Controlling enteric zoonoses: applying new tools and teamwork at the human-animal health interface

Nigel French,
Petra Mullner

Molecular Epidemiology and Public Health Laboratory

ACVS Meeting
July 2010
mEpiLab: Molecular Epidemiology and Public Health Laboratory

- Formerly part of the EpiCentre (28 staff and students)

We work on:

- Food safety
- (Veterinary) Public Health
- Surveillance
- Molecular epidemiology of zoonoses
  - Campylobacter
  - VTEC (E. coli O157)
  - Cryptosporidium, Giardia
  - Leptospira
  - Salmonella
  - ...others

http://mepilab.massey.ac.nz
One health

• Global population and ecosystem health framework (OWOH, Manhattan Principles).

• Long history of ‘One Medicine’ in NZ
  – Late 19\textsuperscript{th} C to combat plague and tb.

• Driver for change in the way we deal with veterinary public health issues, including control of zoonoses.
  – Food safety
  – Ecosystem goods and services (water and recreation)

• Stimulus for closer collaboration between sectors
  – Human and animal health, environment agencies.
Getting it in perspective

• ~1500 agents of human infectious disease - over 60% are (currently) zoonotic.
• Emerging infections: over 75% zoonoses
• Not minor problems
  – Global, Deadly (SARS, H5N1, Nipah.....)
  – Major burden to health services and economy
• Proportion of human infections / burden of illness of animal origin? – unknown.
Emerging zoonoses

• Most infectious agents are multi-host
  – Particularly emerging ones
  – Subset of these are the zoonoses
  – Many enteric infections

• Single host agents relatively rare
  – Subset of these are the anthroponoses
  – Evolved once popn reached critical size
Most important notifiable diseases are zoonoses.

Food and environmental exposures

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**National Surveillance Data**

2006

<table>
<thead>
<tr>
<th>12-Monthly Notification Rate Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Campylobacteriosis</td>
</tr>
<tr>
<td>Pertussis</td>
</tr>
<tr>
<td>Salmonellosis</td>
</tr>
<tr>
<td>Giardiasis</td>
</tr>
<tr>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
</tr>
<tr>
<td>Yersiniosis</td>
</tr>
<tr>
<td>Tuberculosis Disease</td>
</tr>
<tr>
<td>Meningococcal Disease</td>
</tr>
<tr>
<td>Shigellosis</td>
</tr>
<tr>
<td>Acute Rheumatic Fever</td>
</tr>
<tr>
<td>VTEC Infection</td>
</tr>
<tr>
<td>Leptospirosis</td>
</tr>
</tbody>
</table>

Source: ESR
Campylobacteriosis in NZ

Figure 1. Annual number of notifications (1980–2005) and hospitalisations (1995–2005) for campylobacteriosis in New Zealand

From Baker et al 2006
An International Comparison... (A Sears)

Epidemiology: seasonal pattern

Smoothed Time Series: Cases per 1,000 People
Temperature and cases - centred, normalised and smoothed

Campylobacter predicts weather
Meshblock mapping
Cases 2000-9
MS code.

Spatial pattern
Spatio-temporal modelling

meshblocks
Spatio-temporal modelling

\[ Y_{i,t} \sim \text{Pois}(n_i \lambda_{i,t}) \]

\[ \log(\lambda_{i,t}) = R_t + U_i \]

Add s,t term for outbreak indicator modelling

| Temporal prior | Change in risk this week is similar to change in risk last week.  
(Second Order Gaussian Random Walk) |
|----------------|--------------------------------------------------------------------------------|
| Spatial prior  | Risk in a meshblock is similar to risk in neighbouring meshblocks.  
(Gaussian Markov Random Field) |
Epidemiology: spatial pattern

Comparison of Relative Risk vs SDI

Relative Risk

SDI

Wealthy area

Deprived area

>1M pop

MASSEY UNIVERSITY
Spatial epidemiology - age

0-4 year olds

Pre-school children predominantly rural
Spatial epidemiology - age

5-9 year olds

School children predominantly urban
Interventions in poultry industry demanded

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 ~ 40% of meat consumption, no imports or exports
Thu Jul 5: Campylobacter revisited; Oil rig kidnapping; The final curtain

Campylobacter
A year ago an Otago University report described fresh chicken meat as the cheap, dirty food of New Zealand. That report suggested it was largely responsible for our high rate of campylobacter infections. Researcher Dr Michael Baker even called for it to be withdrawn from sale. It made the headlines, but has anything really changed? Well, one year later Close Up put fresh chicken to the test. Paul Henry talks to Dr Michael Baker about what the results mean, and to Andrew McKenzie from the New Zealand Food Safety Authority about what steps are being taken to protect consumers from...
Source attribution

• Essential for:
  – Managing public health risks
  – Prioritising resources
  – Directing research effort
Model-based approaches to 'source attribution'

- (Analytical) epidemiology
  - Population-based epidemiological studies
- Simulation modelling / Risk assessment
- Molecular epidemiology
  - Microbial subtyping / source tracking
  - Applying molecular tools, population genetics and epidemiological modelling to inform public health policy
  - NZFSA and industry funded
Approaches to ‘source attribution’

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Chicken – confusing / conflicting evidence?

<table>
<thead>
<tr>
<th>Risk/Protective factor</th>
<th>Odds ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating undercooked poultry (risk)</td>
<td>4.94 (1.03, 23.62)</td>
</tr>
<tr>
<td>Poultry eaten at a friend’s house (risk)</td>
<td>3.18 (1.0, 10.73)</td>
</tr>
<tr>
<td>Consuming fresh chicken (as opposed to frozen) (risk)</td>
<td>1.8 (0.82, 3.82)</td>
</tr>
<tr>
<td>Eating poultry at home (protective)</td>
<td>0.36 (0.14, 0.9)</td>
</tr>
<tr>
<td>Freezing fresh chicken before consuming (protective)</td>
<td>0.58 (0.18, 1.83)</td>
</tr>
<tr>
<td>Buying frozen chicken (protective)</td>
<td>0.71 (0.34, 1.31)</td>
</tr>
</tbody>
</table>

Ikram 1994, New Zealand Campylobacter study
Approaches to ‘source attribution’

- (Analytical) epidemiology
  - Population-based epidemiological studies
- Simulation modelling / Risk assessment
- Molecular epidemiology
  - Microbial subtyping / source tracking
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Manawatu sentinel surveillance site

• Interdisciplinary collaboration between:
  – MedLab Central
  – Public Health Unit
  – Human health surveillance unit: ESR
  – Regulator: NZFSA
  – Industry body: PIANZ / suppliers
  – Dairy and sheep farmers
  – Regional council
  – Institutes at Massey University
Manawatu study 2005-2010...

- Sentinel site (5 yrs)
Numbers of samples/isolates: 

**C. jejuni**

- **Human** 520 (770 samples)  
- **Poultry** 562 samples 75% +ve  
- **Red meat** 1312 samples 12% +ve  
- **Ruminant faeces** 278 samples 58% +ve  
- **Env. Water** 335 samples 30% +ve  
- **Wild bird** 192 samples 13% +ve

*March 1st 2005 to Feb 29th 2008*
Multi Locus Sequence Typing
MLST

- PCR highly conserved genes
- 7 housekeeping genes
- Used to define:
  - **ST** = sequence type – unique pattern of 7 genes
  - **Clonal complex** = group of related STs

- Website: Oxford University
  http://campylobacter.mlst.net
Host associated sequence types in NZ

Ruminant associated

Poultry associated
Minimum spanning tree: isolates from the Manawatu

Poultry STs

River water STs

Ruminant STs

N=1745 isolates
Need for good epidemiological data
EpiSurv, PHU
Molecular and spatial epidemiology of human campylobacteriosis: source association and genotype-related risk factors

P. MULLNER1,2*, T. SHADBOLT2, J. M. COLLINS-EMERSON1, A. C. MIDWINTER1, S. E. F. SPENCER1, J. MARSHALL1, P. E. CARTER5, D. M. CAMPBELL5, D. J. WILSON6, S. HATHAWAY3, R. PIRIE1 and N. P. FRENCH1
Source attribution

• Source attribution – used 4 approaches
  – Proportional similarity
    • Simple, area of overlap
  – Dutch model
    • Simple assignment
  – Hald model
    • Complex, epidemiology based
  – Island model
    • Complex, population genetics based
Proportional Similarity Index (PS)

The PS estimates the area of overlap between the frequency distributions of e.g. bacterial sub types from different sources.

### Comparison source

<table>
<thead>
<tr>
<th>Comparison source</th>
<th>Proportional Similarity index</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poultry</td>
<td>0.51</td>
<td>0.45</td>
<td>0.55</td>
</tr>
<tr>
<td>Cattle</td>
<td>0.35</td>
<td>0.28</td>
<td>0.40</td>
</tr>
<tr>
<td>Sheep</td>
<td>0.30</td>
<td>0.24</td>
<td>0.34</td>
</tr>
<tr>
<td>Water</td>
<td>0.15</td>
<td>0.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Wild bird</td>
<td>0.10</td>
<td>0.06</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Human origin**

**“Bovine” origin**
The Hald model (Hald et al 2004)

\[ \lambda_{ij} = p_{ij}(M_j a_j)q_i \]

\( p_{ij} = \) matrix of prevalence of different strain types
\( M_j = \) relative amount of food consumed
\( a_j = \) relative ‘danger’ of food (or environmental) sources.
\( q_i = \) relative ‘virulence’ of strains.

Estimates number of cases with measure of uncertainty (Bayesian inference)
Modified Hald Model (Mullner et al 2009)

• Model prevalence uncertainty
• Hierarchical model for bacterial parameters
• Omit food consumption weights (M)

Source Attribution of Food-Borne Zoonosis in New Zealand:
A Modified Hald Model

Petra Mullner,* Geoff Jones, Alasdair Noble, Simon Spencer, Steve Hathaway, and Nigel Peter French

Risk Analysis, June 2009
Island model

- Population genetics approach
- Based on coalescent (mutation and recombination)
- Used to find out source of human infections
- Flow into the human “island” from animal “islands”
- Same approach used to identify source of contamination of river water

Tracing the Source of Campylobacteriosis

Daniel J. Wilson¹, Edith Gabriel², Andrew J. H. Leatherbarrow³, John Cheesbrough⁴, Steven Gee⁴, Eric Bolton⁵, Andrew Fox⁴, Paul Fearnhead⁶, C. Anthony Hart⁷, Peter J. Diggle²
Source attribution

Assigning the source of human campylobacteriosis in New Zealand: A comparative genetic and epidemiological approach

Petra Mulliner, Simon E.F. Spencer, Daniel J. Wilson, Geoff Jones, Alasdair D. Noble, Anne C. Midwinter, Julie M. Collins-Emerson, Philip Carter, Steve Hathaway, Nigel P. French

Now have information on many sources...
Auckland MLST (T. Wong)

Human

Pink = human
Rest poultry

Auckland
Campylobacteriosis Notifications and Hospitalisations

Campylobacter in Poultry – Risk Management Strategy
2007 - 2010

...2006-2009, now 2008-2011
National Micro Database results

<table>
<thead>
<tr>
<th>NMD Results</th>
<th>Number of carcasses tested</th>
<th>Prevalence %</th>
<th>Mean Log Count all samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2 2007</td>
<td>890</td>
<td>57</td>
<td>3.07</td>
</tr>
<tr>
<td>Q3 2007</td>
<td>936</td>
<td>53.8</td>
<td>3.06</td>
</tr>
<tr>
<td>Q4 2007</td>
<td>916</td>
<td>45.1</td>
<td>2.75</td>
</tr>
<tr>
<td>Q1 2008</td>
<td>1309</td>
<td>45</td>
<td>2.70</td>
</tr>
<tr>
<td>Q2 2008</td>
<td>1528</td>
<td>30.6</td>
<td>2.41</td>
</tr>
</tbody>
</table>

Target: 1 log reduction in contamination. Action depends on number of non-compliances.
Modelling post intervention change in attribution

Dynamic Hald model

N=670 human cases
Trends in notified zoonoses
The changing epidemiology of campylobacteriosis in New Zealand

Reduction in case rates most marked in urban adults.

<table>
<thead>
<tr>
<th></th>
<th>% cases rural</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2000-6 ave</td>
</tr>
<tr>
<td>Total</td>
<td>11.19</td>
</tr>
<tr>
<td>Under 5's</td>
<td>27.11</td>
</tr>
</tbody>
</table>
New focus on non-poultry transmission routes

*Campylobacter* in Manawatu rivers

Where do these campylobacters come from???
Manawatu catchment dairy and beef (AgriBase)

Dairy=227,658
Beef=181,196
Identifying potential outbreaks in water supply regions
Tararua outbreak in 2008

### Water flow

<table>
<thead>
<tr>
<th>Lab ID</th>
<th>Source Type</th>
<th>ST</th>
<th>OnsetDt</th>
<th>Outbrk</th>
<th>CurrWSCode</th>
<th>CurrWSSpec</th>
</tr>
</thead>
<tbody>
<tr>
<td>H775</td>
<td>Human</td>
<td>61</td>
<td>20/07/2008</td>
<td>No</td>
<td>PAH001PA</td>
<td></td>
</tr>
<tr>
<td>H791</td>
<td>Human</td>
<td>190</td>
<td>5/08/2008</td>
<td>No</td>
<td>PAH001PA</td>
<td>Muddier than usual &quot;toxic in it's self&quot;</td>
</tr>
<tr>
<td>H787</td>
<td>Human</td>
<td>190</td>
<td>5/08/2008</td>
<td>No</td>
<td>PAH001PA</td>
<td>smells of dirt, brown</td>
</tr>
<tr>
<td>H788</td>
<td>Human</td>
<td>190</td>
<td>5/08/2008</td>
<td>No</td>
<td>PAH001PA</td>
<td>water been brown, &quot;crap&quot;</td>
</tr>
<tr>
<td>H804</td>
<td>Human</td>
<td>3793</td>
<td>6/08/2008</td>
<td>Yes</td>
<td>PAH001PA</td>
<td></td>
</tr>
<tr>
<td>H803 D</td>
<td>Human</td>
<td>50</td>
<td>6/08/2008</td>
<td>No</td>
<td>PAH001PA</td>
<td></td>
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<tr>
<td>H795</td>
<td>Human</td>
<td>190</td>
<td>7/08/2008</td>
<td>No</td>
<td>PAH001PA</td>
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<tr>
<td>H798</td>
<td>Human</td>
<td>50</td>
<td>9/08/2008</td>
<td>Yes</td>
<td>PAH001PA</td>
<td></td>
</tr>
<tr>
<td>H801</td>
<td>Human</td>
<td>61</td>
<td>9/08/2008</td>
<td>Yes</td>
<td>PAH001PA</td>
<td></td>
</tr>
</tbody>
</table>
Surface water sampling

Manawatu – farmland and bush

Toenepi – 22 dairy farms

Key
1. Ororua
2. Himatangi
3. Mangapapa
4. Manawatu A
5. Tokomaru
6. Manawatu H
Prevalence of *Campylobacter* spp.

<table>
<thead>
<tr>
<th>Source site</th>
<th>Number of samples</th>
<th>% presumptive <em>Campylobacter</em></th>
<th>% <em>C. jejuni</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oroua</td>
<td>86</td>
<td>33.7</td>
<td>16.3</td>
</tr>
<tr>
<td>Himatangi</td>
<td>85</td>
<td>30.6</td>
<td>16.5</td>
</tr>
<tr>
<td>Mangapapa</td>
<td>86</td>
<td>54.7</td>
<td>34.9</td>
</tr>
<tr>
<td>Manawatu Albert St</td>
<td>87</td>
<td>52.9</td>
<td>32.2</td>
</tr>
<tr>
<td>Tokomaru</td>
<td>78</td>
<td>24.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Manawatu Hopelands</td>
<td>85</td>
<td>29.4</td>
<td>17.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>507</strong></td>
<td><strong>37.9</strong></td>
<td><strong>21.1</strong></td>
</tr>
</tbody>
</table>
Novel Clonal Complexes with an Unknown Animal Reservoir Dominate *Campylobacter jejuni* Isolates from River Water in New Zealand\(^7\)


![Minimum spanning tree of New Zealand water isolates based on sequence types. Clusters are identified by the clonal complex number associated with the sequence types in the cluster.](Ruminant.png)
Source attribution: water

Most isolates from water are associated with wildlife – even in dairy catchments.

Cattle and sheep isolates more likely to be associated with human infection.
Time series since 2006

Recent increases in central and lower NI

Recent trends

Need for more work with industry...
Extending to other pathogens: STEC O157

NZ: more diversity in clinical genotypes
Less diversity in bovine
Opposite to US.

White bars proportion bovine of types 1-3
NZ 13/14 (>90%)
From Besser et al 2008.
Conclusions

• Success of campaign attributable to many factors.
  – Still more to do, environmental risks, children etc...

• Manawatu sentinel surveillance site provided an important contribution to the recent success in reducing campylobacteriosis across NZ.

• Wouldn’t have been possible without collaboration and cooperation between many individuals and organisations.
  – Human, animal and environmental health sectors

• New tools have been developed of use for local and national surveillance
  – based on epidemiology and population genetics

• Good example of ‘one health’ in action?
Acknowledgements

- Staff – lecturers, RAs
  - Dr Julie Collins-Emerson, Dr Anne Midwinter
  - Dr Simon Spencer, Dr Jonathan Marshall, Dr Patrick Biggs

- Lab team:
  - Rebecca Pattison, Rukhshana Akhter, Errol Kwan, Lynn Rogers, Isabel Li, Jim Learmonth, Anthony Pita, Sarah Moore, Angi Reynolds, Neville Haack

- PhD students
  - Petra Mullner, Vathsala Mohan

- Masters students
  - Particularly Tui Shadbolt, Ann Sears

- MidCentral Public Health
  - Dr Jill McKenzie and team

- MedLab Central

- ESR - Phil Carter, Sharla McTavish, Elaine Moriarty

- AgResearch – Grant Hotter, Adrian Cookson

- CDRP team
  - NIWA – Graham McBride
  - ESR – Rob Lake
  - NZFSA – Peter van de Logt, Dr Donald Campbell

- Michael Baker

- Robert Sanson

- Massey – IMBS, IFNHH, IFS (Dr Barbara Holland, Dr Geoff Jones, Dr Alasdair Noble, Prof Martin Hazelton)
  - Allan Wilson Centre

- Universities of Liverpool, Lancaster, Oxford, Chicago

- Undergraduate student
  - Jeffrey Ling

- Industry

NZFSA, MoH, FRST, Royal Society Marsden and Industry funding
Publications


• + NZFSA website – science for number of reports