Antibiotic resistance in Australian animals in 2010 – what lies ahead?

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Outline

- Why are we interested in AMR in animals?
- Some history…
- Major AMR problems in humans in Australia
- The Australian picture in animals – what information is there?
- Is there a link between AMR in animals and humans in Australia?
- Where are we heading?

AMR in animals

- Resistance in animal pathogens
- Resistance in zoonotic bacteria and transfer of resistance determinants from animal isolates (commensals) to human pathogens
- Widespread distribution of antimicrobial resistance genes – animals, humans, environment
- Pressure to remove antimicrobial growth promoters and restrict range of antibiotics used in animals

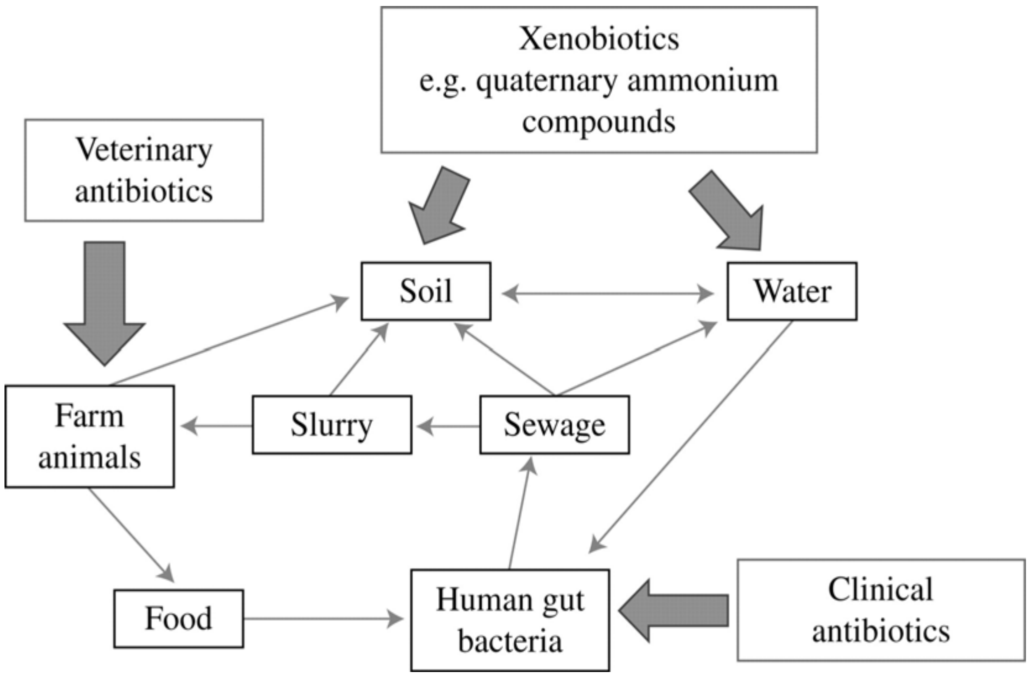
History

- Swan 1969
- Working Party on Antibiotics
- Danish report on link between avoparcin use in animal feeds and vancomycin resistance in human isolates of enterococci – 1995
- JETACAR – 1998
- European action on growth promotants – 1998-2000
- EAGAR 2001-2007

Major AMR problems in humans in Australia

- Hospital acquired MRSA
- Community acquired MRSA
- *van*B Vancomycin resistant enterococci
- Penicillin resistant *Streptococcus pneumoniae*
- Multi-drug resistant Gram-negative bacteria (*Pseudomonas, Acinetobacter*,…)
- Extended-spectrum beta-lactamase producing *Enterobacteriaceae*

Flow of antibiotic resistance genes in E. coli in the biosphere



Hawkey, P. M. et al. J. Antimicrob. Chemother. 2009 64:i3-10i; doi:10.1093/jac/dkp256

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Antibiotic resistance in animals

- Therapeutic failure due to antibiotic resistance not commonly reported in animals
- Systematic studies on isolates from animals limited
  - Animal Health Committee study 1976-1981 – *E coli* and salmonella from cattle and pigs mainly, bovine mastitis *Staph aureus* isolates
  - 2004 DAFF pilot surveillance study – *E coli*, enterococci, campylobacter from cattle, pigs and chickens
- National Enteric Pathogen Surveillance Scheme (MDU Melbourne) and Salmonella Reference Laboratory (SA Pathology, IMVS) – now test salmonella isolates for resistance

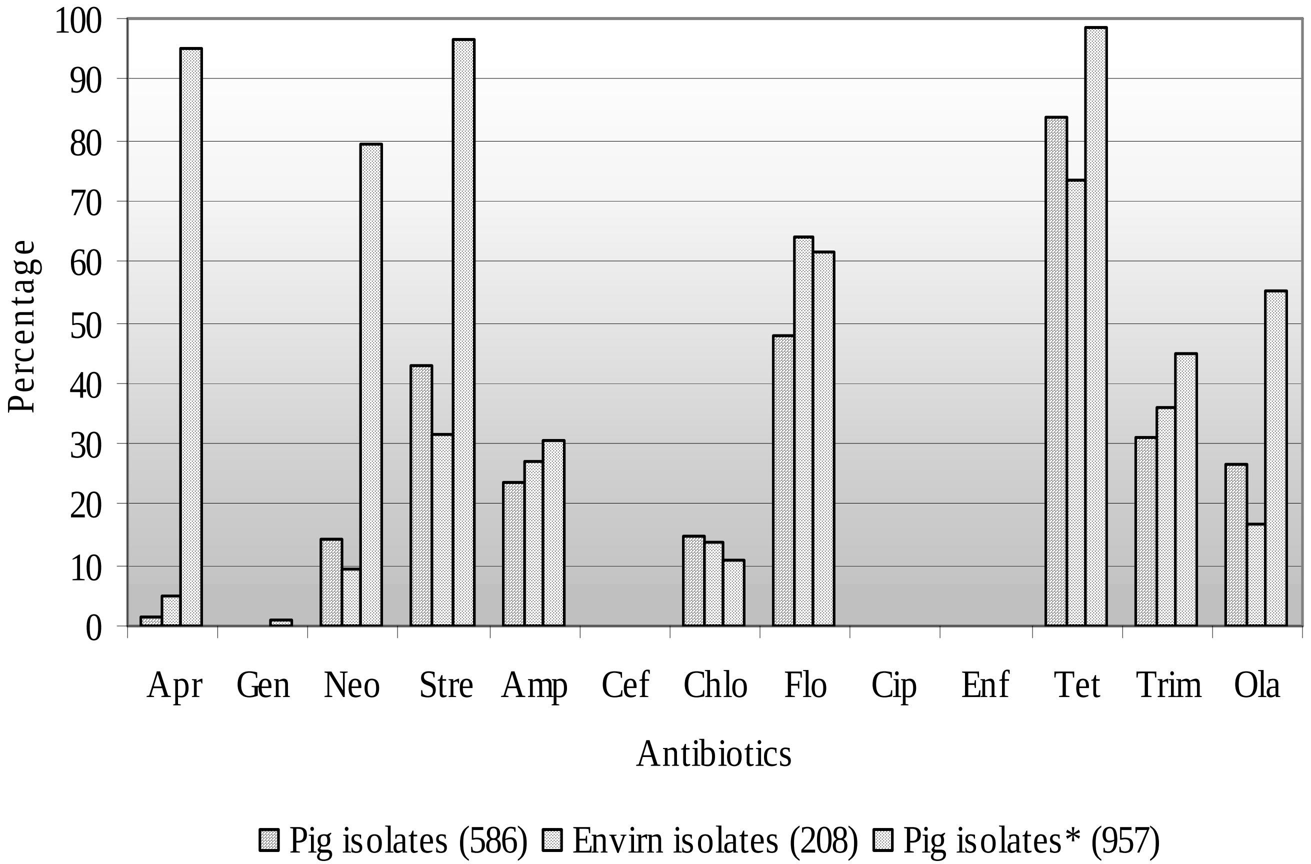
Antibiotic resistance in animal pathogens in Australia

- *E coli* and salmonella from calf scours (laboratory records)
- *E coli* from neonatal and post-weaning diarrhoea in pigs (laboratory records)
- Salmonella in dairy cattle (lab records) & pigs, chickens, cattle (Salmonella Reference Laboratory)
- Dog ears (lab records)
- Limited other studies – atypical mycobacteria from cats (Malik et al 2000); cat bite organisms (Love et al 2000)Verotoxigenic *E coli* from various animals (Bettelheim et al 2003); salmonella and *E coli* from horses (Bucknell et al 1997);

E coli

	1976-1981 (Barton et al 2003)	2004 (DAFF pilot study)
tetracycline	Pig -72-86% Cattle – 39-79%	Pig – 76% Cattle – 3%
ampicillin	Pig – 6-12% Cattle – 8-29%	Pig – 35% Chickens – 33%
Chloramphenicol	Pig – 2-8% Cattle – 3-24%	Pig – 44% Chicken – 2%
florfenicol	NT	Pig – 34% Cattle – 1% Chickens – 3%
Trimethoprim/ sulfamethoxazole	NT	Pig – 33% Chicken – 27%
Gentamicin	NT	Pig 3%
Nalidixic acid	NT	Pig 5% Chicken – 2%
ciprofloxacin	NT	Chicken - 0.4%
ceftiofur	NT	0

Figure 2 Antibiotic resistance in *E. coli* isolated from pigs and piggery environments



Barton and Peng (2005) Report to Australian Pork Ltd. Epidemiology of antibiotic resistant bacteria and genes in piggeries.

Salmonella (1990-1997)

	Cattle (396)	Chicken (108)	Pig (51)
Ampicillin	31%	17%	35%
chloramphenicol	18	5	10
streptomycin	86	5	10
tetracycline	47	44	92
sulphathiazole	70	19	41
trimethoprim	29	17	41
Nalidixic acid	0.5	0	0
Ciprofloxacin	0	5	7
gentamicin	0.6	4	5

Barton et al (2003) CDI 27:S121

Multiple resistance in *E coli* - DAFF

	Cattle (194)	Pigs (182)	Chickens (269)
0 classes of antibiotics	192 (96%)	24 (13%)	106 (40%)
1	8 (4%)	43 (24%)	70 (26%)
2		34 (19%)	56 (21%)
3		32 (18%)	29 (11%)
4		34 (19%)	8 (3%)
5		12 (7%)	
6		2 (1%)	

DAFF (2007) Pilot Surveillance Program for Antimicrobial Resistance in Bacteria of Animal Origin. http://www.daff.gov.au/__data/assets/pdf_file/0004/950431/AMR-pilot-survey-report.pdf

Multi-drug resistant salmonella – pigs 2005

	Pig isolates (41)	Environmental isolates (32)
O classes of antibiotics	10 (24)	8 (25)
1	26 (63)	12 (38)
2	4 (10)	4 (13)
3	0	4 (13)
4	0	2 (6)
5	1 (2)	1 (3)
6	0	1 (3)

Barton and Peng (2005) Report to Australian Pork Ltd. Epidemiology of antibiotic resistant bacteria and genes in piggeries.

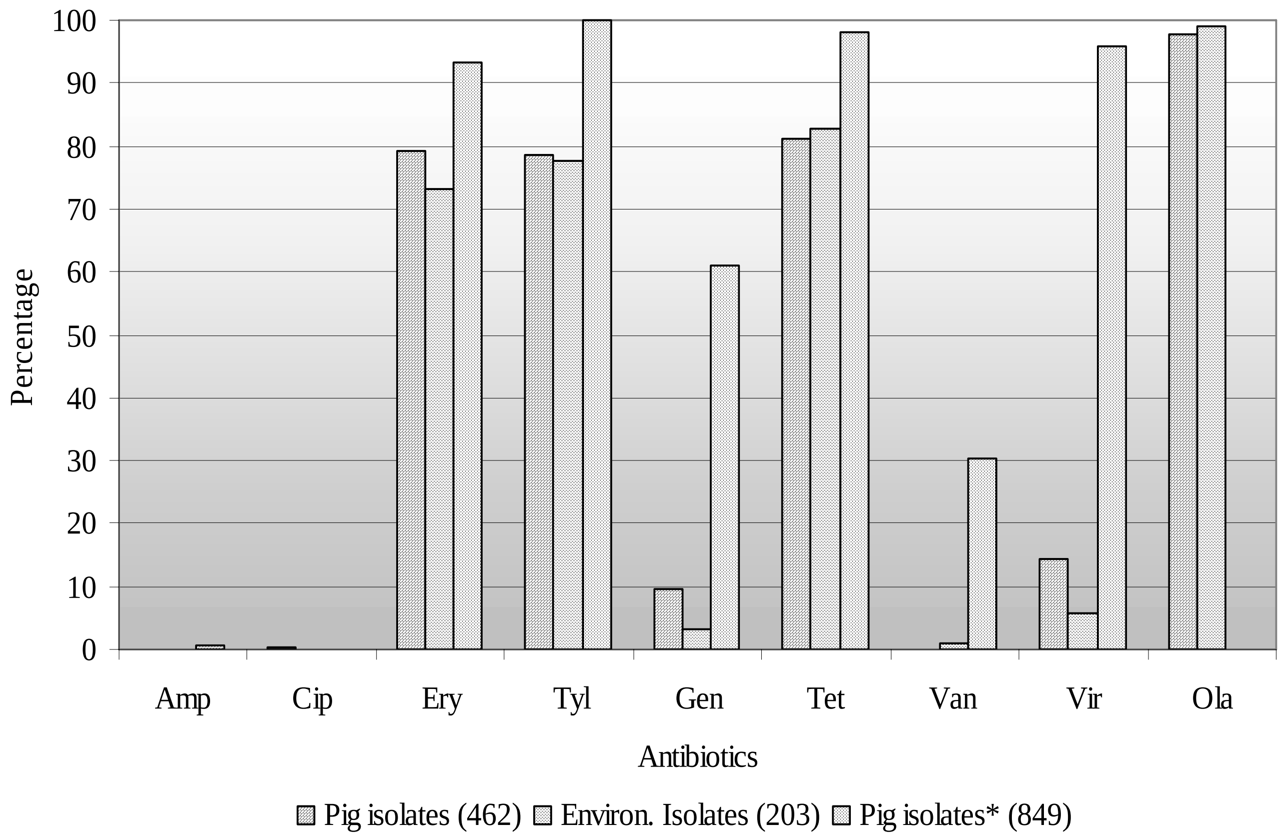
Enterococcus faecium (DAFF study)

	Cattle (21)	Pigs (30)	Chickens (61)
Erythromycin + virginiamycin	2 (9.5%)	13 (43.3%)	7 (11.5%)
erythromycin		14 (46.7%)	19 (31.2%)
Ampicillin + erythromycin		1	
ampicillin			1
Virginiamycin			7 (11.5%)
Ampicillin + erythromycin + virginiamycin			2 (3.3%)
gentamicin	21 ≥16 ≤512	30 ≥16 ≤512	61 ≥16 ≤512

Enterococci – chickens (2000)

	Company 1 (200)		Company 2 (70)	
	E faecium (102)	*E faecalis* (9)	*E faecium* (17)	*E faecalis* (39)
Ampicillin	3	0	0	0
avoparcin	83	0	0	0
Vancomycin	72	0	0	3
bacitracin	91	89	88	97
erythromycin	51	44	24	56
flavophospholipol	14	0	0	0
Lasolocid, salinomycin	0	0	0	0
lincomycin	41	44	65	97
narasin	24	33	35	49
spectinomycin	30	56	53	87
tetracycline	58	89	82	97
Tylosin	46	44	6	54

Figure 1 Antibiotic resistance in enterococci isolated from pig and environmental samples



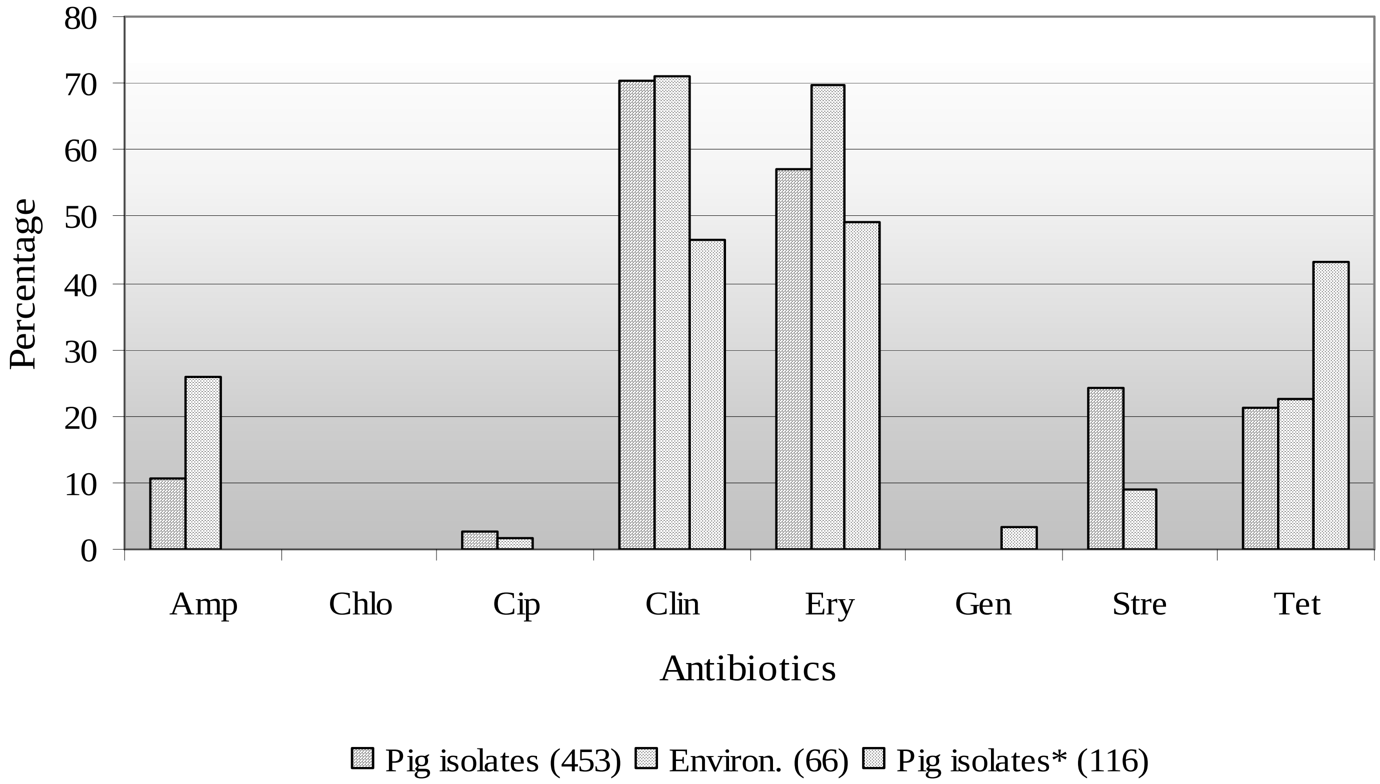
Barton and Peng (2005) Report to Australian Pork Ltd. Epidemiology of antibiotic resistant bacteria and genes in piggeries.

Campylobacter jejuni

	Company 3 (2000) - 113	DAFF study -131	Mifkin et al 2007 - 125
ampicillin	50%	NT	19%
erythromcyin	3%	11%	11%
Gentamicin	1%	0	NT
lincomycin	4%	NT	NT
tetracycline	15%	21%	19%
tylosin	4%	NT	NT
ciprofloxacin	1%	0	0
Nalidixic acid	NT	0	0

Barton & Wilkins (2001) Antibiotic resistance in bacteria isolated from poulty. RIRDC publication no. 01/105; RIRDC project No USA-9A.

Figure 4 Antibiotic resistance in Campylobacter isolated from pigs and piggery environments



Barton and Peng (2005) Report to Australian Pork Ltd. Epidemiology of antibiotic resistant bacteria and genes in piggeries.

So what is the significance?

Fluoroquinolones

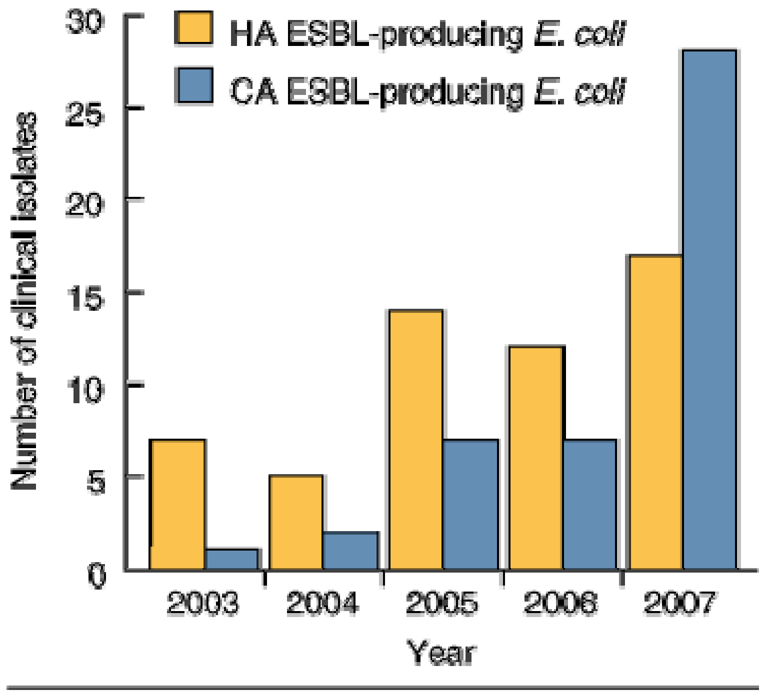
- Not registered for use in food producing animals
- Rare detection of resistance in pig and chicken isolates (cf overseas studies with very high resistance rates in campylobacter, salmonella and *E coli* from range of food producing animals)
- Very little resistance in Australians – mostly linked with overseas travel (cf overseas studies – resistance common)

Multi-drug resistant salmonella

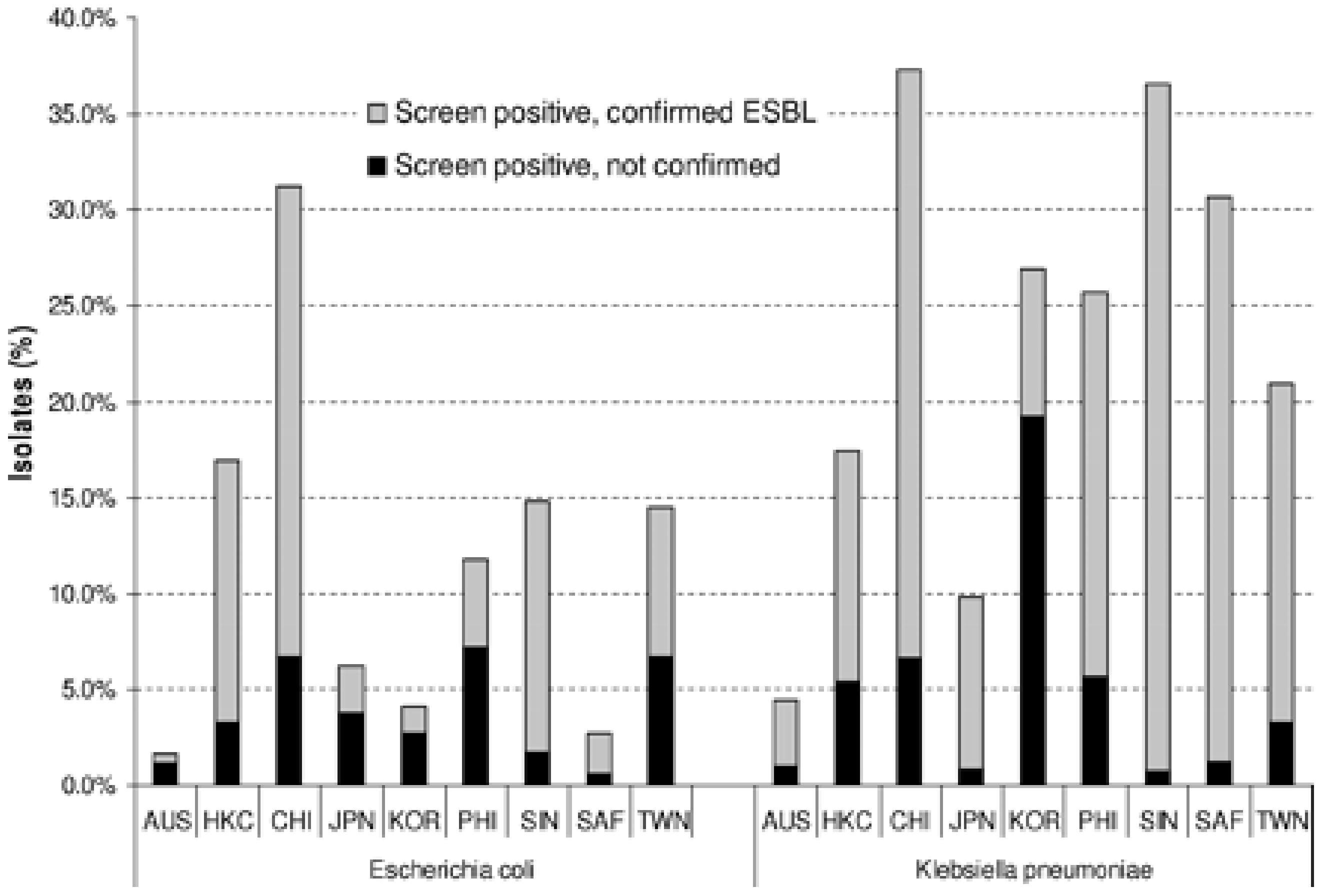
- Less multi-drug resistance than in *E coli*
- Multi-drug resistant human isolates uncommon in Australia (cf USA and UK)
- No *Salmonella* Typhimurium DT 104 or multi-drug resistant *Salmonella* Newport or similar epidemic strains
- Multi-drug resistant strains in horses (Bucknell et al 1997), dairy cattle (lab records) & pigs & chickens (Sal Ref Lab)
- No ceftiofur resistance (3^{rd} gen cephalosporin)
- Is this because we don't use fluoroquinolones? (ceftiofur is used off-label in cattle and in pigs)
- What about ESBL (extended spectrum β-lactamase) or AmpC in animal salmonella – not investigated.

ESBLs and AmpC

- ESBL producing Gram negatives (*Enterobacter, Klebsiella, E coli, Acinetobacter*) of increasing concern in Australian hospitals
- Denholm et al (2009) – 1.5% of nearly 16,000 Gram neg isolates collected 2003-2007

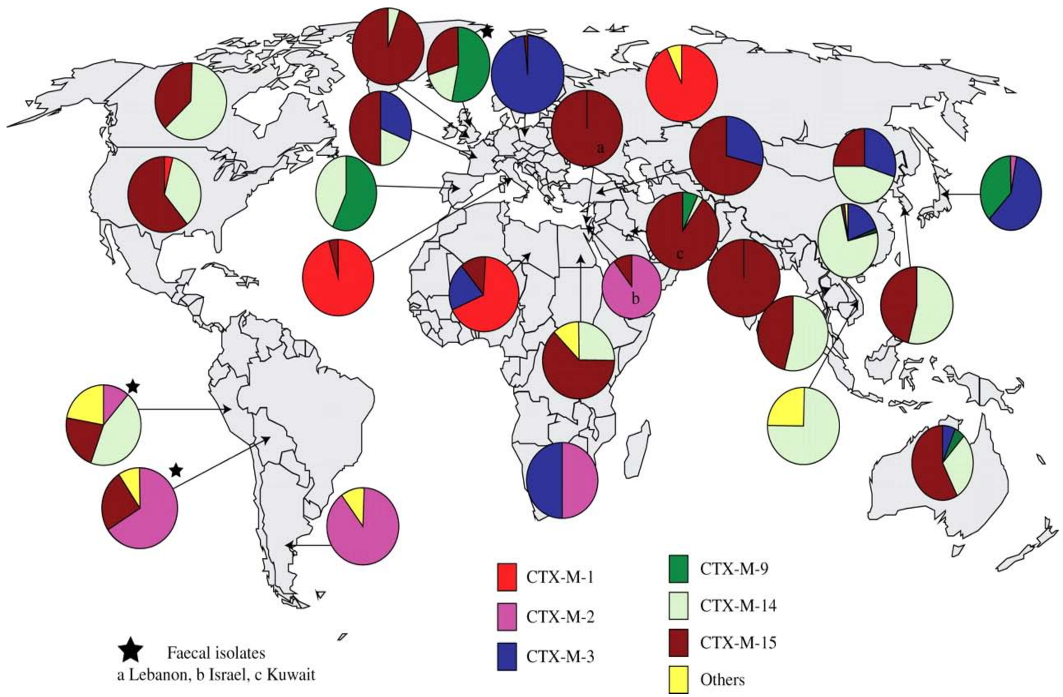


Denholm et al 2009 MJA 190:45



Bell et al (2007) J Clin Micro 45:1478

Global distribution of CTX-M genotypes



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ESBLs and AmpC in animals

- Qld – Extra-intestinal infections in dogs (mainly), cats, horses and 1 koala – multi-drug resistant *E coli* – plasmid-borne ampC β-lactamase (Gibson et al (2010) J Med Microbiol , 59:592)
- AmpC and ESBL phenotypes well-established in *E coli* and salmonella in food producing animals overseas
- Not yet reported in Australia – limited investigation
  - Risk in salmonella in horses, pigs, dairy cattle if ceftiofur or other 3rd/4th gen cephalosporins are used?

Vancomycin resistant enterococci

- *van*B *E faecium* main problem in Australia – now endemic in many major hospitals
- *van*B found in non-enterococcal (anaerobic) human gut flora
- *van*A enterococci found in 2000 poultry study but not in subsequent studies; not found in pigs

Streptogramin resistant *E faecium*

- Divisive issue – shortage of antimicrobials to treat multi-resistant Gram positive infections
- Streptogramin Synercid retrieved but virginiamycin had been extensively used in food producing animals ….
- Resistance in poultry isolates of *E faecium* and other enterococci – low levels generally (10-12% in Australia; up to 60% overseas)
- Link between handling or consuming poultry and Synercid resistant *E faecium* (Kieke et al 2006)

Methicillin resistant *Staph aureus* (MRSA)

- Major problem in many tertiary care hospitals
  - Hospital acquired multi-resistant MRSA
  - Shortage of antimicrobials –Linozelid, Daptomycin, Telavancin and Synercid
- Now community acquired MRSA – not as resistant but often more virulent (Panton Valentin Leukocidin – PVL)
- Bovine mastitis *S aureus* monitored from 1970s to mid-1990s –no MRSA found

MRSA in dogs and horses in Australia

- MRSA found in dogs in Adelaide and in isolates from Qld – probably much more widespread
  - All human hospital acquired strains - strain dependent on which strains dominant in human cases
  - Mostly colonisation of healthy dogs, some wound infections
- MRSA in horses – Scone studs – ST8 – clone associated with horses world-wide
  - Variant of a human hospital strains
  - Wound and joint infections in foals
  - Rifampicin resistant – related to R equi treatment?
- Overseas studies indicate risk of occupational colonisation for vets – also animal owners
  - Survey of vets in 2010 – results available soon

MRSA in pigs

- Significant issue overseas
- First report from France (2005)
- Now widespread in Europe (high prevalence in the Netherlands), USA and Canada
- ST398 – a pig clone – spreads from pig to pig
- Now turning up in bovine mastitis, chicken infections and human infections
- No information on the Australian situation

Where are we heading?

- Some in the medical sector still see use of antibiotics in animals and antibiotic resistance in animal isolates as the major source of human problems – animals and vets convenient scapegoats
- Some vets, agricultural advisors and farmers still think they can use antibiotics willy-nilly with no consideration of potential consequences
- Clearly animal use has an impact in some areas
  - Enteric zoonotic infections (salmonella, campylobacter and possibly non-intestinal *E coli*) - ESBLs
  - Dogs and horses reservoirs for re-infection of humans with MRSA

Emerging issues

- ESBL or more probably AmpC producing *E coli* and *Enterobacteriaceae*
  - Concern that use of ceftiofur or similar antibiotics will drive emergence of AmpC and ESBLs
- Avian pathogenic *E coli* and extra-intestinal infections in humans
- MRSA in pigs
- Contamination of water and environment with antibiotic resistance genes
- Virginiamycin resistance in *E faecium* - very little detected so far

Conclusions

- We need to establish systems in Australia for monitoring and surveillance of antimicrobial resistance in human and animal isolates
- Medical implications of registration and use of animal antimicrobial agents needs to be taken into account as part of review process
  - No justification for use of 3rd/4th gen cephalosporins or generalised off-label use of medical antibiotics eg carbapenems and new macrolides in small animals/horses
- Antimicrobial resistant bacteria and antimicrobial resistance genes are widely distributed in animals, humans and the environment
- Although most attention on growth promotant use in animals, any use of antimicrobials drives resistance