM**
- **NDM (New Delhi metallo-β-lactamase)**

3 **Class D:**

- **OXA-48-like**
- **OXA-23-like, OXA-40-like, OXA-58-like**

Carbapenemases confer resistance to all β-lactams (exceptions by class, for example, aztreonam not hydrolysed by MBLs).

AND carbapenemase-producing organisms typically multiresistant to many other antibiotic classes.

Carbapenemases: the threat

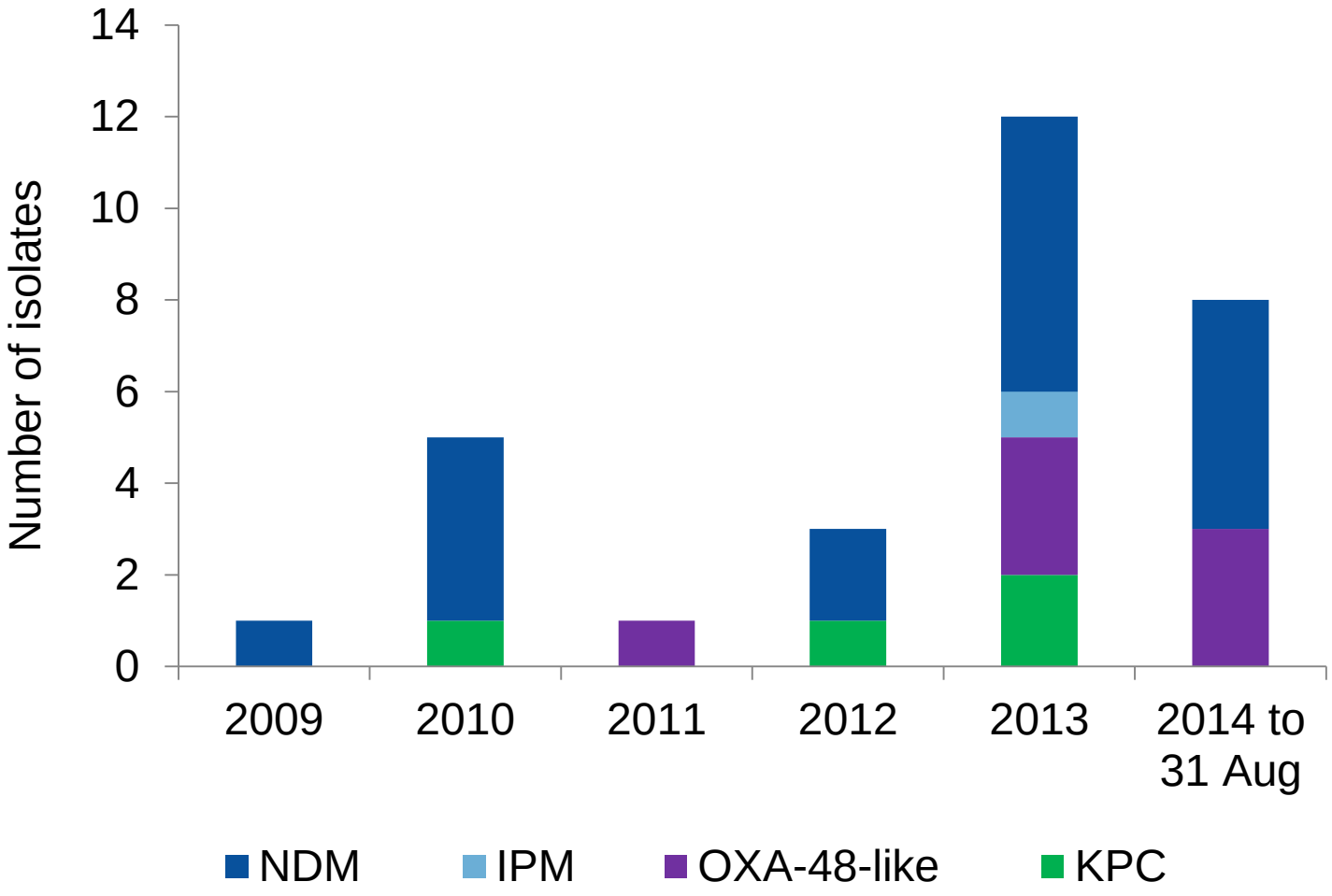
Patient earlier this year who had recently been in a Mumbai hospital

MDRO screening upon admission to a NZ hospital found:

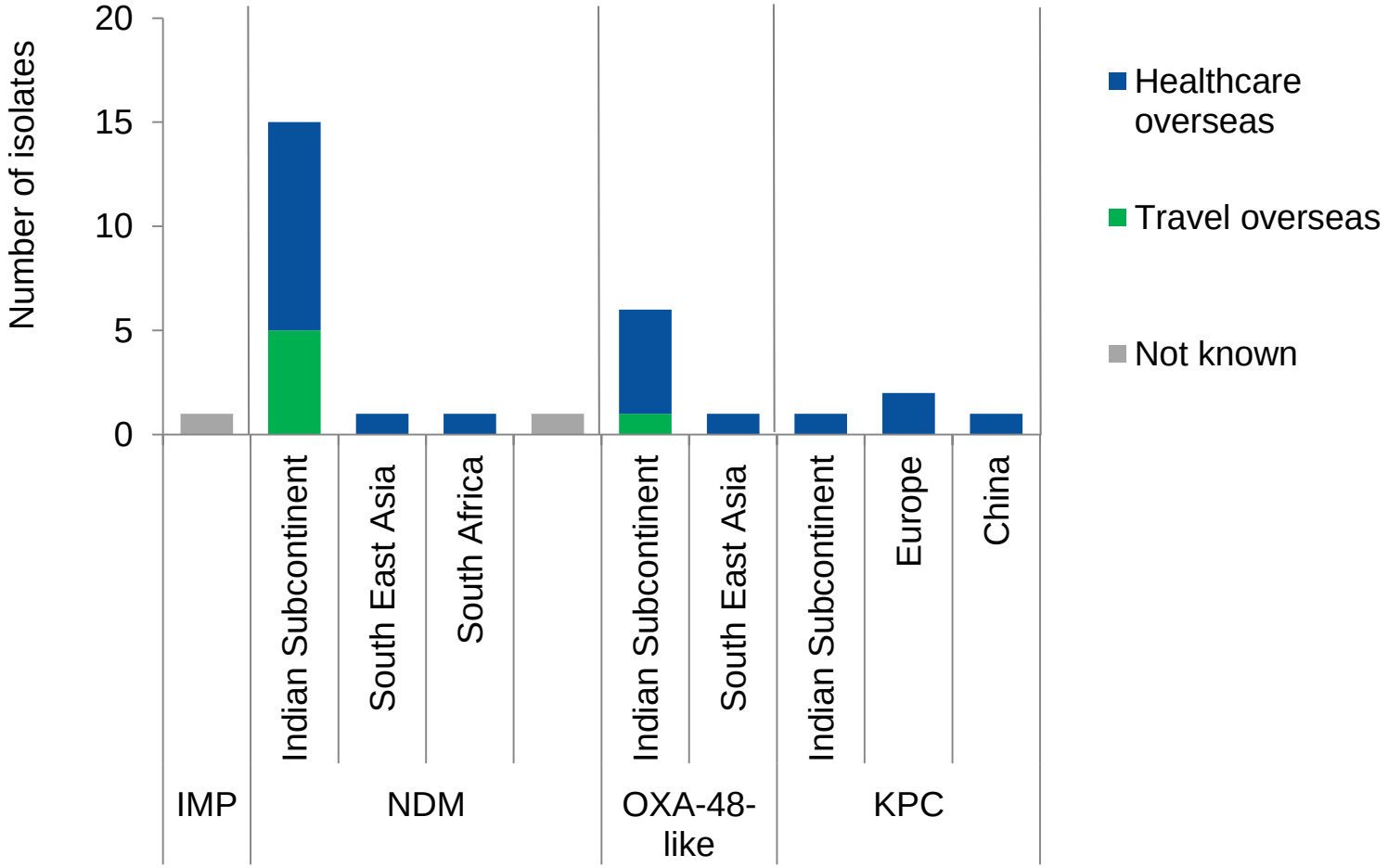
1. ***E. coli*** **with New Delhi metallo-β-lactamase (NDM-7)**
2. ***C. freundii*** **with New Delhi metallo-β-lactamase (NDM-1)**
3. ***E. coli*** **with OXA-48-like carbapenemase (OXA-181)**
4. ***P. aeruginosa*** **with VIM-2 metallo-β-lactamase**
5. **vanA *E. faecium* with linezolid resistance**

and both *E. coli* isolates also had a group1 CTX-M ESBL and plasmid- mediated AmpC β-lactamase

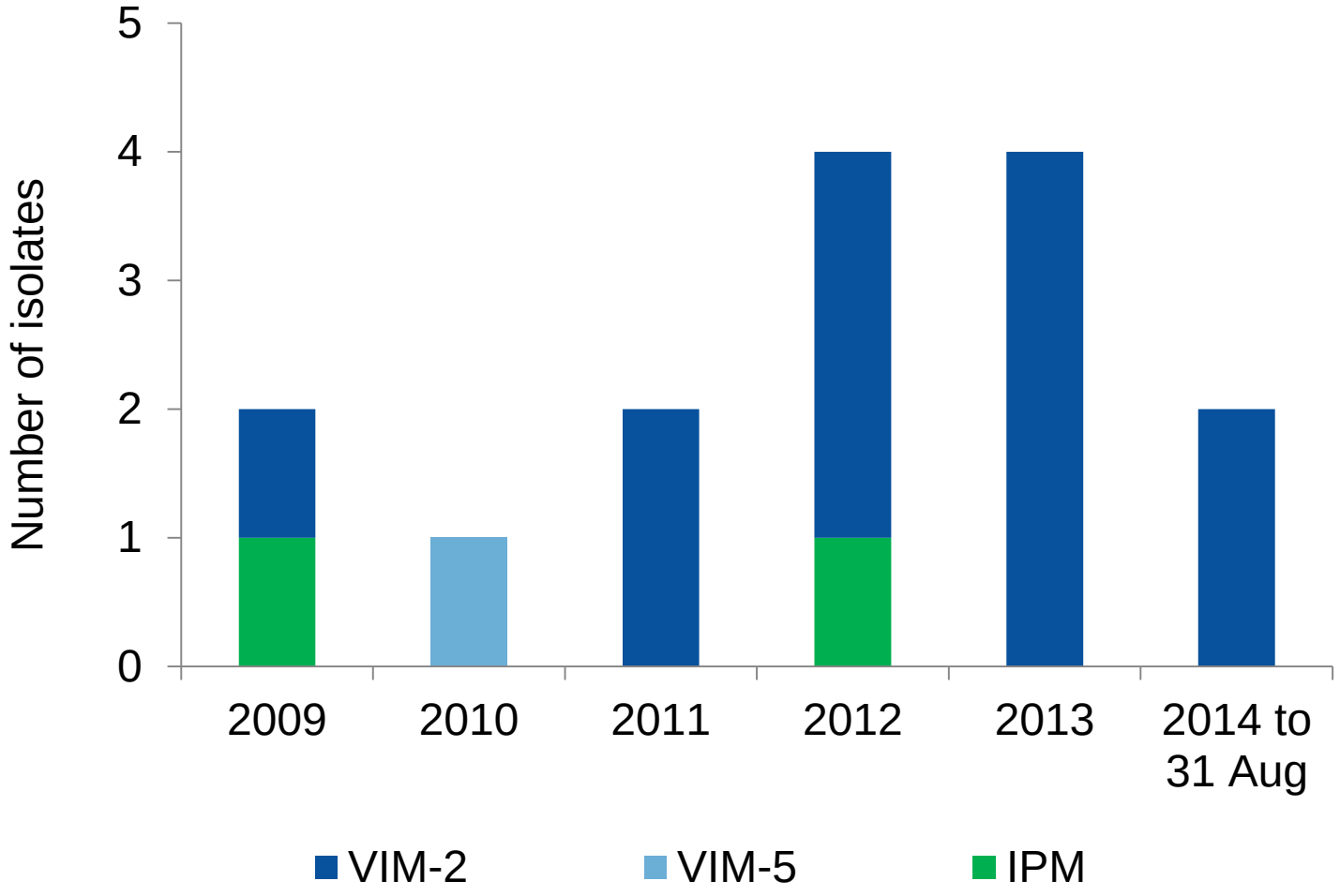
Carbapenemases in Enterobacteriaceae confirmed in NZ, 2009 - August 2014



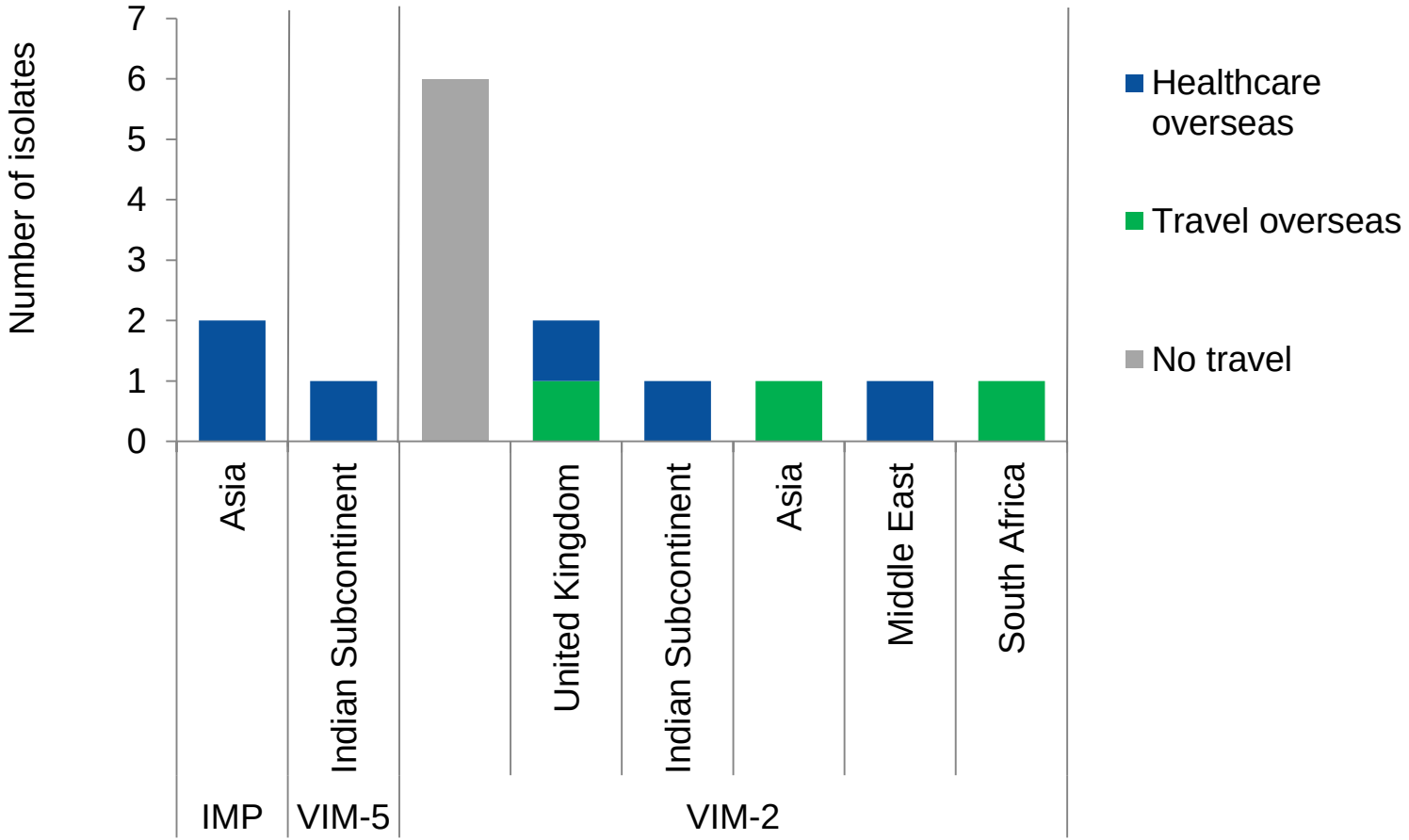
Overseas healthcare and travel of patients with carbapenemase-producing Enterobacteriaceae identified in NZ, 2009 - August 2014



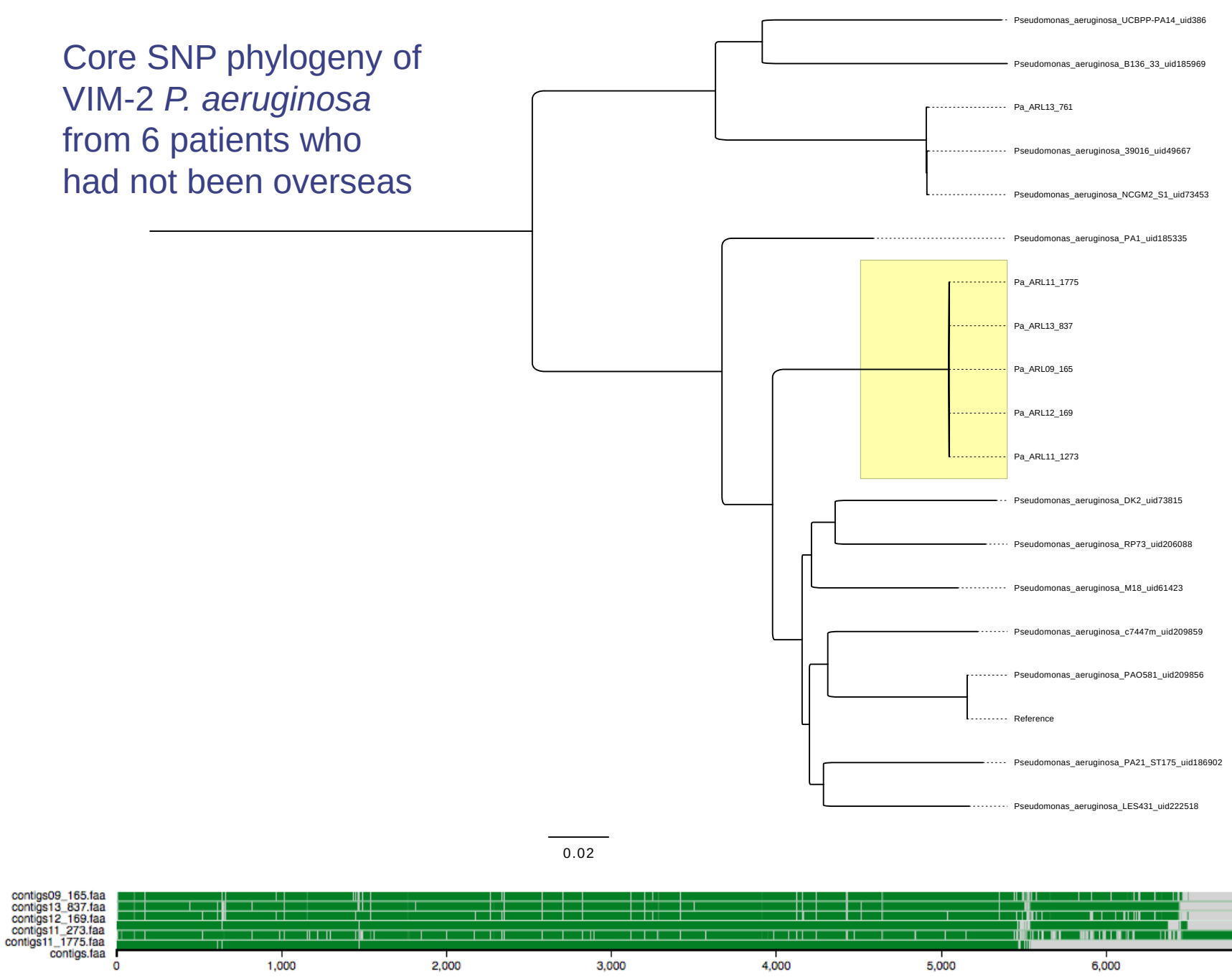
Carbapenemases in *Pseudomonas aeruginosa* confirmed in NZ, 2009 - August 2014



Overseas healthcare and travel of patients with carbapenemase-producing *P. aeruginosa* identified in NZ, 2009 – August 2014



Core SNP phylogeny of VIM-2 *P. aeruginosa* from 6 patients who had not been overseas



VIM-2 *P. aeruginosa* apparently acquired in NZ

- 6 of total 12 patients with VIM-2 *P. aeruginosa* had not been overseas
- was the very first carbapenemase-producing isolate identified in NZ – 2009
- 5 patients from the Auckland area, 1 in Northland
- WGS has identified the 5 isolates from Auckland as same strain and quite distinct from the 1 Northland isolate
- two of the Auckland isolates from patients in the same LTCF
- suggestive of NZ reservoir of VIM-2 *P. aeruginosa*

Resistance in food-producing animals

- **NZFSA-funded 12-month survey, Oct 2009 to Oct 2010**
- **'piggy-backed' off sampling routinely undertaken as part of the microbiological QC of carcasses in abattoirs and poultry processing plants: *National Microbiological Database* (*NMD*) programme**
- ***Campylobacter*, *Salmonella, E. coli* and *E. faecalis/E. faecium***
- **from very young (bobby) calves, pigs, broiler poultry, and culled dairy cows**
- **target was to obtain 300 isolates of each bacterial group from each of the 3 animal groups**
- **antimicrobials tested included those important in human medicine and veterinary practice**

Antimicrobial susceptibility testing methods

- **CLSI microbroth dilution**
- **antibiotics tested: ampicillin, co-amoxiclav, cephalothin, cefotaxime (+ ceftazidime screen), cefoxitin, chloramphenicol, nalidixic acid, ciprofloxacin, gentamicin, streptomycin, neomycin, spectinomycin, tetracycline, sulphamethoxazole and trimethoprim**
- **interpretive standards:**

  - CLSI

  - CLSI for animals

  - DANMAP 'epidemiological cut-off' values

- ***E. coli* and *Salmonella* screened for ESBLs and AmpC β-lactamases**

E. coli resistance

	% resistance among *E. coli*		
	Calves n=300	Pigs n=303	Poultry n=306
ampicillin	23.7*	8.9	4.9
co-amoxiclav	1.0	0.7	0
cefotaxime	0	0	0
cefoxitin	1.0	1.3	0.3
nalidixic acid	0.3	0.7	5.6*
ciprofloxacin	0	0	0
gentamicin	0	0	0
trimethoprim	12.7	8.3	6.7

* = significant difference ($p \leq 0.05$) between animal groups

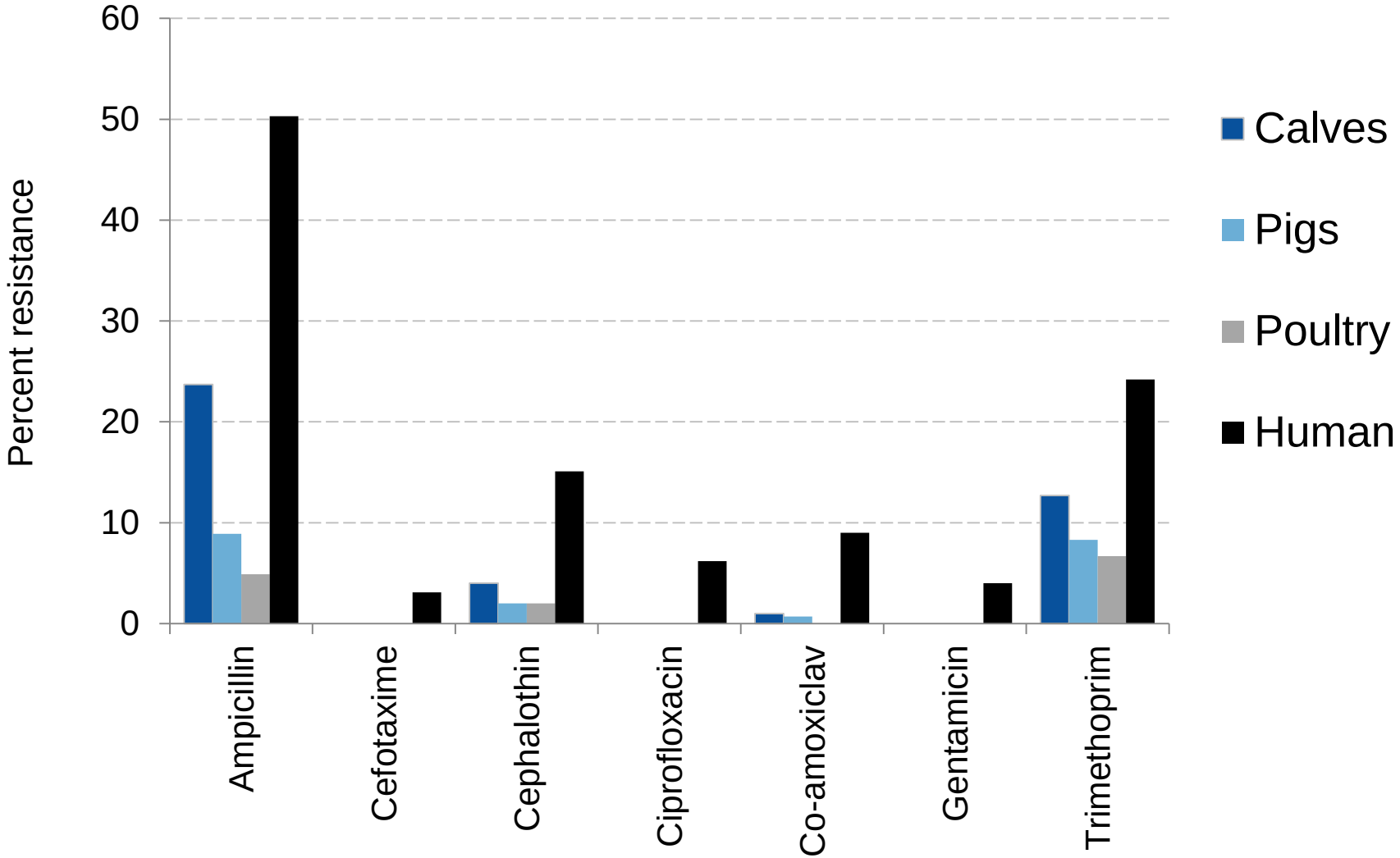
E. coli resistance

High prevalence of streptomycin, sulphonamide and tetracycline resistance in calves and pigs:

	% resistance among *E. coli*	
	Calves n=300	Pigs n=303
streptomycin	44.3	32.3
sulphamethoxazole	45.0	32.7
tetracycline	40.7	48.5

78% MDR (≥3 antibiotics*)* among *E. coli* from calves, 55% from pigs.
SmSfTe (± others) common resistance pattern

Comparison of resistance among animal and 2009 human (urinary) *E. coli* isolates



Significant (p≤0.05) differences in resistance among bacteria from NZ and Danish pigs and poultry

	NZ vs Denmark (DANMAP 2009)	
	Pigs	**Poultry**
E. coli		
ampicillin	↓	↓
sulphamethoxazole		↑
trimethoprim	↓	

Summary

- **No cefotaxime, ciprofloxacin or gentamicin resistance in *E. coli.* No extended-spectrum or AmpC β-lactamases identified.**

- **?? Resistance lower than in NZ human isolates**

- **Compared with Danish (ie, DANMAP) data for bacteria from pigs and poultry, with one exception (sulphonamide resistance in *E. coli* from poultry), resistance lower or not significantly different for the antibiotics commonly tested.**