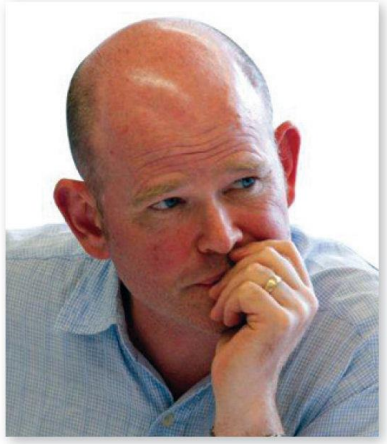


Professor Nigel French

Food Safety and Veterinary Public Health
Massey University
Palmerston North

Friday, June 9, 2017

9:20 - 9:45 Who is Responsible for the Loss of Effective Antimicrobials... Vets or Medics?

Who is responsible for the loss of effective antimicrobials?

Nigel French

Director, Infectious Disease Research Centre, Massey University

Director, Food Safety Science and Research Centre

GPCME, Rotorua, 9th June 2017

Collaborating Centre OIE

mEpiLab

New Zealand FOOD SAFETY SCIENCE & RESEARCH CENTRE

IDReC Infectious Disease Research Centre

Te Kunenga ki Pūrehuroa MASSEY UNIVERSITY

Outline

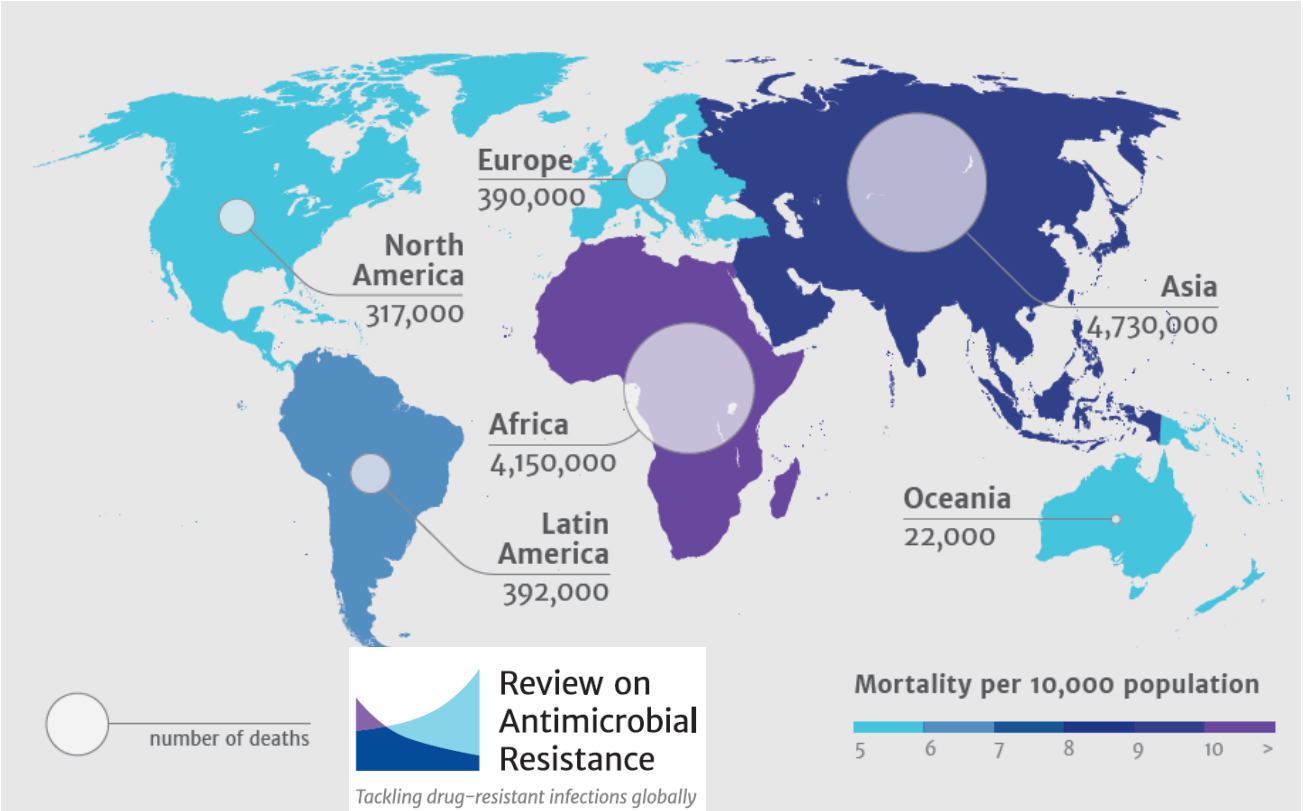
- Antimicrobial resistance – a global concern
- Importance of medical and veterinary use
- How NZ compares with the rest of the world
  - Antimicrobial use (humans and animals)
  - AMR in foodborne pathogens
- Emerging resistance in *Campylobacter*
  - What does it mean for public health?
- Pets and ESBLs

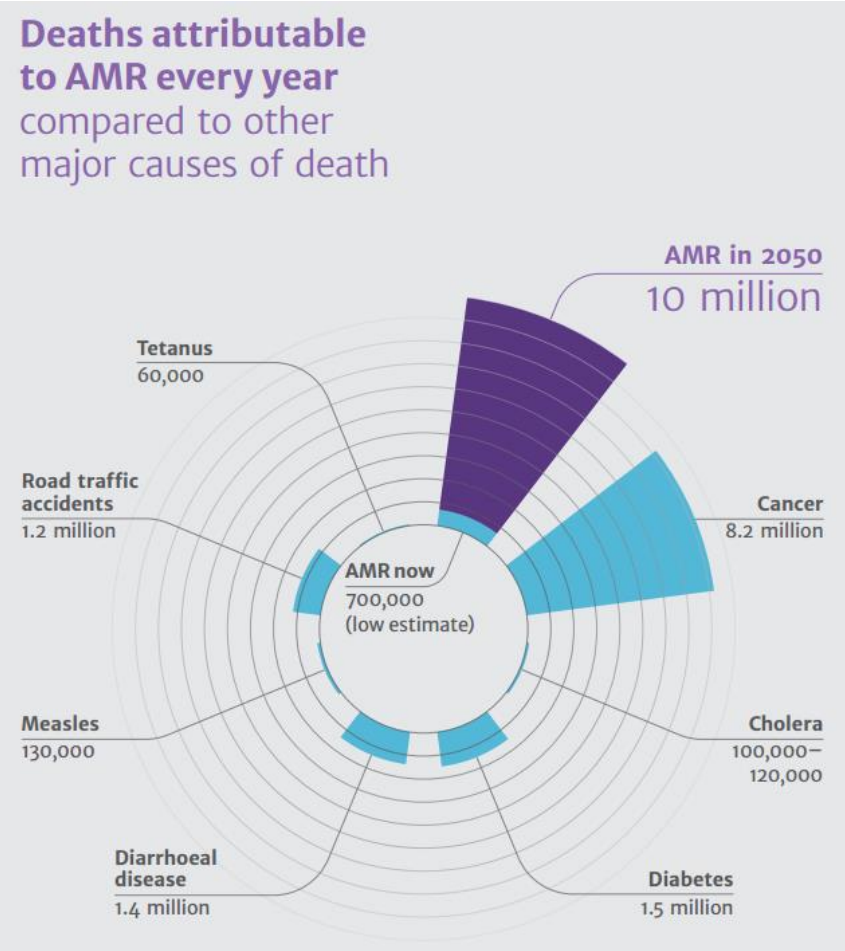
Some important questions?

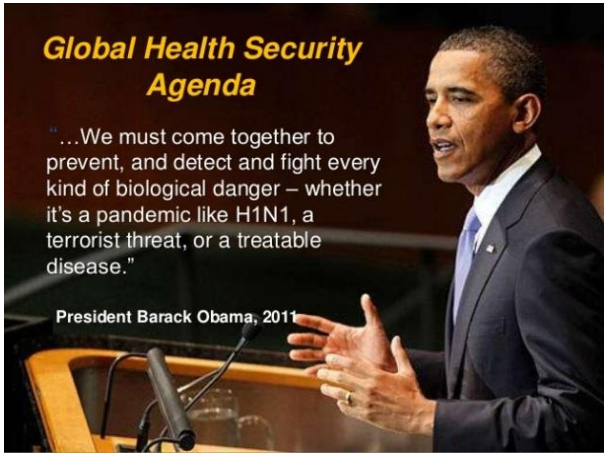
- How much antimicrobial use is there in animals compared humans? (plants too?)
- Does use in animals correlate with AMR
  - in animals?
  - in humans?
- What is the evidence for transmission of AMR organisms from animals to humans?
  - Are they the same strains?
  - Does reduction in use in animals reduce AMR in animals?
  - Does reduction in use in animals reduce AMR in people?
- How can we reduce the impact of AMU in general?

Deaths attributable to AMR every year by 2050

(O'Neill report 2014)







AMR 1st item on GHSA

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill
December 2014

New Zealand participating in Global response

Development of National Action Plan

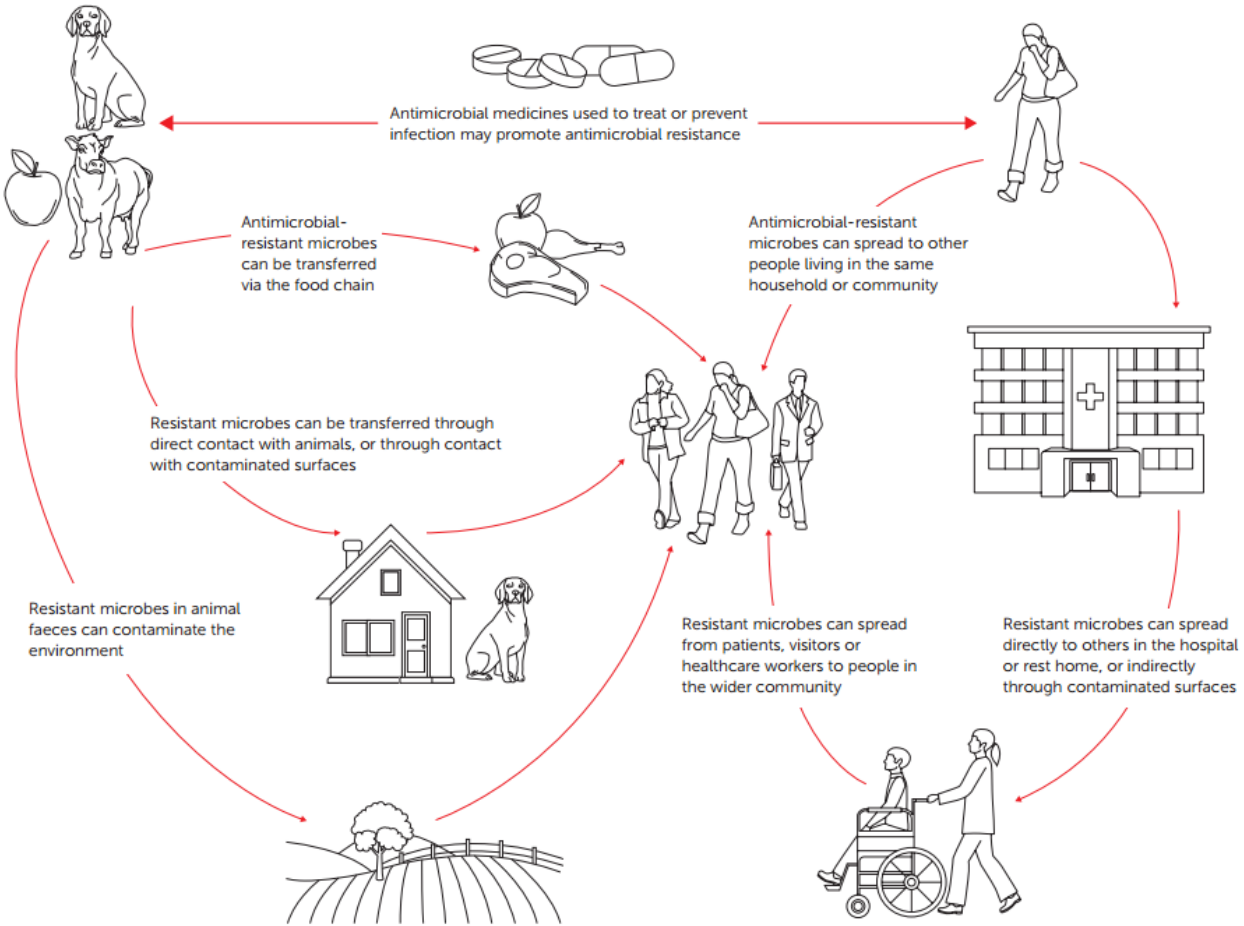
One Health approach jointly with Ministry of Health and Ministry for Primary Industries

Includes:

- Surveillance (AM use and AM resistance)
- Infection prevention and control
- Stewardship

Emergence, amplification and spread

One Health Approach



https://royalsociety.org.nz/assets/documents/Antimicrobial-resistance-factsheet-May-2017.pdf

Global antibiotic consumption in livestock

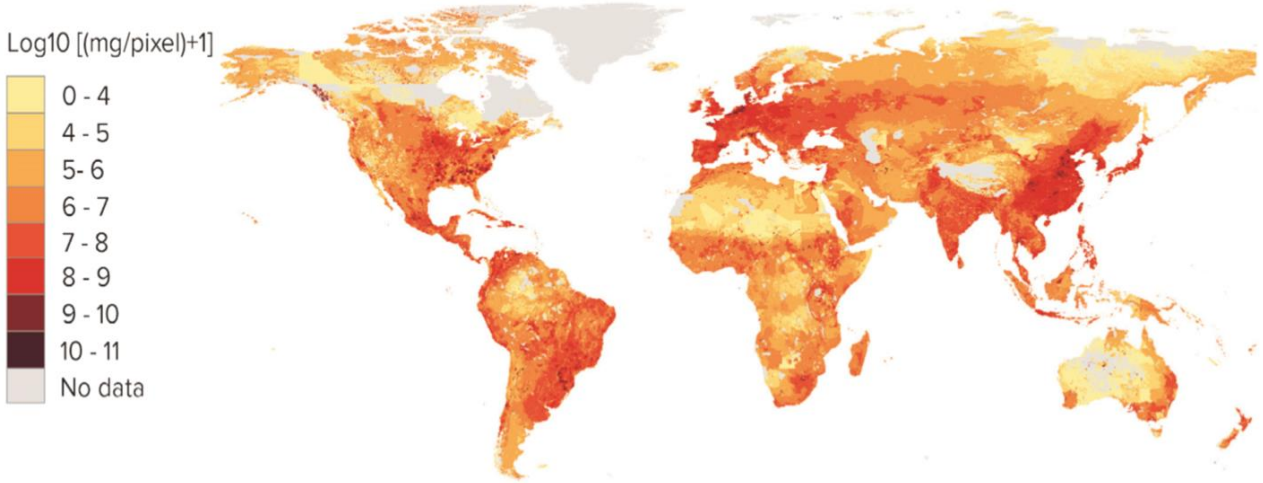
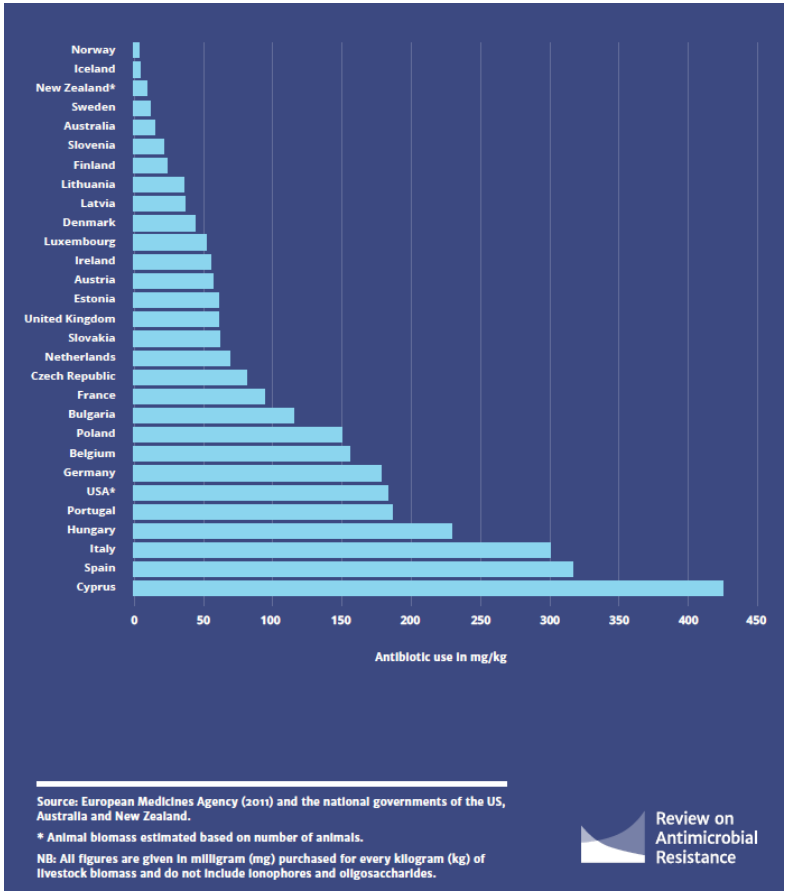


FIGURE 3-1: Global antibiotic consumption in livestock (milligrams per 10 km² pixels) 2010

Source: Van Boeckel et al. 2015

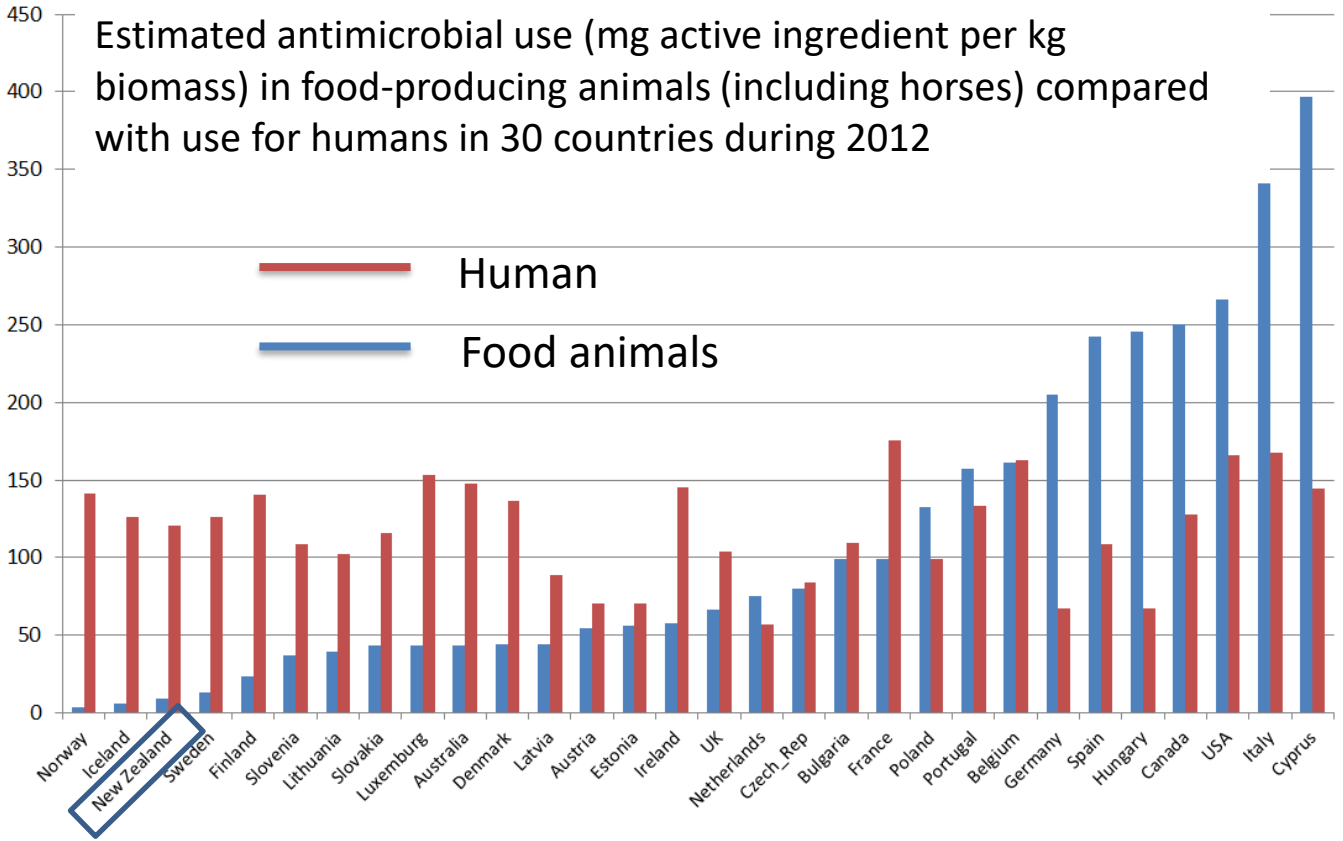
CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI



NZ roughly 50:50 - high use per unit area due to high animal biomass / area

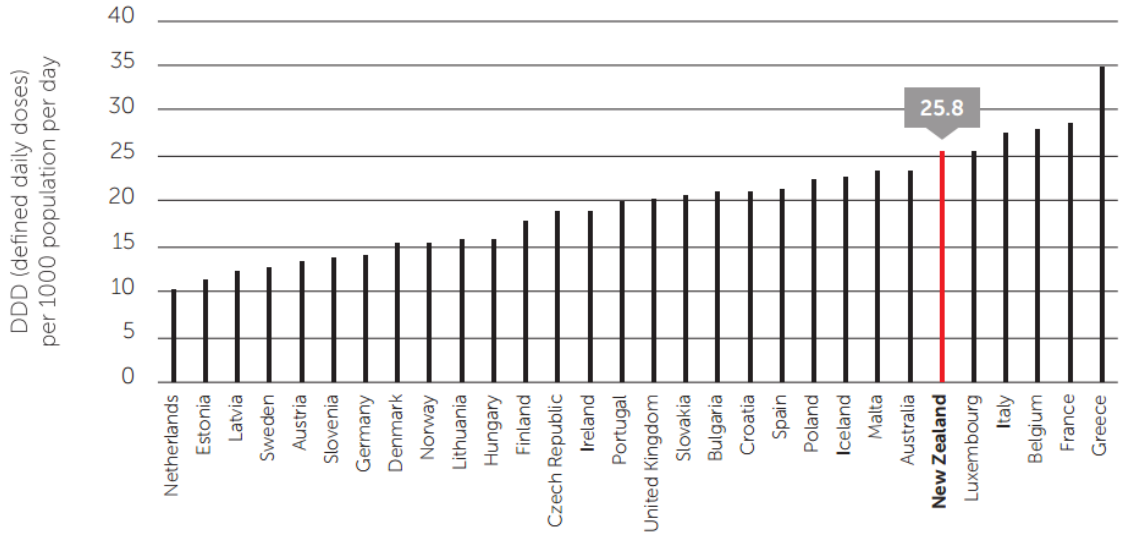
Use of antimicrobials for animals in New Zealand compared with other countries

JE Hillerton, CR Irvine, MA Bryan, D Scott & SC Merchant, NZVJ, 2016



Human use in NZ: comparison with the rest of the world

Rates of antibiotic use in the community*, 2014

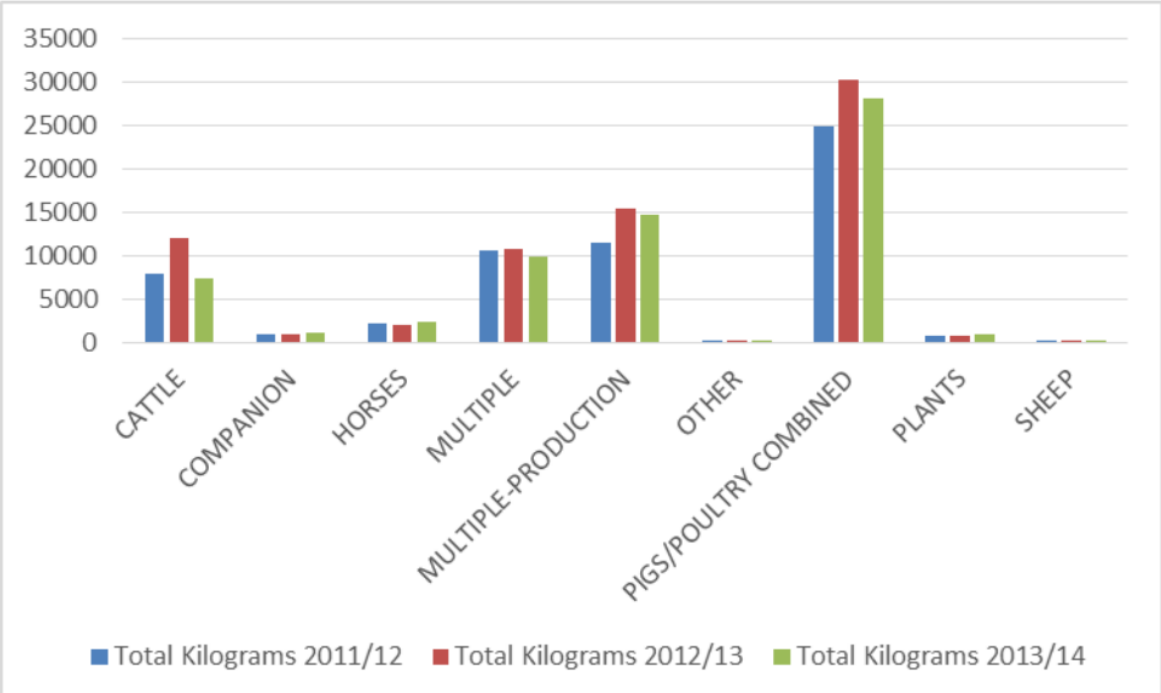


* Prescriptions in the community only. Hospital prescriptions excluded.

Source data from ESR,[49] ECDC[56] and ACSQHC[57]

Use by species of animal (and plants)

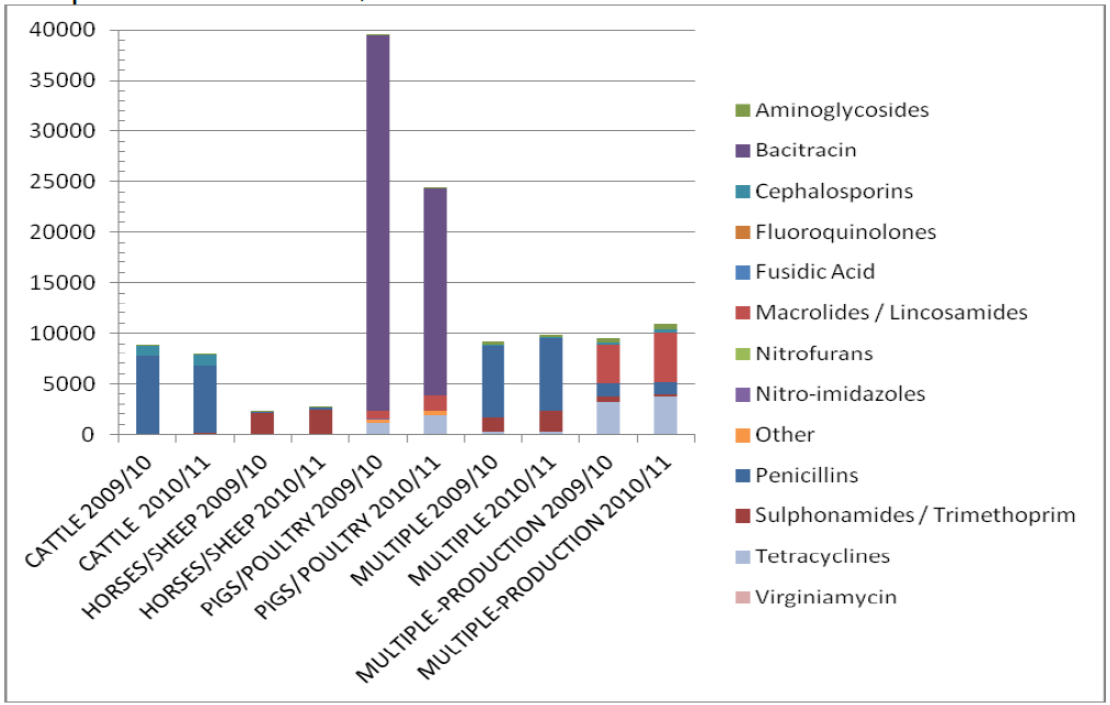
Figure 2. Total Antibiotic sales by species (in kilograms)



Most in-feed, followed by injectable and intramammary

Use by type and species of farm animal

Figure 2: Antibiotic sales (in kilograms of active ingredient) for use in production animals by approved label species and antibiotic class, 2009/10 and 2010/11



Antibiotics Sales Analysis: 2009-2011

MPI Information Paper

Doesn't include ionophores

www.nzva.org.nz

The NZVA's aspirational statement on AMR:

'By 2030, NZ Inc will not need antibiotics for the maintenance of health and welfare in animals'

Motivation

'By 2030, NZ Inc will not need antibiotics for the maintenance of health and welfare in animals'

- Raise awareness
- Reset the agenda
- Recognise that vets have an important role
- Take leadership role
- Because NZ Agri are already low users/ marketing opportunity
- To be aspirational

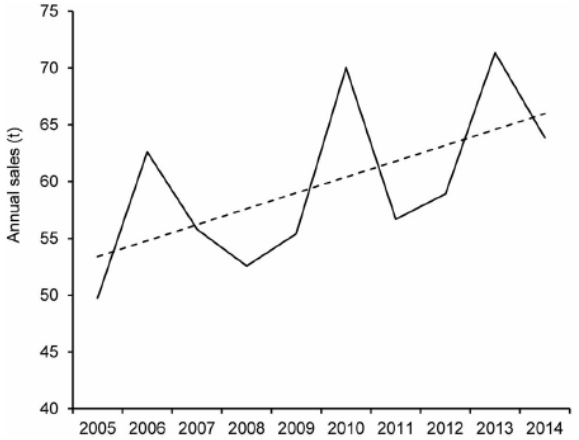
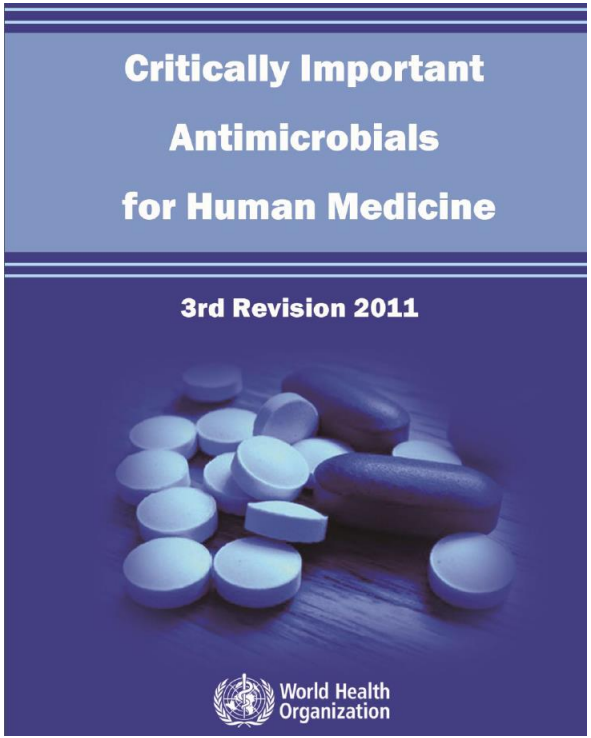


Figure 1. Total antimicrobial sales (tonnes) for veterinary use in New Zealand between 2005–2014 (solid line), as reported by manufacturers to the Ministry for Primary Industries. The overall trend in sales is shown by the dotted line.

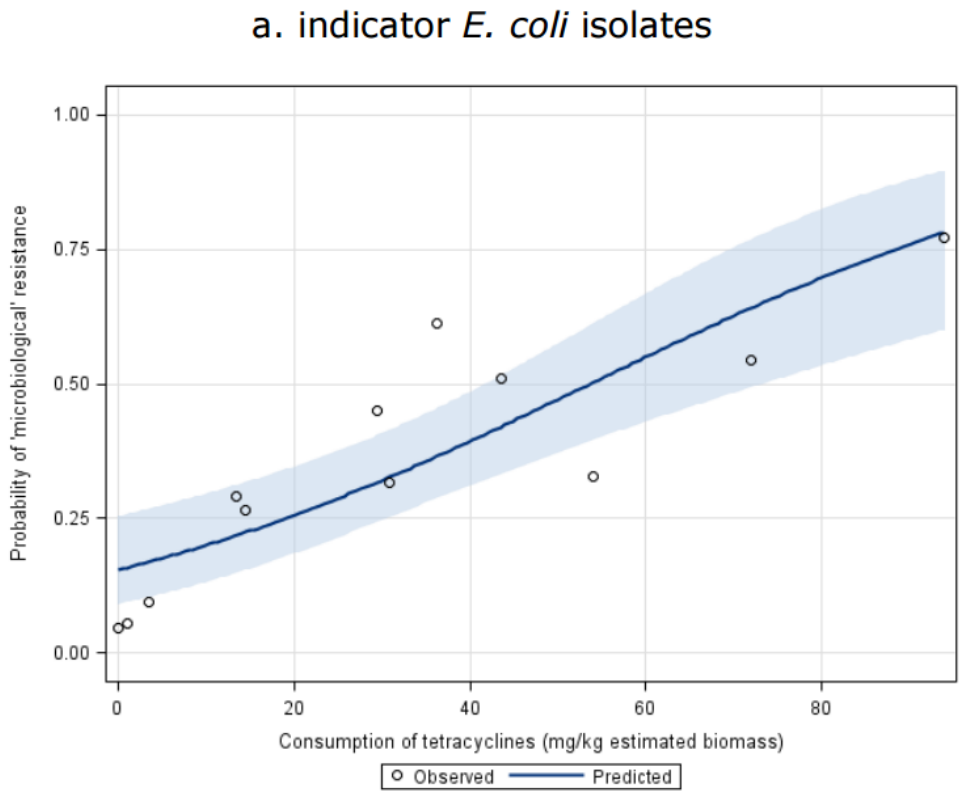
Judicious use in animals?



Subset used in NZ animals, many ‘Veterinary Only’

Importance of cross-resistance not well understood (e.g. Bacitracin, peptides, polymixin)

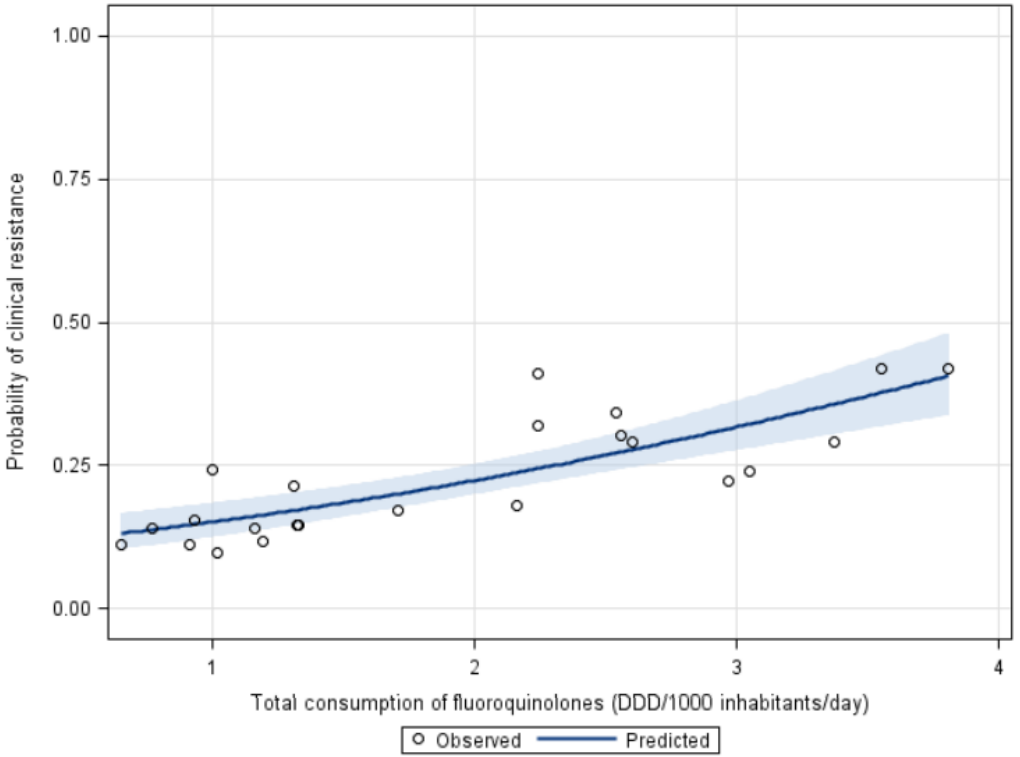
Antimicrobial use in animals is correlated with resistance in animals



Correlation at country-level

ECDC/EFSA/EMA joint report 2015

Likewise human use is correlated with resistance in humans

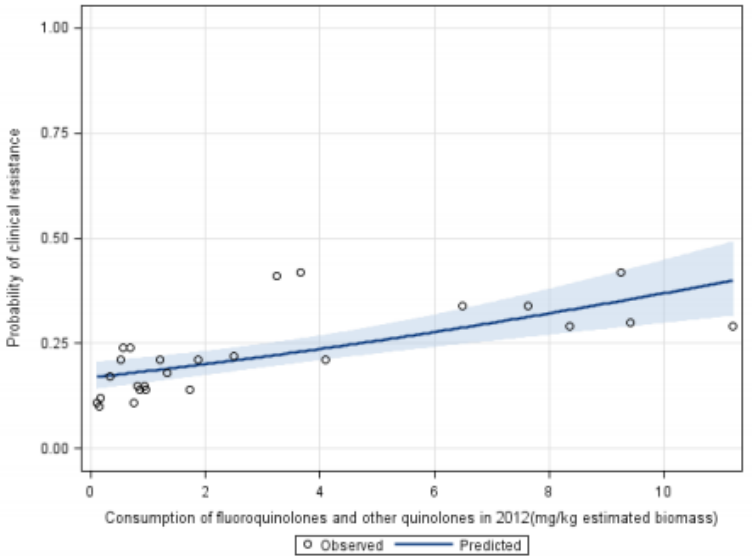


National total (community and in hospitals) consumption of fluoroquinolones and the probability of clinical resistance to fluoroquinolones in *E. coli* isolates from human BSIs, in 2012

Is there a correlation between food animal use and AMR in humans?

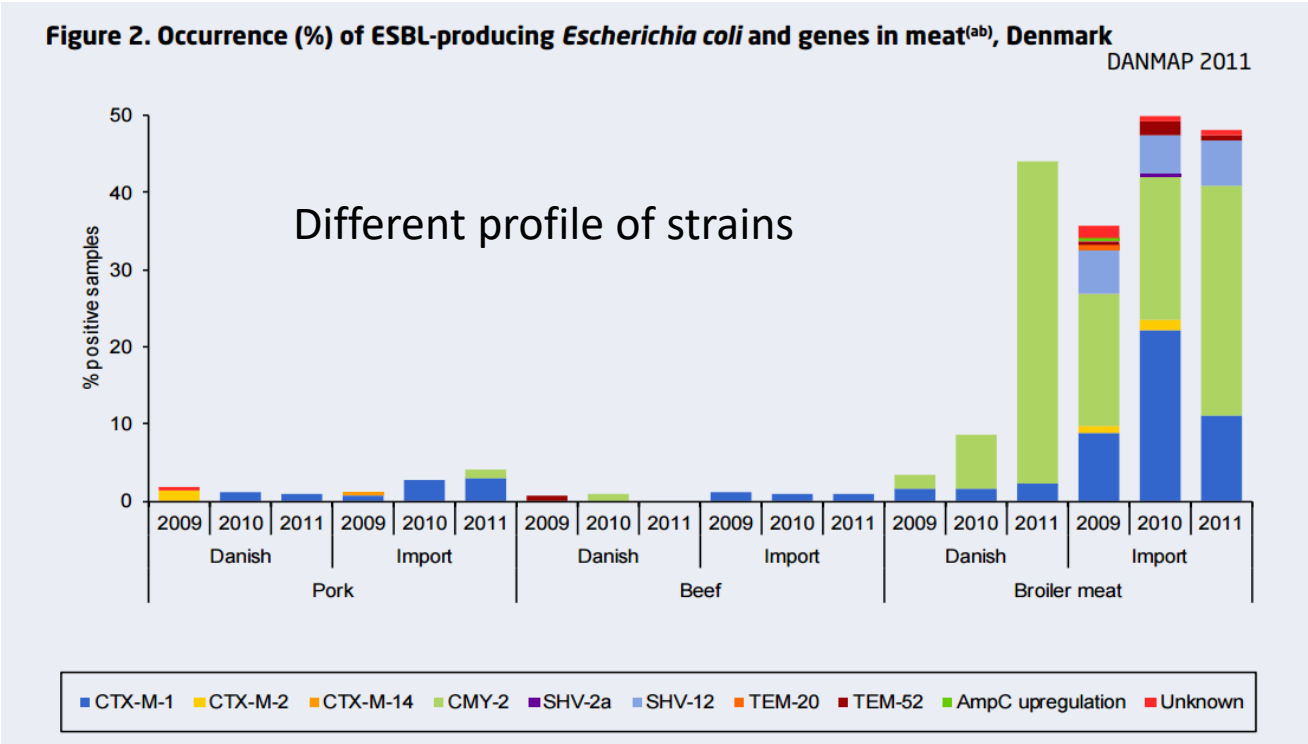
- Depends on bacteria/Ab combination
  - Cephalosporin resistance – correlated with human but not animal use
  - FQ resistance correlated with both
- N.B. These are crude analyses…

Quinolone use



EU countries

Pathogens with multiple transmission routes: How many are spread via zoonotic pathways?



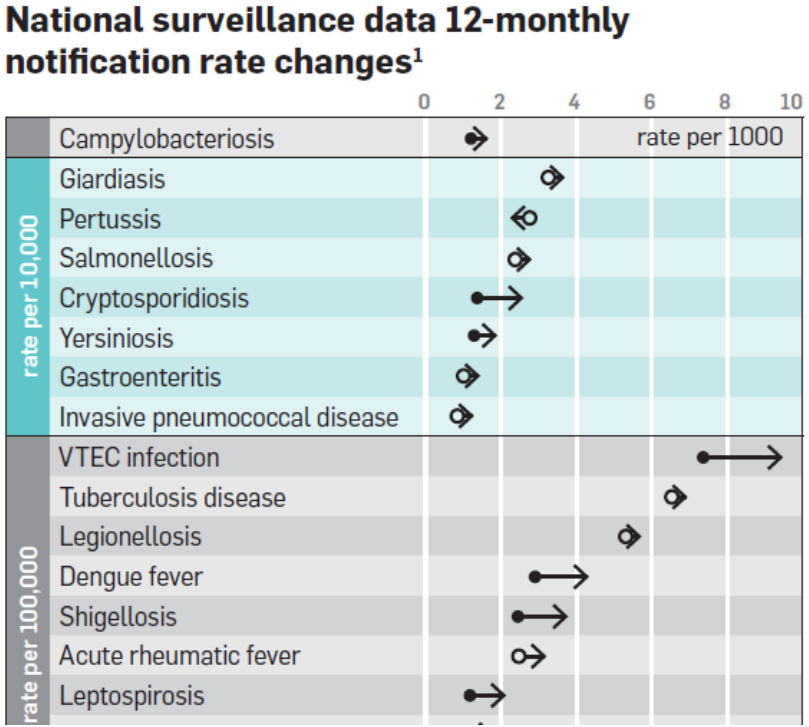
e.g. food, water, direct contact

ESBL-producing *E. coli* in meat in Denmark

Human UTI and BSI in 2011	
CTX-M-1	7%
CTX-M-14	15%
CTX-M-15	60%
CMY-2	~2%

What about New Zealand?
Food and waterborne diseases high on the list of notifiable diseases

Most ‘zoonotic’



Source: ESR Ltd
Quarter to March 2017

Food and farming: Ecosystem health
Faecal outputs of cattle…and humans in NZ

- Cattle: Number of defecations
  - 9 – 16, average 12 per day
  - Average 2kg per defaecation
  - Total output of 25kg per cow per day.
- 9 million cattle in NZ
- 230,000 tonnes faecal material per day…
- 84 million tonnes per year….
- Humans 800 tonnes per day…

Source Dr Brent Gilpin ESR Ltd

Not just cattle... The chicken lahar

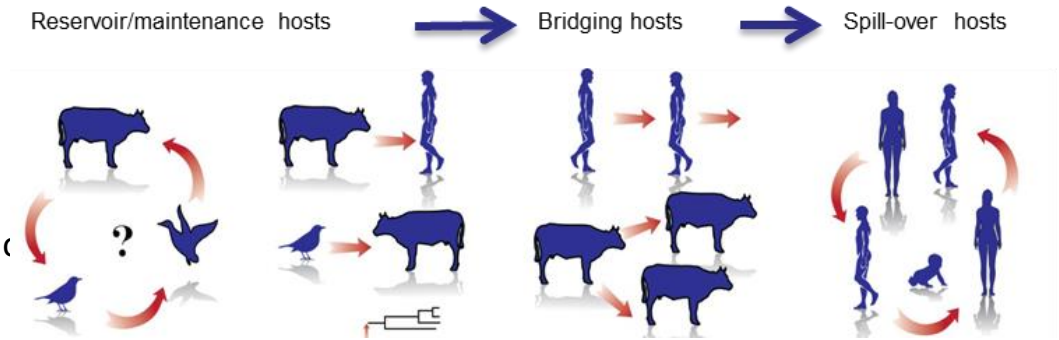
Waikato Times

'Reckless and negligent' farm to pay $42,000 24/08/2011

A Pukekohe chicken farm has been fined after a ''lahar'' of chicken effluent cascaded into a nearby stream.

Foodborne pathogens and AMR

- Many foodborne pathogens maintained livestock reservoir
  - *Salmonella, Campylobacter, E. coli, Enterococci*
- AB use in livestock may lead to:
  - Emergence of new resistant clones, including multi-resistant clones, and mo elements
  - Amplification of circulating clones
- Resistant clones
  - *Salmonella* Typhimurium DT104 (multiresistant)
  - *Campylobacter jejuni* ST-6964



Campylobacter in NZ: 1980-2006

The New Zealand Herald ★ Friday, July 11, 2003 A5

Stomach bug rise linked to effluent

HEALTH: Untreated manure infecting waterways, conference told

by Simon Collins
science reporter

Cows producing the equivalent of untreated effluent from 52 million people are being partly blamed for an escalating epidemic of campylobacter food poisoning.

Reported cases of the campylobacter stomach bug have multiplied more than 16-fold in the past 20 years, from 769 cases in 1982 to a record 12,489 cases last year.

New Zealand's rate is now several times higher than in any other developed country.

A public health doctor with the Ministry of Health in Dunedin, Dr Marion Poore, told the New Zealand Geographic Society conference in Auckland yesterday that one of the reasons for the increase was effluent from cows seeping into waterways.

"Between 1990 and 2002, the national dairy herd increased 51 per cent to 5.2 million cows.

"They produce the same effluent to 52 million people," she said.

"Only a very small proportion of that effluent around our agricultural

Food poisoning

Campylobacter cases per year 1982 - 2002

15000
12000
9000
6000

87 92 97 02

...te of cases

Next Article: Government probes claims NZ exported Agent Orange

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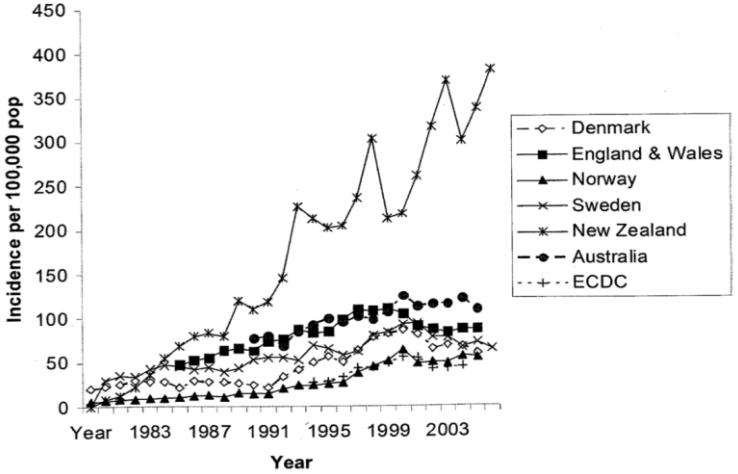
Cattle linked to common stomach bug

National

By Simon Collins
5:00 AM Tuesday Jan 11, 2005



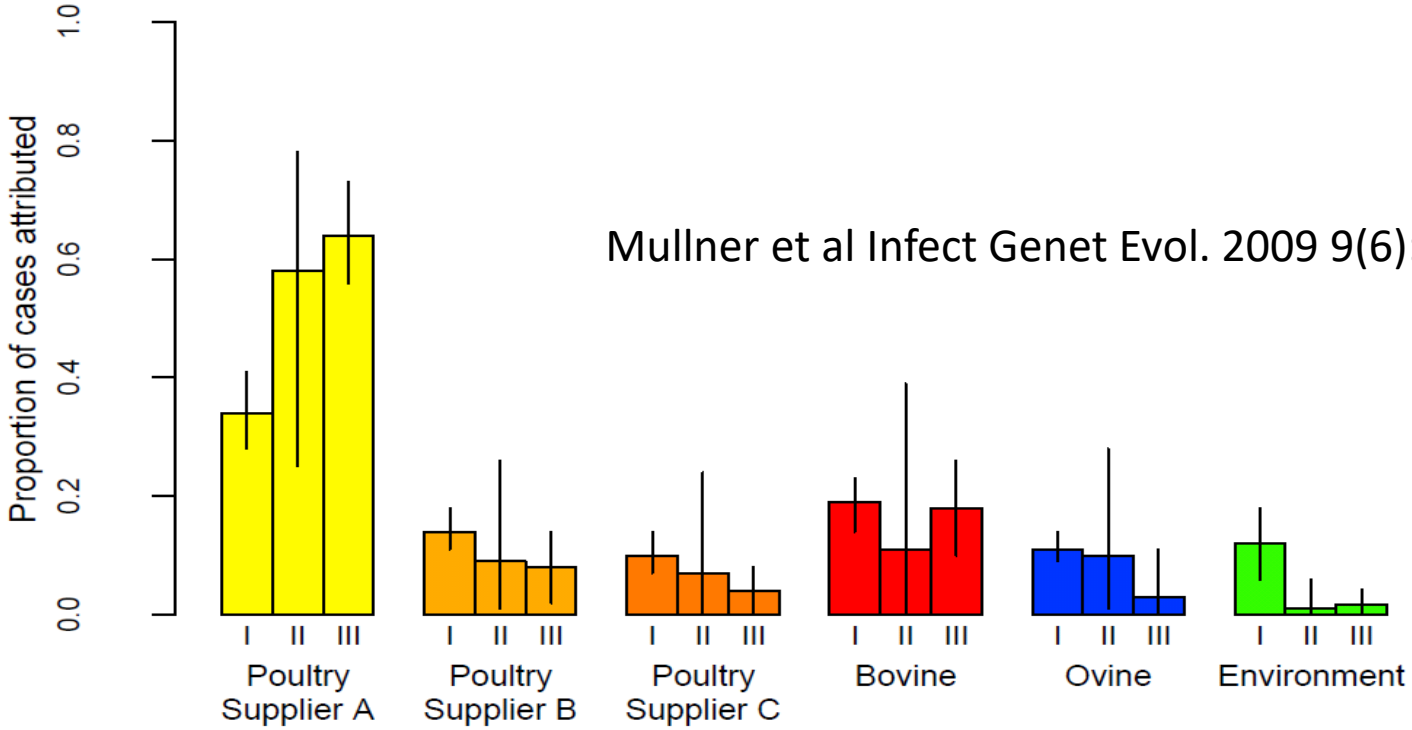
THE NEW ZEALAND MEDICAL JOURNAL
Vol 119 No 1243 ISSN 1175 8716

2006

Regulation of chicken contamination urgently needed to control New Zealand's serious campylobacteriosis epidemic

Michael Baker, Nick Wilson, Rosemary Ikram, Steve Chambers, Phil Shoemack, Gregory Cook

Poultry identified as main source

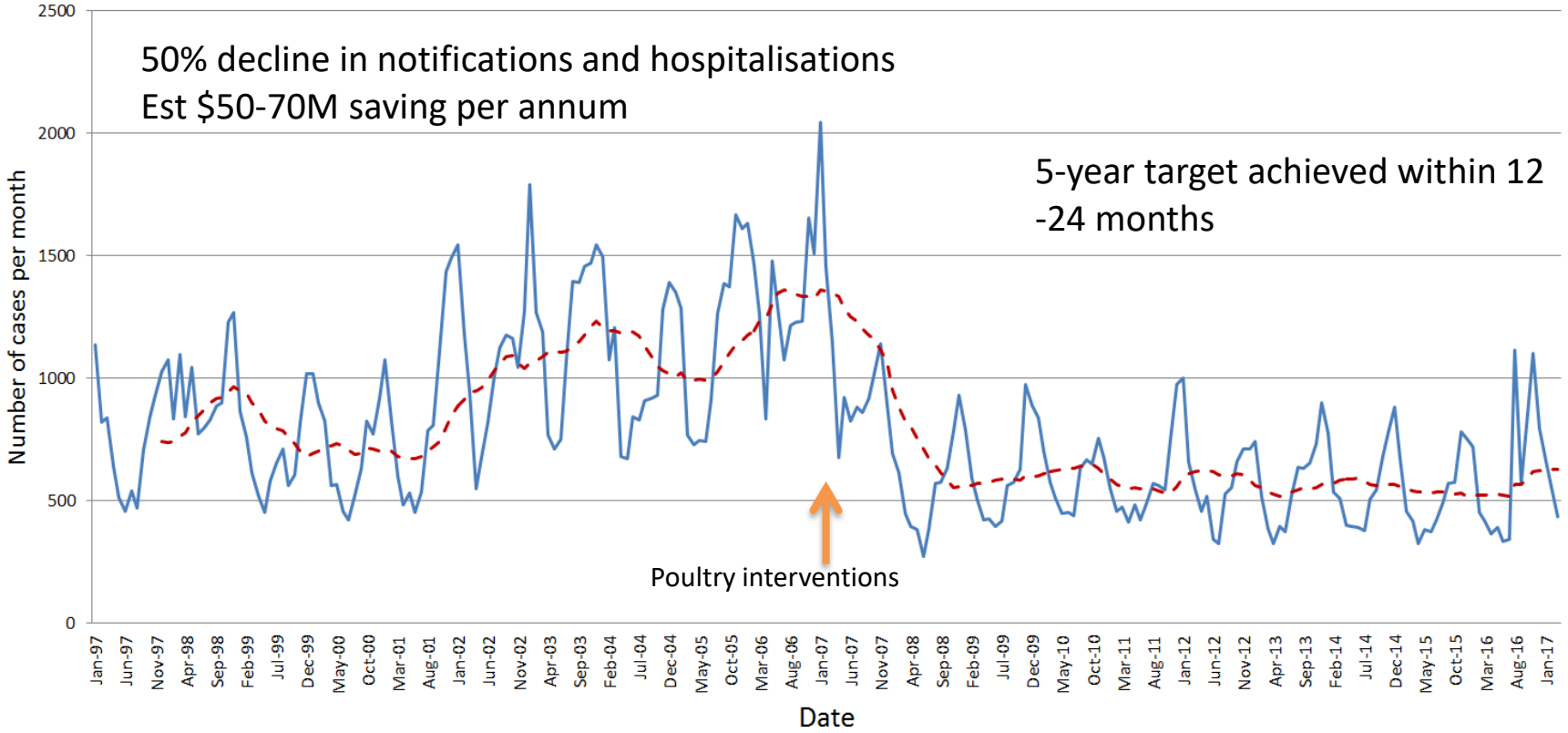


Mullner et al Infect Genet Evol. 2009 9(6):1311-9

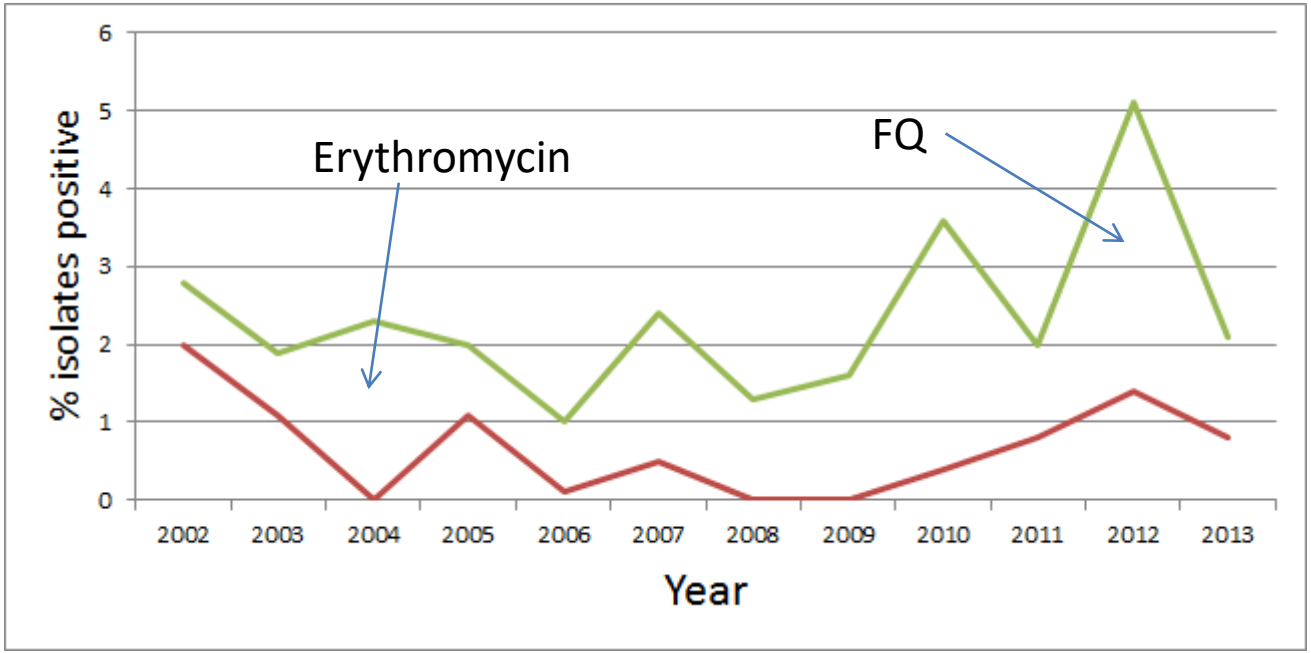
Marked Campylobacteriosis Decline after Interventions Aimed at Poultry, New Zealand

Ann Sears, Michael G. Baker, Nick Wilson, Jonathan Marshall, Petra Muellner, Donald M. Campbell, Robin J. Lake, and Nigel P. French

Sears et al 2011,
Emerging Infectious Diseases 17, 1007-15



AMR in *Campylobacter* in NZ: Human cases up to 2013 (data from ESR Ltd)



Low levels of resistance by international standards (Europe >50%)

AMR in Campylobacter in NZ: Poultry

New Zealand Veterinary Journal 58(5), 229-236, 2010 229

Scientific Article

Low levels of antibacterial drug resistance expressed by Gram-negative bacteria isolated from poultry carcasses in New Zealand

EJ Pleydell*§, L Rogers*, E Kwan* and NP French*

Drug	Disc[a] (µg)	Res (%)[b]	Zone size (mm) ≤6	7–15	16	17	18	19	20	21	22	23	24	25	26	27	≥28
Erythromycin	15	0.5	1				1			2	3	4	8	19	12	21	122
Ciprofloxacin	5	0											1	1	1	2	188
Enrofloxacin	5	0											1		3	4	185
Nalidixic acid	30	0			2	2	3	8	12	13	19	24	22	33	17	12	26
Chloramphenicol	30	0								1	1				9	10	172
Tetracycline	30	0													1		192

[a] Concentration of drug within the disc
[b] Percentage of isolates with zone sizes within the resistant category for that drug

Very low by international standards
Low use of Abs in New Zealand poultry industry

Arrival of ST-6964 in 2014 and Antimicrobial Resistance (AMR)

(not a superbug!)

SUNDAY STAR★TIMES November 22, 2015 | NEWS A3

Superbug found in chicken

Scientists are alarmed at the unprecedented discovery of a strain that resists drugs and has crossed into humans around NZ, writes Susan Edmunds.

A new superbug has been found in chicken from three of New Zealand's four major poultry suppliers. Groundbreaking research reveals the new antibiotic-resistant strain of campylobacter spreads to humans, which could make it hard to treat serious cases of infections.

Campylobacter occurs naturally in the gut of chickens but is the leading cause of food poisoning, with about 7000 cases reported in New Zealand each year.

The antibiotic-resistant strain was first found in 2014 and has now been identified in human cases in Manawatu, Auckland and Wellington.

The study, by Nigel French of Massey University and ESR microbiologist Debbie Williamson, found three of the major poultry suppliers in the North Island tested positive for the strain. A fourth was still waiting for test results. The pair would not name the companies.

The resistance means two antibiotics – fluoroquinolones and tetracyclines – would fail in treating the infection. But erythromycin, which is most

Which comes first?

The chicken or the campylobacter

1 Campylobacter develops in the gut

2 Consumers buy fresh chicken

3 Campylobacter spreads through handling, left in fridges

4 Humans ingest the bacteria from surfaces or improperly cooked meat

Photo: CHRIS McKEEN / FAIRFAX NZ
Graphic: NEIL BOND

Emergence of ST-6964

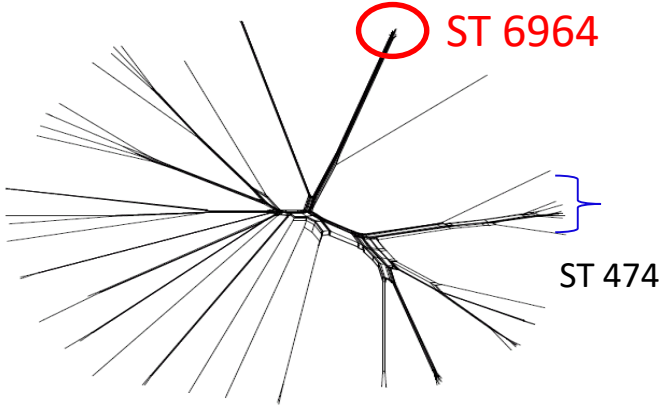
(in collaboration with Dr Debbie Williamson, MDU and ESR ERL)

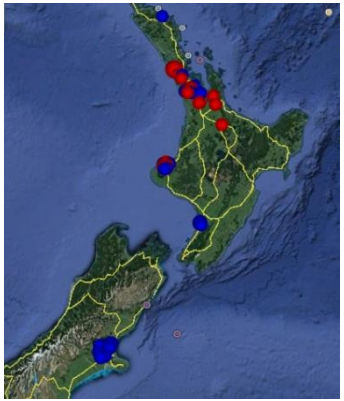
- August 2014: first two human cases of new *C. jejuni* ST-6964 detected in sentinel site
- Found straight away in 3 poultry companies and 'breeder' (parent) flocks
- Resistant to tetracycline and fluoroquinolones
  - **0->37% in poultry**
  - Sharp increase in AMR and ST 6964 in human cases across NZ (ESR study)
  - Chicken liver outbreak, Wellington
  - No overall increase in human cases?

Key questions?

- Genetic basis for resistance?
- How long has it been in NZ?
- How has it been transmitted between poultry companies?
- What has driven the emergence?
- What is the main source of human infection?
- How is it evolving?

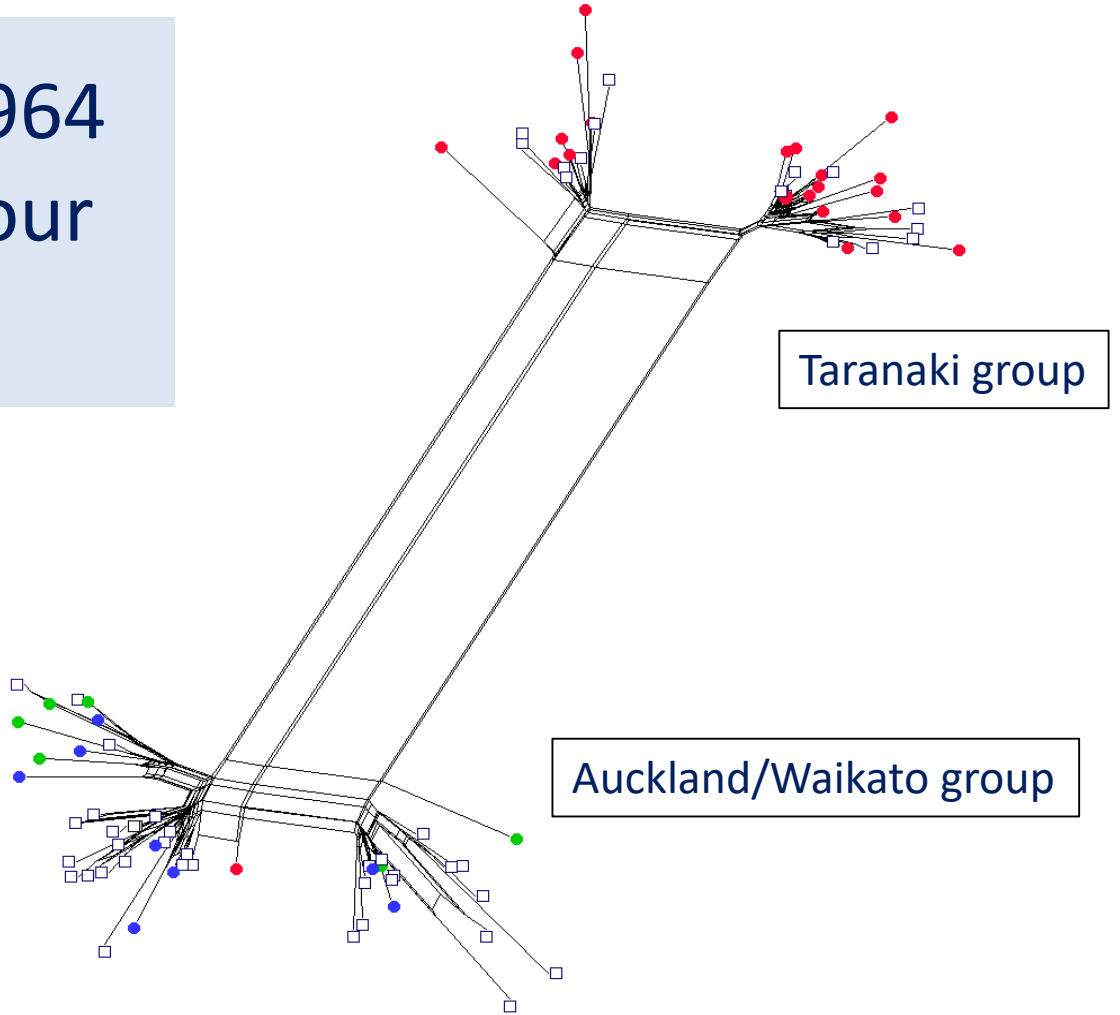
These can best/only be addressed by Whole Genome Sequencing



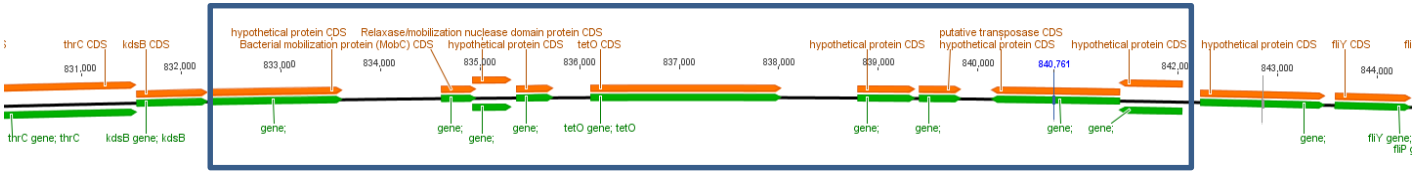


Sequencing of ST-6964 (N=230) including four reference genomes

Green=Poultry A
Blue=Poultry B
Red=Poultry C
Squares=Human



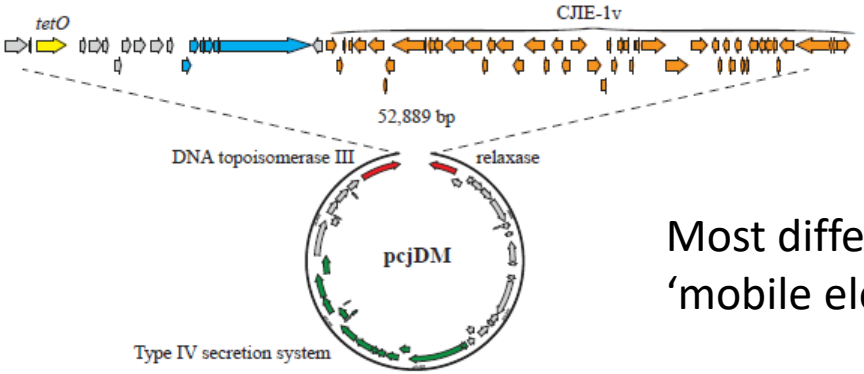
Tetracycline resistance genes and phage inserted into chromosome, leaving ‘remnant’ plasmid



Over 100 *tet*O insertion alleles in *C. jejuni* (Cody et al 2015).

Remnant plasmid

Absent from poultry supplier C isolates



Most differences in ‘mobile elements’

Key questions

- Genetic basis for resistance?
  - *tet*O plasmid and C257T mutation in *gyr*A
- How long has it been in NZ?
  - ~mid-late 2013.
- What drove the emergence?
  - Reverse zoonosis initially?
  - Limited tetracycline use in breeder flocks?
- How has it been transmitted between poultry companies?
  - Shared parent and grandparent stock? Feed?
  - Local spread seems likely
- Source attribution
  - All companies causing human infection

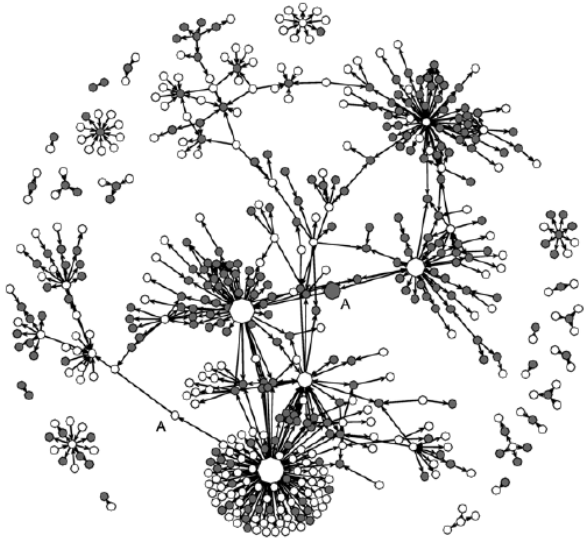


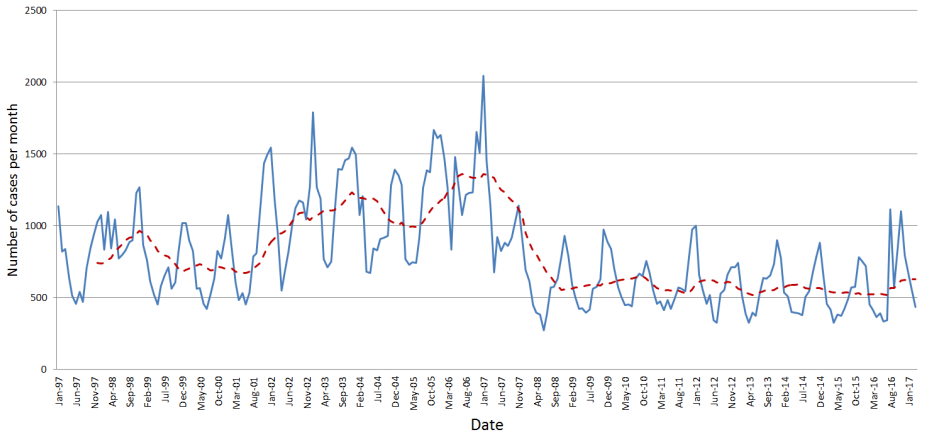
Fig. 2. Social network analysis of feed-related contacts in the New Zealand

Poultry farm network
(from Lockhart et al 2010)

Required cooperation and support from poultry industry

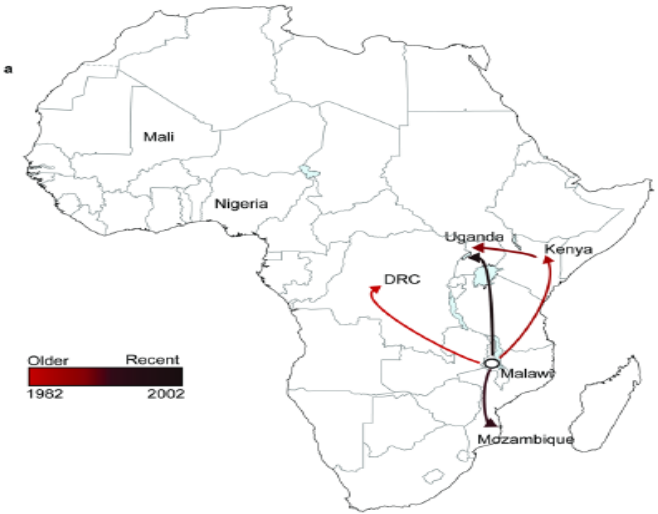
Public health significance?

- Resistant to two classes
  - Unless invasive, Abs not recommended
  - Erythromycin drug of choice (ST-6964 sensitive to Ery)
  - …but FQs still given by some GPs?
- New strain hasn't caused increase in notifications



Public health significance?

- Could have been worse…
  - *Salmonella* Enteritidis or resistant *S.* Typhimurium?
- Resistance still low compared to other countries
  - But shown it can change very rapidly…



Spread of ST 313

Reducing use in animals

- What effect will it have on AMR in animals and humans?
- Clear evidence of reduction in AMR in animal commensals
- But some persist
- Less clear impact on AMR in humans
  - Zoonotic transmission less important than previously thought?

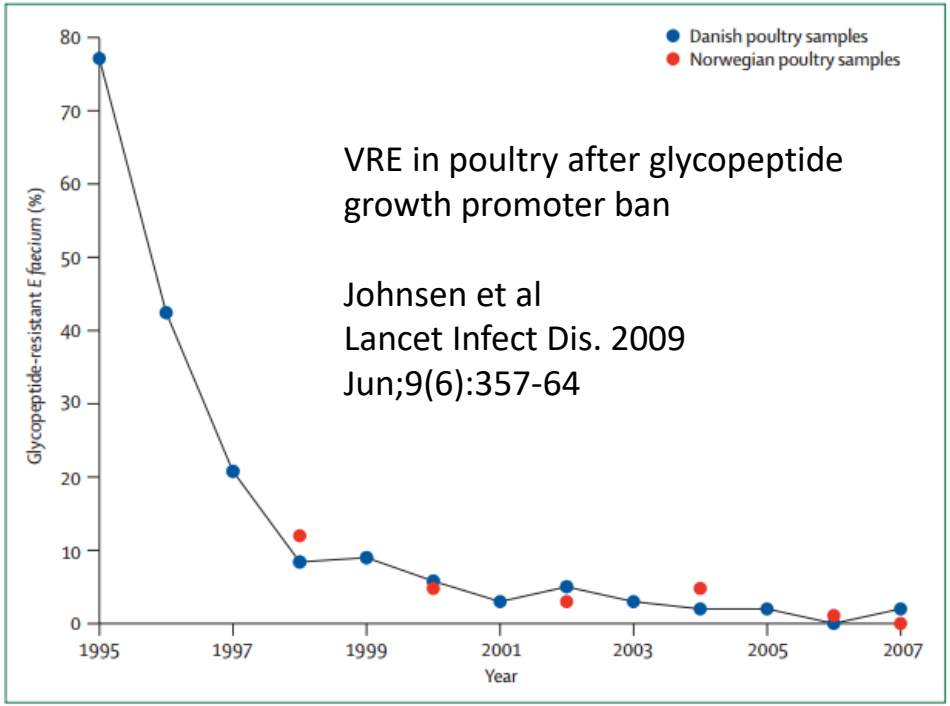
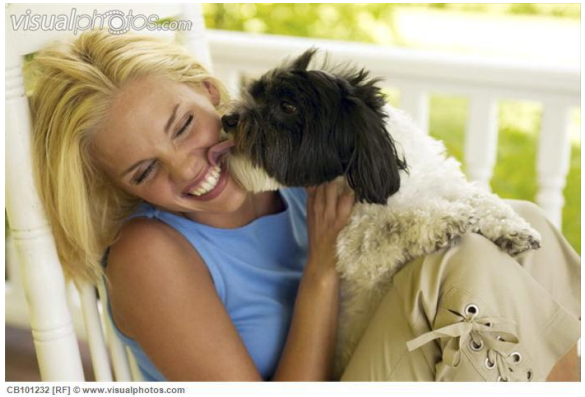


Figure 2: Occurrence of glycopeptide-resistant *Enterococcus faecium* in Danish and Norwegian poultry samples

Pet ownership in New Zealand

- 5 million companion animals in New Zealand
- 68% of households own pet, highest in world
- Biggest cat owners, 1.4M (48% at least one)
- Dogs 700,000, 88,000 rabbits, 527,000 birds, 1.7M fish.



Our relationship with pets is changing

- Indoors
- In bedroom
- In bed….

Dog behaviour

http://theoatmeal.com/comics/dog_paradox

Stewardship and judicious use
Prescribing practices – companion animal vets

New Zealand Veterinary Journal 60(2), 115–122, 2012

Scientific Article

Descriptive epidemiological study of the use of antimicrobial drugs by companion animal veterinarians in New Zealand

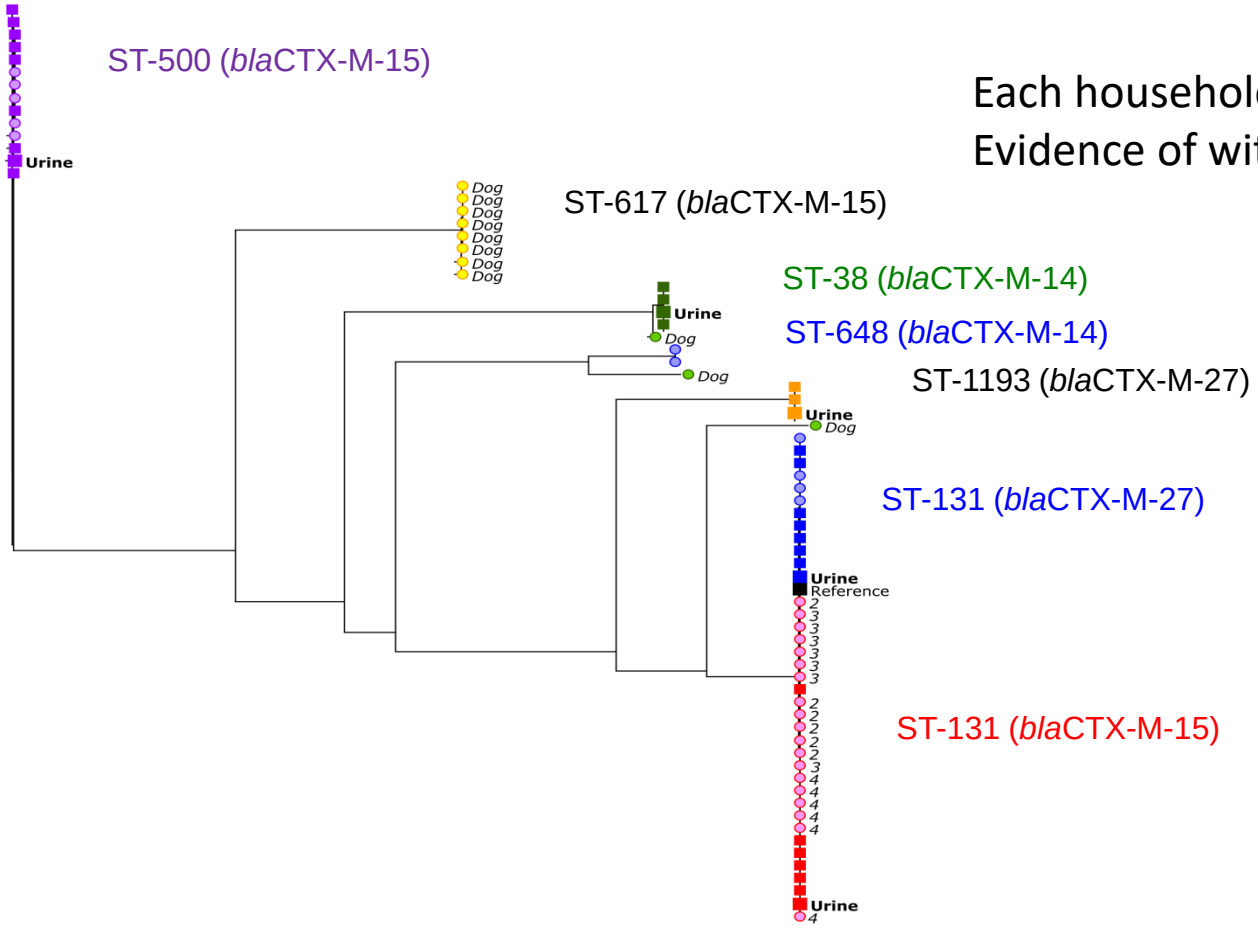
EJ Pleydell*§, K Souphavanh*†, KE Hill*, NP French* and DJ Prattley*

Skin, ear and UTI infections
Probability of submitting for culture and sensitivity prior to treatment
376/1984 (19%)
More likely if specialist and attended CPD in last 12 months

Convenience and AMR

Cefovecin, 3rd generation cephalosporin

ESBLs in pets and people in 5 Auckland households



Each household had a unique genotype
Evidence of within household spread

Dog in green household

ST-4553 (*bla*CTX-M-15)

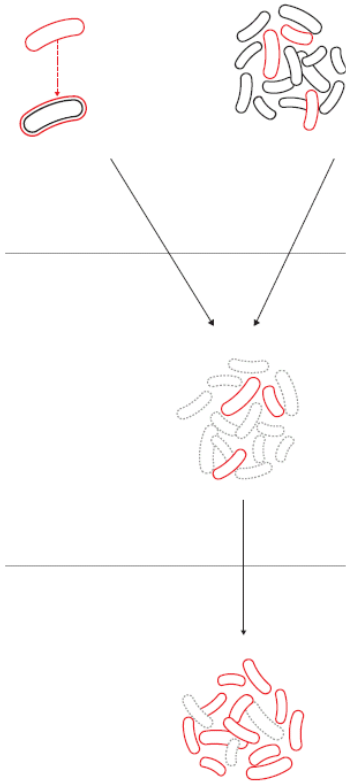
ST-38 (*bla*CTX-M-14)

ST-538 (Chr AmpC)

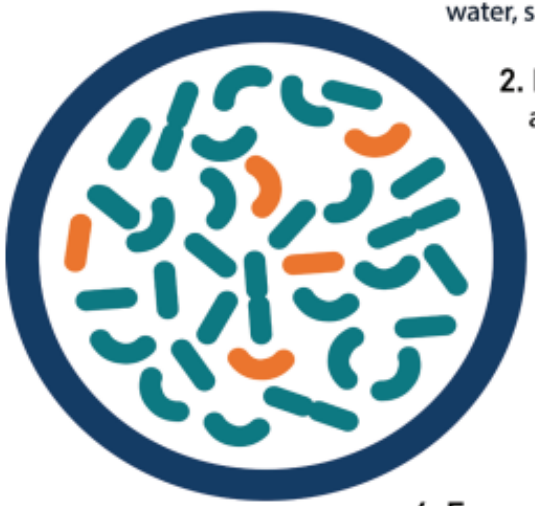
Leah Toombs-Ruane

Summary

- Globally human and animal use both contribute to:
  - Evolution and emergence of new resistant clones
  - Amplification of resistant clones
- Inadequate infection prevention and control in humans and animals contribute to spread of AMR
  - Zoonotic transmission important
    - Foodborne pathogens
    - Direct contact
- Contribution of animal use in NZ relatively low?
  - But no room for complacency



Way forward: A One Health Approach



1. **Reduce** the need for antibiotics through improved water, sanitation, and immunization
2. **Improve** hospital infection control and antibiotic stewardship
3. **Change** incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship
4. **Reduce** and eventually phase out subtherapeutic antibiotic use in agriculture
5. **Educate** health professionals, policy makers, and the public on sustainable antibiotic use
6. **Ensure** political commitment to meet the threat of antibiotic resistance

And in animals!

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy WASHINGTON DC • NEW DELHI

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- University of Melbourne, MDU Prof Ben Howden, Dr Dieter Bulach, Dr Debbie Williamson
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- PIANZ – Kerry Mulqueen, Michael Brooks

MARSDEN FUND
TE PŪTEA RANGAHAU A MARSDEN

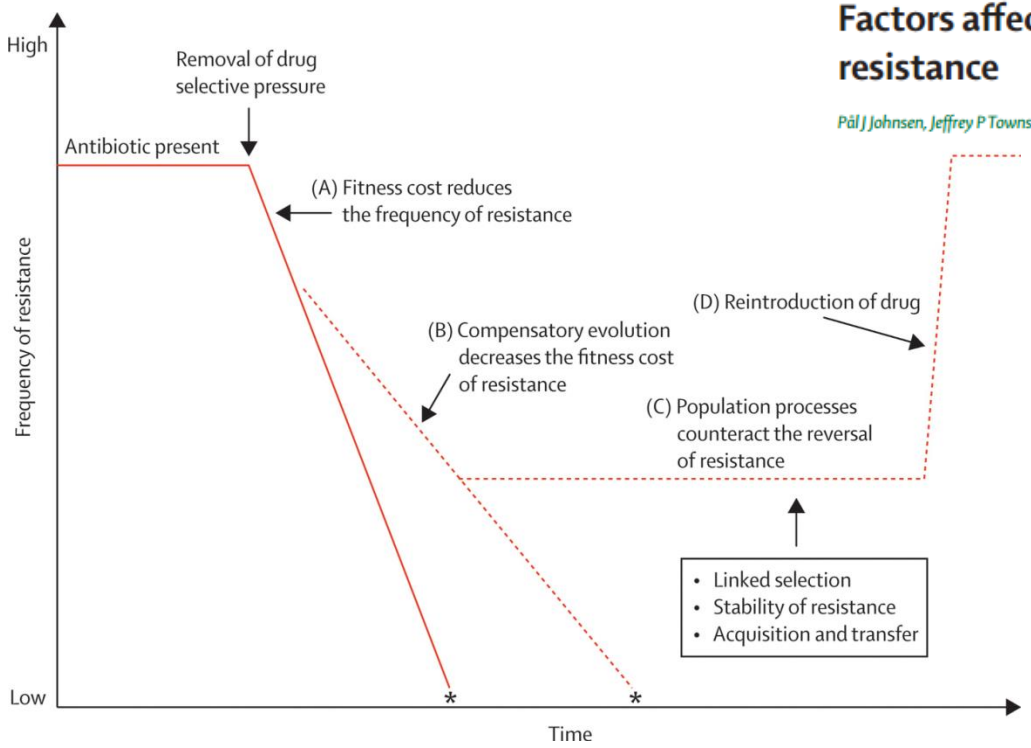
Ministry for Primary Industries
Manatū Ahu Matua

PIANZ
Poultry Industry Association NZ

hrc Health Research Council of New Zealand

Extra slides for questions

Reducing use doesn't always result in elimination of AMR

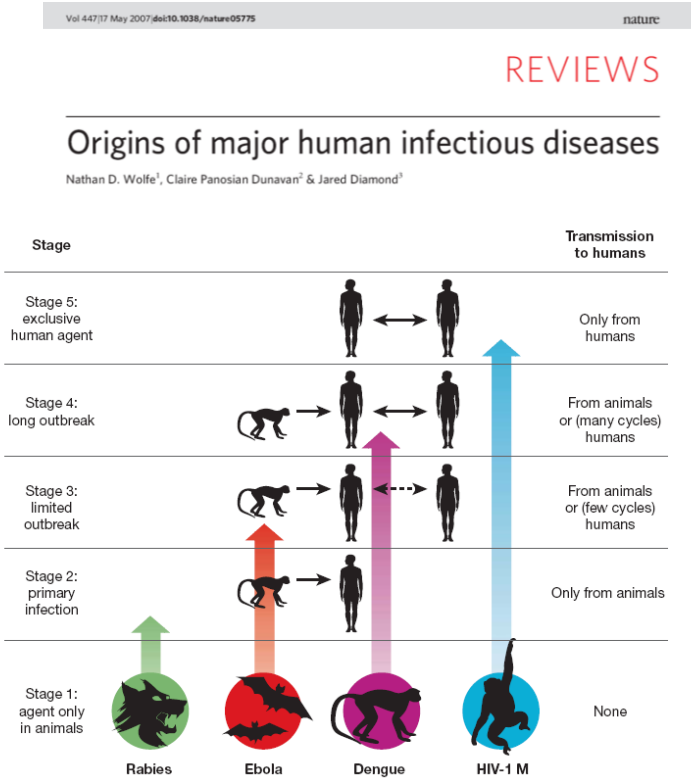


Factors affecting the reversal of antimicrobial-drug resistance

Pål J Johnsen, Jeffrey P Townsend, Thomas Bøhn, Gunnar S Simonsen, Arnfinn Sundsfjord, Kaare M Nielsen

Lancet Infect Dis. 2009 Jun;9(6):357-64

Animal use and the emergence of antimicrobial resistant pathogens



Antimicrobial <u>use in animals</u> can evolve resistant organisms that can behave like:

- <u>Stage 1</u> resistant primary animal pathogens/commensals
- <u>Stage 2</u> zoonotic pathogens (e.g. fluoroquinolone resistant *Campylobacter jejuni)*

Through to…….

- <u>Stage 5</u> anthroponoses (e.g. multidrug resistant *Salmonella* Typhimurium ST313)

Human survey in NZ 2015

Table 2. Ciprofloxacin and tetracycline resistance among *Campylobacter jejuni*, by geographic location, 2015

District Health Board(s)	Number of isolates	Percent (number) resistant		
		Ciprofloxacin	Tetracycline	Co-resistance to ciprofloxacin and tetracycline
Northland	48	10.4 (5)	10.4 (5)	10.4 (5)
Waitemata/Auckland/ Counties Manukau	45	31.1 (14)	31.1 (14)	31.1 (14)
Bay of Plenty/Lakes	37	5.4 (2)	2.7 (1)	2.7 (1)
Capital and Coast/ Hutt Valley	60	25.0 (15)	23.3 (14)	21.7 (13)
Canterbury	53	9.4 (5)	11.3 (6)	9.4 (5)
Southern	54	9.3 (5)	5.6 (3)	3.7 (2)
Total	297	15.5 (46)	14.5 (43)	13.5 (40)

Campylobacter resistance: international (2013)

Region	Ciprofloxacin		Tetracyclines	
	N	% Res	N	% Res
Europe (EU/EEA countries)	11,948	54.4	5,451	33.6
Africa	24	54.2	24	29.2
Asia	102	90.2	99	55.6

NZ
FQ: 15.5%
Tet: 14.5%

efsa European Food Safety Authority

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

EFSA Journal 2015;13(2):4036

Salmonella resistance much higher in overseas travellers

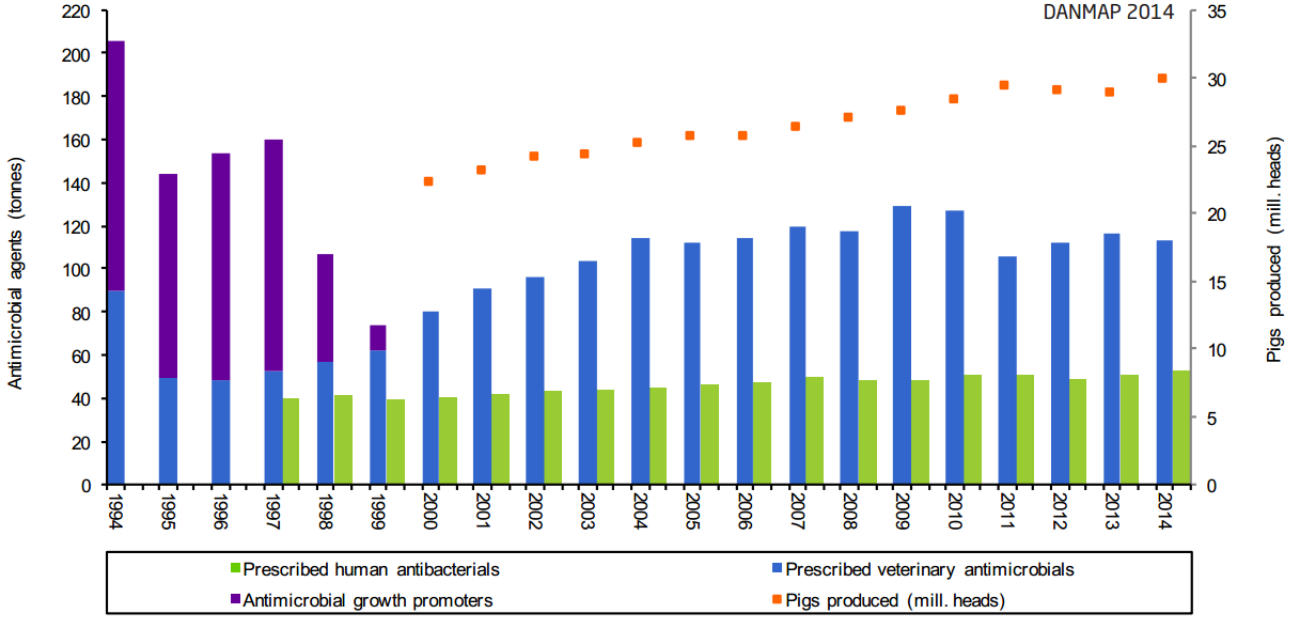
Table 2. Antimicrobial resistance among non-typhoidal *Salmonella* from cases who had travelled overseas compared with non-travellers, 2014

Antimicrobial	Percent resistant		P value for significance of any difference in resistance between travellers and non-travellers[1]
	Cases who had travelled overseas n = 38	Cases who had not travelled overseas n = 167	
Ampicillin	26.3	6.0	<0.001
Cephalothin	2.6	2.4	1.000
Chloramphenicol	7.9	3.0	0.168
Ciprofloxacin	2.6	0.6	0.337
Co-amoxiclav	2.6	1.2	0.461
Co-trimoxazole	2.6	2.4	1.000
Gentamicin	0.0	0.6	1.000
Nalidixic acid	26.3	4.2	<0.001
Streptomycin	18.4	4.8	0.009
Sulphonamides	13.2	5.4	0.144
Tetracycline	21.1	6.6	0.011
Trimethoprim	2.6	2.4	1.000
Multiresistant to ≥3 antimicrobials[2]	18.4	5.4	0.014

1 Chi-square test or Fisher's Exact test as appropriate.
2 For estimates of multidrug resistance, ciprofloxacin and nalidixic acid resistance, and co-trimoxazole and trimethoprim resistance, was counted as one resistance.

Banning use of antimicrobials for growth promotion can result in increase in therapeutic use

Figure 4.1. Prescribed antimicrobial agents for humans, and for animals compared with the number of pigs produced, Denmark



Sources: Human therapeutics: The Danish Medicines Agency. Veterinary consumption: Until 2001, data are based on reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996-2000). Data from 2001-2014 originate from VetStat.

Vancomycin resistant enterococci

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Oct. 2004, p. 5764–5768 Vol. 70, No. 10
0099-2240/04/$08.00+0 DOI: 10.1128/AEM.70.10.5764–5768.2004

Persistence of Vancomycin-Resistant Enterococci in New Zealand Broilers after Discontinuation of Avoparcin Use

Janet M. Manson, John M. B. Smith, and Gregory M. Cook*
Department of Microbiology, Otago School of Medical Sciences, University of Otago, Dunedin, New Zealand

2004 paper 22/382 isolates resistant (Avoparcin use 1977-2000)

2006 survey 1/223 isolates fully resistant to vancomycin with *van*A gene

Microb Ecol (2010) 59:678–688
DOI 10.1007/s00248-009-9625-6

ENVIRONMENTAL MICROBIOLOGY

Evidence for the Clustering of Antibacterial Resistance Phenotypes of Enterococci Within Integrated Poultry Companies

Eve Pleydell · Lynn Rogers · Errol Kwan · Nigel French

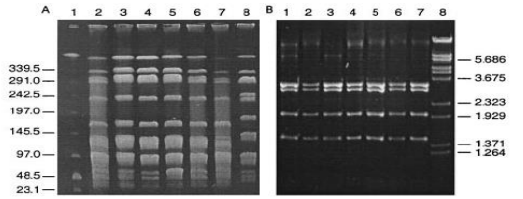


FIG. 4. Comparison of poultry and human VRE in New Zealand. (A) PFGE of *Sma*I macrorestriction patterns in vancomycin-resistant *E. faecalis*. Lane 1, lambda DNA ladder standard; lanes 2 and 3, poultry isolates; lanes 4 to 8, human clinical isolates. (B) Long-tem-

Campylobacter resistance: international

Table 22. Antimicrobial resistance in Campylobacter jejuni *from humans per country in 2013*

Country	Ciprofloxacin		Tetracyclines	
	N	% Res	N	% Res
Austria[(a)]	303	63.0	303	21.5
Denmark[(a)]	65	23.1	65	20.0
Estonia	293	57.7	248	21.4
France	3,816	49.7	–	–
Italy	235	67.2	208	57.2
Lithuania	178	88.2	–	–
Luxembourg[(a)]	566	59.4	566	43.8
Malta	138	69.6	–	–
Netherlands	2,811	56.9	1,414	36.4
Romania[(a)]	44	77.3	44	56.8
Slovakia	992	39.9	1,184	19.8
Slovenia	877	64.1	877	27.7
Spain	281	91.5	281	80.1
United Kingdom	1,110	46.9	32	34.4
Total (MSs 14)	**11,709**	**54.6**	**5,222**	**33.5**
Iceland	6	NA	1	NA
Norway[(a)]	106	20.8	106	14.2

NZ
FQ: 15.5%
Tet: 14.5%

‘By 2030, NZ Inc will not need antibiotics for the maintenance of health and welfare in animals’

www.nzva.org.nz

What it ***did not*** say:

- We will not *have* any antibiotics in 2030
- We will not *use* any antibiotics in 2030
- We will not use antibiotics to *treat disease*
- We invite you (someone) to restrict and/or control our antibiotic use
- AMR is the veterinary profession’s fault

Antibiotic resistance in foodborne pathogens

- 100% attributable to animals, however….
- Antibiotic therapy is only recommended for severe systemic infections
- 99% of infections can be managed by first line agents
  - Macrolides (erythromycin) for *Campylobacter*
  - Cephalosporins and fluoroquinolones for *Salmonella*

Danmap 2011

Figure 1. Stages in the adaptive evolution of *S. aureus* CC398. The original MSSA CC398 strains were, and still are, circulating in the human population (stage 1). The human-to-animal host jump by an MSSA strain was accompanied by loss of *scn* and acquisition of *tet*(M) (stage 2). In the livestock reservoir, geographically distinct MRSA CC398 strains have emerged through acquisition of the methicillin resistance gene *mecA* (stage 3). LA-MRSA CC398 strains are able to reacquire the *scn* gene, which may be a first step in the adaption back to humans (stage 4).