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
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 to 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)
Deaths attributable to AMR every year compared to other major causes of death

AMR in 2050
10 million

- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Measles: 130,000
- Diarrhoeal disease: 1.4 million
- Cholera: 100,000–120,000
- Cancer: 8.2 million
- Diabetes: 1.5 million

Global Health Security Agenda

"...We must come together to prevent, and detect and fight every kind of biological danger – whether it's a pandemic like H1N1, a terrorist threat, or a treatable disease."

President Barack Obama, 2011

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

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
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

Estimated antimicrobial use (mg active ingredient per kg biomass) in food-producing animals (including horses) compared with use for humans in 30 countries during 2012

Human
Food animals
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, ECDC and ACSQHC
Use by species of animal (and plants)

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
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
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?

Figure 2. Occurrence (%) of ESBL-producing *Escherichia coli* and genes in meat (ab), Denmark

**Different profile of strains**

- **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
'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 mobile elements
  - Amplification of circulating clones
- Resistant clones
  - *Salmonella Typhimurium DT104* (multiresistant)
  - *Campylobacter jejuni ST-6964*
Stomach bug rise linked to effluent

Health: Untreated manure infecting waterways, conference told

by Simon Collins
science reporter

Cases producing the equivalent of untreated effluent from 6 million people are being reported for an emerging epidemic of campylobacter food poisoning.

Reported cases of the campylobacter stomach bug have multiplied more than 10-fold in the past 5 years, from 369 cases in 1985 to a record 14,899 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 Martin Popp, told the New Zealand Geographic Society conference in Auckland yesterday that one of the causes for the increase was effluent from cows spouting into waterways.

"Between 1980 and 2004, the national dairy herd increased by 10-15% in each of these cases. They produce an average of 30-50 million cows.

"Only a small of the effluent is used as slurry, on the remaining 60% of the land it is used in effluent production."

Cattle linked to common stomach bug

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

THE NEW ZEALAND MEDICAL JOURNAL
Vol 119 No 1243 ISSN 1175 8716
Poultry identified as main source

Marked Campylobacteriosis Decline after Interventions Aimed at Poultry, New Zealand

50% decline in notifications and hospitalisations
Est $50-70M saving per annum

5-year target achieved within 12-24 months

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*

**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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disc (µg)</th>
<th>Res (%)</th>
<th>Resistant Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enthromycin</td>
<td>15</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Enrufloxacin</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>30</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>30</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>30</td>
<td>0</td>
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<table>
<thead>
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<th>Zone size (mm)</th>
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<tr>
<td>≤6</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Enthromycin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Enrufloxacin</td>
</tr>
<tr>
<td>Nalidixic acid</td>
</tr>
<tr>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

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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!)
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 \textit{tetO} insertion alleles in \textit{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?
  - \textit{tetO} plasmid and C257T mutation in \textit{gyrA}
- How long has it been in NZ?
  - \textasciitilde\text{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

\textit{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

![Graph showing number of cases per month over time](image)
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?

VRE in poultry after glycopeptide growth promoter ban
Johnsen et al
Lancet Infect Dis. 2009 Jun;9(6):357-64
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-500 (blaCTX-M-15)
ST-617 (blaCTX-M-15)
ST-38 (blaCTX-M-14)
ST-648 (blaCTX-M-14)
ST-1193 (blaCTX-M-27)
ST-131 (blaCTX-M-27)
ST-131 (blaCTX-M-15)
ST-4553 (blaCTX-M-15)
ST-38 (blaCTX-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!
Acknowledgements

• mEpiLab team: Patrick Biggs, Jonathan Marshall, Anne Midwinter, Julie Collins-Emerson, Rukhshana Akhter, Jackie Benschop, David Hayman, Lynn Rogers, David Wilkinson, Leah Toombs-Ruane
• ESR Dr Phil Carter, Dr Brent Gilpin Dr Muriel Dufour, Dr Stephen On, Helen Hefernan, ERL team
• University of Melbourne, MDU Prof Ben Howden, Dr Dieter Bulach, Dr Debbie Williamson
• MPI – Prof Steve Hathaway, Dr Donald Campbell, Dr Craig Thornley
• PIANZ – Kerry Mulqueen, Michael Brooks
Extra slides for questions
Reducing use doesn’t always result in elimination of AMR

**Factors affecting the reversal of antimicrobial-drug resistance**

- (A) Fitness cost reduces the frequency of resistance
- (B) Compensatory evolution decreases the fitness cost of resistance
- (C) Population processes counteract the reversal of resistance
- (D) Reintroduction of drug

- Linked selection
- Stability of resistance
- Acquisition and transfer

Lancet Infect Dis.
2009 Jun;9(6):357-64
Antimicrobial use in animals can evolve resistant organisms that can behave like:

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

Through to.......

- **Stage 5** anthroponoses (e.g. multidrug resistant *Salmonella Typhimurium* ST313)
<table>
<thead>
<tr>
<th>District Health Board(s)</th>
<th>Number of isolates</th>
<th>Percent (number) resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Northland</td>
<td>48</td>
<td>10.4 (5)</td>
</tr>
<tr>
<td>Waitemata/Auckland/Counties Manukau</td>
<td>45</td>
<td>31.1 (14)</td>
</tr>
<tr>
<td>Bay of Plenty/Lakes</td>
<td>37</td>
<td>5.4 (2)</td>
</tr>
<tr>
<td>Capital and Coast/Hutt Valley</td>
<td>60</td>
<td>25.0 (15)</td>
</tr>
<tr>
<td>Canterbury</td>
<td>53</td>
<td>9.4 (5)</td>
</tr>
<tr>
<td>Southern</td>
<td>54</td>
<td>9.3 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>297</td>
<td>15.5 (46)</td>
</tr>
</tbody>
</table>
Campylobacter resistance: international (2013)

<table>
<thead>
<tr>
<th>Region</th>
<th>Ciprofloxacin</th>
<th>Tetracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Res</td>
</tr>
<tr>
<td>Europe (EU/EEA countries)</td>
<td>11,948</td>
<td>54.4</td>
</tr>
<tr>
<td>Africa</td>
<td>24</td>
<td>54.2</td>
</tr>
<tr>
<td>Asia</td>
<td>102</td>
<td>90.2</td>
</tr>
</tbody>
</table>

NZ
FQ: 15.5%
Tet: 14.5%
Salmonella resistance much higher in overseas travellers

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Cases who had travelled overseas n = 38</th>
<th>Cases who had not travelled overseas n = 167</th>
<th>P value for significance of any difference in resistance between travellers and non-travellers$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>26.3</td>
<td>6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>2.6</td>
<td>2.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>7.9</td>
<td>3.0</td>
<td>0.168</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2.6</td>
<td>0.6</td>
<td>0.337</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>2.6</td>
<td>1.2</td>
<td>0.461</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>2.6</td>
<td>2.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.0</td>
<td>0.6</td>
<td>1.000</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>26.3</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>18.4</td>
<td>4.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>13.2</td>
<td>5.4</td>
<td>0.144</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>21.1</td>
<td>6.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>2.6</td>
<td>2.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Multireistant to ≥3 antimicrobials$^2$</td>
<td>18.4</td>
<td>5.4</td>
<td>0.014</td>
</tr>
</tbody>
</table>

$^1$ 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
Vancomycin resistant enterococci

2006 survey 1/223 isolates fully resistant to vancomycin with \textit{van}A gene
# Campylobacter resistance: international

<table>
<thead>
<tr>
<th>Country</th>
<th>Ciprofloxacin</th>
<th>Tetracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Res</td>
</tr>
<tr>
<td>Austria</td>
<td>303</td>
<td>63.0</td>
</tr>
<tr>
<td>Denmark</td>
<td>65</td>
<td>23.1</td>
</tr>
<tr>
<td>Estonia</td>
<td>293</td>
<td>57.7</td>
</tr>
<tr>
<td>France</td>
<td>3,816</td>
<td>49.7</td>
</tr>
<tr>
<td>Italy</td>
<td>235</td>
<td>67.2</td>
</tr>
<tr>
<td>Lithuania</td>
<td>178</td>
<td>88.2</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>566</td>
<td>59.4</td>
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<tr>
<td>Malta</td>
<td>138</td>
<td>69.6</td>
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<tr>
<td>Netherlands</td>
<td>2,811</td>
<td>56.9</td>
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<tr>
<td>Romania</td>
<td>44</td>
<td>77.3</td>
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<tr>
<td>Slovakia</td>
<td>992</td>
<td>39.9</td>
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<tr>
<td>Slovenia</td>
<td>877</td>
<td>64.1</td>
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<tr>
<td>Spain</td>
<td>281</td>
<td>91.5</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1,110</td>
<td>46.9</td>
</tr>
<tr>
<td><strong>Total (MSs 14)</strong></td>
<td>11,709</td>
<td>54.6</td>
</tr>
<tr>
<td>Iceland</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>Norway</td>
<td>106</td>
<td>20.8</td>
</tr>
</tbody>
</table>

NZ
FQ: 15.5%
Tet: 14.5%

*Table 22. Antimicrobial resistance in Campylobacter jejuni from humans per country in 2013*
‘By 2030, NZ Inc will not need antibiotics for the maintenance of health and welfare in animals’

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*
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).