New approaches to source attribution: their role in reducing campylobacteriosis notifications in New Zealand

Nigel French
EFSA December 2008

http://epicentre.massey.ac.nz/
Outline

• Epidemiology
  - Recent studies of human case data
• Genotyping - human and animal reservoirs
  - MLST
• Source attribution modelling
• Recent trends - post intervention
### National Surveillance Data

#### 12-Monthly Notification Rate Changes (1)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Rate per 1,000</th>
<th>Rate per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacteriosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonellosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giardiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yersiniosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigellosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Rheumatic Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTEC Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td></td>
<td></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
Epidemiology: seasonal pattern

Smoothed Time Series: Cases per 1,000 People

- The Manawatu
- Canterbury
- Auckland
Epidemiology: spatial pattern

Comparison of Relative Risk vs SDI

Relative Risk

SDI

Wealthy area

Deprived area

>1M pop\(^n\)
Spatial epidemiology - age

Manawatu region: 0 to 4 year-olds

Pre-school children predominantly rural
Spatial epidemiology - age

Manawatu region: 5 to 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
Source attribution

• Essential for:
  - Managing public health risks
  - Prioritising resources
  - Directing research effort
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’

- (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
Population-based epidemiological studies

- Cross-sectional, cohort, case-control, case-case.
- Can estimate relative risk / odds ratios / PAF for different exposures
  - e.g. *Campylobacter* and eating poultry, foreign travel, environmental, occupational

Source/exposure → disease
Issues with case-control studies

• Can be very valuable but...

• Prone to reporting bias
  - “I must have eaten chicken....”

• If high level immunity, similar exposures in cases and controls – low power
Chicken - confusing / conflicting evidence?

Ikram 1994, New Zealand Campylobacter study

<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>
Approaches to ‘source attribution’

- (Analytical) epidemiology
- Simulation (RA) modelling
  - Multiple pathways / exposures
  - Food and environmental sources
  - Simulation of propagation of pathogen along pathway
  - Hazard or risk based (need D-RR)
  - Good for assessing interventions
- Molecular epidemiology
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 funded
Multi Locus Sequence Typing

- PCR highly conserved genes
- 7 housekeeping genes
- Use allelic variation to describe subtypes:
  - ST = sequence type - unique pattern of 7 alleles
  - Clonal complex = group of related STs identified by progenitor ST
  - Website: Oxford University
    http://campylobacter.mlst.net

1.6Mbp
Campylobacter populations

Minimum spanning tree of all known isolates on PubMLST website

2954 STs, ~5000 isolates
### ST-61 complex

<table>
<thead>
<tr>
<th>source</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>human stool</td>
<td>62</td>
<td>35.2%</td>
</tr>
<tr>
<td>cattle</td>
<td>53</td>
<td>30.1%</td>
</tr>
<tr>
<td>sheep</td>
<td>17</td>
<td>9.7%</td>
</tr>
<tr>
<td>ruminant offal/ meat</td>
<td>8</td>
<td>7.9%</td>
</tr>
<tr>
<td>lamb</td>
<td>8</td>
<td>4.5%</td>
</tr>
<tr>
<td>Chicken</td>
<td>3</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
NZ Manawatu study 2005-

- Are human isolates the same as those found in different sources?
- Identify genotypes common to particular sources
- Modelling (risk attribution)
- Feasibility study: useful approach to embed within surveillance in NZ?
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
<table>
<thead>
<tr>
<th>ST</th>
<th># of cases</th>
<th>%</th>
<th>2006 rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>474</td>
<td>66</td>
<td>27.3</td>
<td>1</td>
</tr>
<tr>
<td>48</td>
<td>24</td>
<td>9.9</td>
<td>2</td>
</tr>
<tr>
<td>190</td>
<td>18</td>
<td>7.4</td>
<td>4</td>
</tr>
<tr>
<td>45</td>
<td>17</td>
<td>7.0</td>
<td>3</td>
</tr>
<tr>
<td>53</td>
<td>13</td>
<td>5.4</td>
<td>8</td>
</tr>
<tr>
<td>42</td>
<td>11</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>61</td>
<td>10</td>
<td>4.1</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>9</td>
<td>3.7</td>
<td>7</td>
</tr>
<tr>
<td>2026</td>
<td>9</td>
<td>3.7</td>
<td>11</td>
</tr>
</tbody>
</table>

**Rare internationally**

**MLST**

**Human cases in Manawatu**

Red = Ruminant associated strains

---

Massey University
Minimum spanning tree: isolates from the Manawatu

Poultry strains

Ruminant strain

Water strain

Legend:
- Human
- Sheep
- Company B
- Company A
- Cattle
- Other poultry
- Environmental water
- Wild bird
Human cases over 3-year period
Host associated sequence types in NZ

- **Ruminant associated**
  - ST 61
  - ST 2026
  - ST 422
  - ST 474
  - ST 48
  - ST 257

- **Poultry associated**
  - ST 475
  - ST 57
  - ST 482
  - ST 140

<table>
<thead>
<tr>
<th>Host Type</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poultry</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Sheep faeces</td>
<td></td>
</tr>
<tr>
<td>Lamb mince</td>
<td></td>
</tr>
<tr>
<td>Lamb liver</td>
<td></td>
</tr>
<tr>
<td>Cattle faeces</td>
<td></td>
</tr>
<tr>
<td>Beef mince</td>
<td></td>
</tr>
<tr>
<td>Beef liver</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Host Type</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poultry</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Sheep faeces</td>
<td></td>
</tr>
<tr>
<td>Lamb mince</td>
<td></td>
</tr>
<tr>
<td>Lamb liver</td>
<td></td>
</tr>
<tr>
<td>Cattle faeces</td>
<td></td>
</tr>
<tr>
<td>Beef mince</td>
<td></td>
</tr>
<tr>
<td>Beef liver</td>
<td></td>
</tr>
</tbody>
</table>
Manawatu region: ST 474

Relative Risk

- 0.55 - 0.71
- 0.72 - 0.84
- 0.85 - 0.94
- 0.95 - 1.03
- 1.04 - 1.10
- 1.11 - 1.15
- 1.16 - 1.22
- 1.23 - 1.31
- 1.32 - 1.41
- 1.42 - 1.54
- 1.55 - 1.70
- 1.71 - 1.89
- 1.90 - 2.13
- 2.14 - 2.42
- 2.43 - 2.78

Locations:
- Norsewood
- Feilding
- Sanson
- Ashhurst
- Woodville
- Palmerston North
- Shannon
- Pahiutua
- Levin
- Eketahuna
- Foxton
- Otaki
Manawatu region: Other poultry associated STs

Relative Risk
- 0.63 - 0.81
- 0.82 - 0.94
- 0.95 - 1.02
- 1.03 - 1.07
- 1.08 - 1.11
- 1.12 - 1.13
- 1.14 - 1.17
- 1.18 - 1.22
- 1.23 - 1.30
- 1.31 - 1.43
- 1.44 - 1.61
- 1.62 - 1.89
- 1.90 - 2.32
- 2.33 - 2.96
- 2.97 - 3.92
Chi sq 18.13, P<0.011
N=71 ruminant
N=394 poultry

Case-case comparison
Generalised outbreak

ST-474 and ST-190 responsible for over 40% of 2006 winter outbreak cases...nationally
Auckland MLST (T. Wong)

Pink = human
Rest poultry
Source attribution

- Molecular tools and modelling
  - Proportional similarity
    - Area of overlap
  - Dutch model
    - Simple deterministic assignment
  - Hald model
    - Bayesian model assignment with uncertainty
  - Island model
    - Population genetics approach
Proportional Similarity Index (PS)

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

- Model prevalence uncertainty
- Hierarchical model for bacterial parameters (q)
- Exponential prior for source specific parameters (a)
- Omit food consumption weights (M)
- Include potentially pathogenic subtypes
Island model (Wilson et al 2008)

- Population genetics approach
- Genealogical method based on ‘coalescent’
  - Cross-validation
- Use MLST data in animal populations (“islands”) to estimate:
  - Mutation rates
  - Recombination rates
  - Migration rates (inter-host transmission)
- From these estimate ‘migration’ into human population
  - Source attribution

Tracing the Source of Campylobacteriosis

Daniel J. Wilson¹ᵃ, Edith Gabriel²ᵇ, Andrew J. H. Leatherbarrow³, John Cheesbrough⁴, Steven Gee⁴, Eric Bolton⁵, Andrew Fox⁴,⁵, Paul Fearnhead¹, C. Anthony Hart⁶, Peter J. Diggle²
Source attribution in New Zealand: Island model
Source of human cases, Lancashire, England

Figure 2. Probability of source for human cases. The source probability for 1,231 human cases (vertical columns) is depicted for Chicken (yellow), Cattle (red), Sheep (blue), Pig (pink), Bird (green), Rabbit (purple), Sand (beige) and Water (cyan). The isolates have been ordered horizontally to aid visualization.
Source attribution: comparing models

Attribution of 520 human cases in the Manawatu

Left column: Dutch model
Middle column: modified Hald model
Right column: Island model
Comparing models

- PS index and Dutch models easy to compute
- m. Hald and Island models include more of information from data – more complex
- m. Hald model captures food and pathogen factors
- Island model can assign all human cases
- Therefore... recommend multiple, comparative approach...
Campylobacter in Poultry –
Risk Management Strategy
2007 - 2010
Poultry industry intervention trials

Post spin-chill:

Tasker blue (Sulphuric acid and copper)

Sanova (ASC)

Pre spin chill:

Inspexx (hydrogen peroxide and peroxyactic acid)
Poultry - count data at retail

Company A

Company B

Company C
Dramatic drop in risks from chicken

Consumers can feel less nervous about putting chicken on the table after a dramatic reduction in food-poisoning rates.

Notifications of campylobacter cases have fallen by more than a third in the past year, suggesting poultry producers are finally limiting the spread of the bacteria on farms and in processing plants.

The downturn is accelerating – notifications in the first four months of this year are down by more than half.

Contaminated chicken is the biggest single source of campylobacter illness, which causes vomiting, diarrhea, fever, headaches and muscle pain.

New Zealand’s reported rates of the illness are higher than those of comparable countries, and chicken is blamed for about 50 per cent of cases.

Up to 1000 people are hospitalised each year because of campylobacter. 
Recent trends in NZ

Decline in carcase counts observed
Mandated standard and performance target set

NMD
50% reduction
Conclusions

• NZ has unique epidemiology
  - Rural ruminant exposure in young children
  - Urban poultry across all ages
  - Dominant strain: ST474
• Source attribution modelling
  - Tools advanced in recent years
  - Applied to *Campylobacter* identified food, particularly poultry, most important source, cattle second
• Focussing on poultry - early signs of success
• Environmental exposures less well defined
  - May become more important
  - Ruminants and wildlife
Acknowledgements

- **Staff - lecturers**
  - Dr Eve Pleydell, Dr Deb Prattley
- **Postdocs / RAs**
  - Dr Simon Spencer, Dr Jonathan Marshall, Dr Anne Midwinter, Dr Julie Collins-Emerson
- **Lab team:**
  - Rebecca Pattison, Rukhshana Akhter, Errol Kwan, Lynn Rogers, Isabel Li, Jim Learmonth, Anthony Pita, Sarah Vaughan,
- **PhD students**
  - Petra Mullner, Vathsala Mohan,
- **Masters students**
  - Particularly Tui Shadbolt,....
- **ESR** - Phil Carter, Sharla McTavish
- **AgResearch** - Grant Hotter
- **CDRP team**
  - NIWA - Graham McBride
  - ESR - Rob Lake
  - NZFSA - Peter van de Logt
- **Palmerston North Hospital / MedLab**
- **Massey** - IMBS, IFNHH, IFS
  - Allan Wilson Centre
- **Universities of Liverpool, Lancaster, Oxford**
- **Industry**

NZFSA-funded