Source attribution modelling

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Source Attribution

There are many potential sources of infection and pathways through which that infection may occur.

Source attribution is the process of determining which proportion of a particular disease is acquired from a given source and through a given pathway.

Knowledge of which sources are contributing the most to the disease burden allows targeting of intervention strategies.

How can we determine the origin of a human case?

- Often cases are sporadic rather than being part of outbreaks (e.g. *Campylobacter*).
- Epidemiological information associated with a case may be minimal.
- We often have no information on the exposure for sporadic cases.
- Often the only thing we have is genotype information for each case.

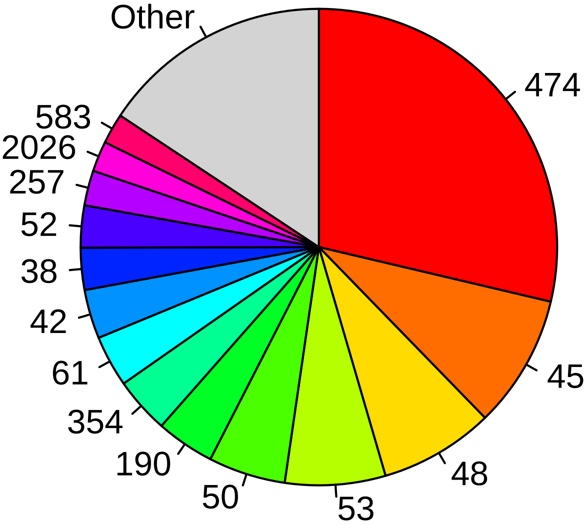
MLST for *Campylobacter*

Seven housekeeping genes around the genome (loci).

The combination of alleles at the seven loci gives the **multilocus sequence type**.

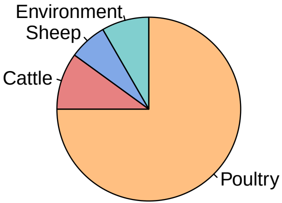
ST	aspA	glnA	gltA	glyA	pgm	tkt	uncA
474	2	4	1	2	2	1	5
61	1	4	2	2	6	3	17
190	2	1	5	3	2	3	5
2381	175	251	216	282	359	293	102
48	2	4	1	2	7	1	5

Human MLST types

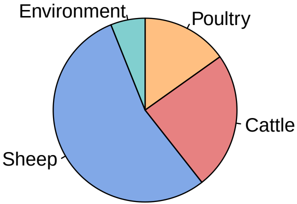


Source specific types

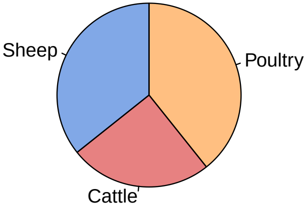
ST-474: $n = 60$



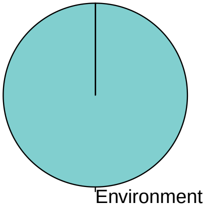
ST-61: $n = 33$



ST-190: $n = 28$



ST-2381: $n = 22$



Attribution using MLST

For each human ST, assign to the most likely source, given the distribution of STs on the source.

Use **Bayes Theorem**

$$P(\text{source} = k | \text{ST} = i) = \frac{P(\text{ST} = i | \text{source} = k) P(\text{source} = k)}{\sum_k P(\text{ST} = i | \text{source} = k) P(\text{source} = k)}$$

where

- $P(\text{ST} = i | \text{source} = k)$ is the distribution of STs on each source.
- $P(\text{source} = k)$ is the prior probability that an isolate picked at random is from source k.

The Dutch model

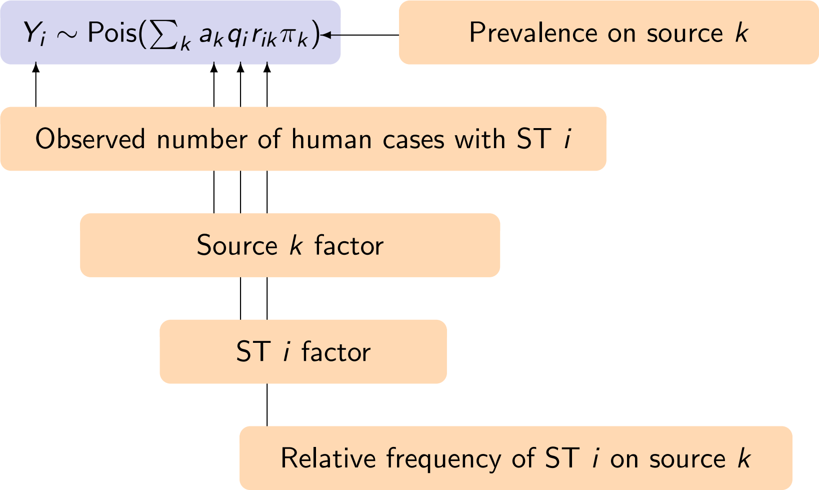
- The simplest way to estimate $P(\mathrm{ST} = i | \mathrm{source} = k)$ is to use the relative frequency r_{ik} of ST i on source k.

- The simplest way to estimate $P(\mathrm{source} = k)$ is to assume *apriori* that all sources are equally likely.

- This yields the Dutch model:

$$P(\mathrm{source} = k | \mathrm{ST} = i) = \frac{r_{ik}}{\sum_k r_{ik}}$$

Hald model (Hald et. al. 2004, Müllner et. al. 2009)



$Y_i \sim \text{Pois}(\sum_k a_k q_i r_{ik} \pi_k)$

Prevalence on source k

Observed number of human cases with ST i

Source k factor

ST i factor

Relative frequency of ST i on source k

Hald model

- Estimates the source and isolate-specific parameters a_k and q_i by matching up the expected number of human cases of type i with the observed number of cases.

- We have an identifiability problem, in that we have $I + K$ parameters to estimate, and only I data points (number of human isolates of each type).

- Add in some prior information to reduce this problem and fit in a Bayesian framework.

Island model (D. Wilson, 2008)

Model the sampling distribution of the allelic profiles on the sources by assuming that the observed sequences arise due to:

- **Mutation**, where an allele at a locus is novel.
- **Migration** between sources, where the allelic profile has been observed before in one of the sources, including the current one.
- **Recombination**, where the allele at a given loci has been observed before but not in this allelic profile.

Island model

Let M_{jk} is the probability of sampling an allele from source k that has already been observed in source j.

Let f^l_{aj} be the frequency with which allele a has been observed at locus l in those genotypes sampled from source j.

Then, in the absense of mutation and recombination, the probability of sampling allele a at locus l in source k is

$$B^l_{ak} = \sum_{j=1}^{K} M_{jk} f^l_{aj}$$

Island model: Unlinked loci

Let μ_k be the probability of sampling an allele from source k that is a novel mutant (among all sources).

Then if we assume the loci are independent, the sampling formula for observing sequence $y = (y^1, y^2, \dots, y^7)$ on source k is

$$\phi(y|k) = \prod_{l=1}^{7} \begin{cases} \mu_k & \text{if } y^l \text{ is novel,} \\ (1-\mu_k) B^l_{y^l k} & \text{otherwise.} \end{cases}$$

Island model: Linked loci

In the absense of mutation, recombination and migration, we assume that a genotype y sampled from source k will be identical to one already observed in the sample of source k.

Migration allows y to be a copy of a genotype c from a source C other than k.

Mutation and recombination mean that y may contain novel alleles, or comprise of a novel combination of existing alleles.

Island model: Linked loci

Let μ_k be the probability, per locus, that a genotype sampled from source k contains a novel mutant allele.

Let R_k be the probability, per locus, that a genotype sampled from source k has undergone recombination. The allele is independently sampled from other alleles observed at that locus.

The sampling formula for observing sequence $y = (y^1, y^2, \dots, y^7)$ in source k is

$$\phi(y|k) = \sum_c \frac{M_{Ck}}{N_C} \prod_{l=1}^{7} \begin{cases} \mu_k & \text{if } y^l \text{ is novel,} \\ (1-\mu_k) R_k B^l_{y^l k} & \text{if } y^l \neq c^l \\ (1-\mu_k)\left[1 - R_k(1 - B^l_{y^l k})\right] & \text{if } y^l = c^l \end{cases}$$

Island model: Linked loci

ST	aspA	glnA	gltA	glyA	pgm	tkt	uncA
474	2	4	1	2	2	1	5
?	2	4	1	2	29	1	5

We have a novel allele at the pgm locus. We assume this genotype has arisen through **mutation**.

Island model: Linked Loci

ST	aspA	glnA	gltA	glyA	pgm	tkt	uncA
474	2	4	1	2	2	1	5
?	2	4	1	2	1	1	5

The pgm allele looks familiar...

ST	aspA	glnA	gltA	glyA	pgm	tkt	uncA
45	4	7	10	4	1	7	1
3718	2	4	1	4	1	1	5

But we haven't seen this genotype before. We assume it arose through **recombination**.

Island model: Linked loci

ST	aspA	glnA	gltA	glyA	pgm	tkt	uncA
474	2	4	1	2	2	1	5
?	2	4	1	2	2	1	5

This is just 474 - we've seen this before, but possibly not in this source. We assume it arose through **migration**.

Island model: Likelihood of human sequences

Let F_k be the proportion of human sequences h_i from source k.

The posterior distribution of F, given the probabilities μ, M and R is

$$p(F|h,\mu,M,R) \propto \prod_i \left[\sum_k F_k \phi(h_i|k)\right] p(F)$$

where $p(F)$ is the prior distribution, where we assume each source is equally likely.

Island model: Parameter estimation

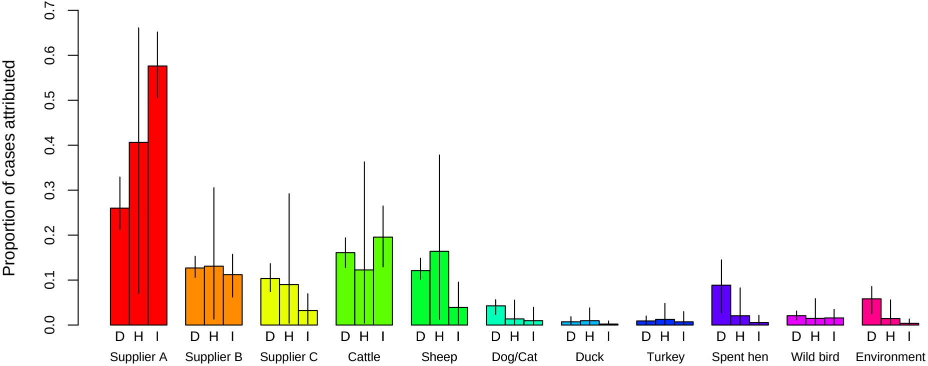
The parameters are estimated in two passes:

- The probabilities μ, M, and R are estimated from the known source cases with likelihood approximated by a leave-one-out approach.

- For each posterior sample of these, an MCMC side-chain is run to estimate the probabilities F_k.

- Within the MCMC, various Metropolis-Hastings updates are used.

Dutch, Hald, Island attribution



Temporal associations: Attribution through time

- Extend existing source attribution models to be dynamic in time.
- Assume mutation, recombination, migration rates are static, as are the distribution of STs on sources.
  - Due to practicality (lack of data) - may be extended later.
- Assume the probability of sources F_j may change through time.

Temporal model for F_j

Assume F_k arises from a linear model on the logit scale.

$$F_{kt} = \begin{cases} \dfrac{e^{-f_{kt}}}{1 + \sum_{k=1}^{K-1} e^{-f_{kt}}} & k = 1 \dots K-1, \\ \dfrac{1}{1 + \sum_{k=1}^{K-1} e^{-f_{kt}}} & k = K. \end{cases}$$

where

$$\begin{aligned} f_{kt} &= X_t \beta_k + e_{kt}, \\ e_{kt} &\sim \text{Normal}(\rho_k e_{k(t-1)}, \sigma_k^2). \end{aligned}$$

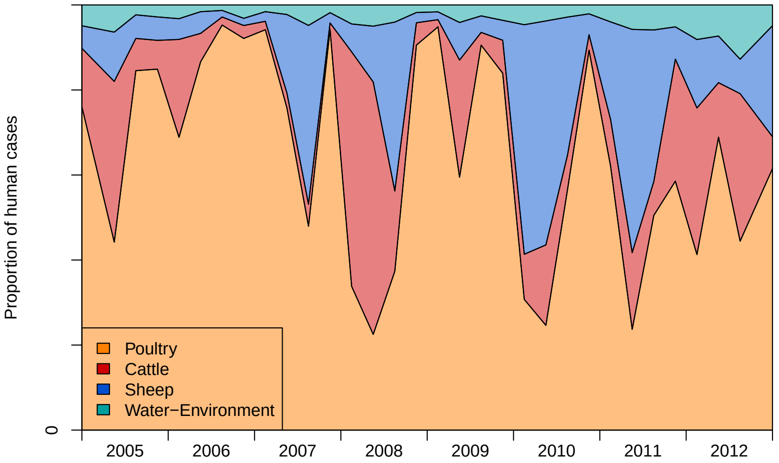
- X is the design matrix, specifying covariates in time.
- β_k measures the effect of those covariates on F_k.
- ρ_k is an auto-correlation AR(1) parameter.
- σ_k^2 is the variance.

Temporal model for F_j

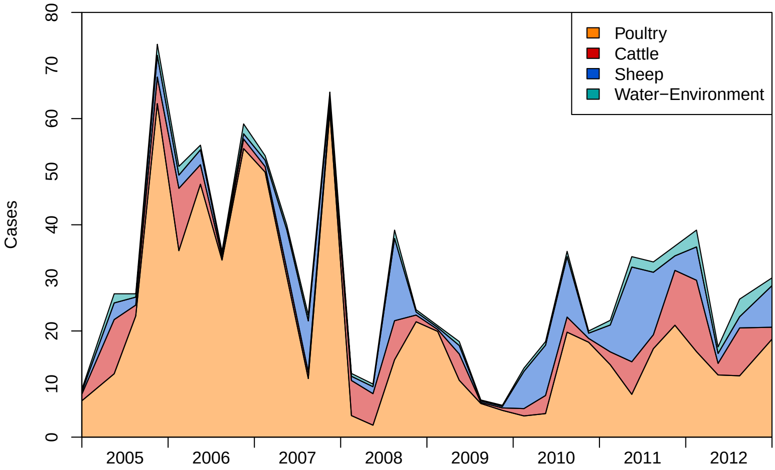
Start simple:

- Assume $X_t = 1$ for all t.
- Thus, the model represents potentially different means within each group.
- Assume also that $\sigma_k^2 = \sigma^2$ for all k.
- Let t be quarters from 2005-2012.

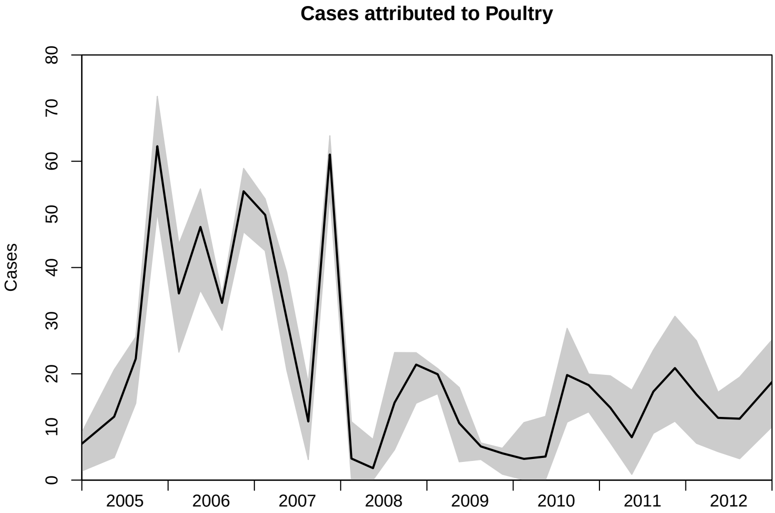
Campylobacter in the Manawatu



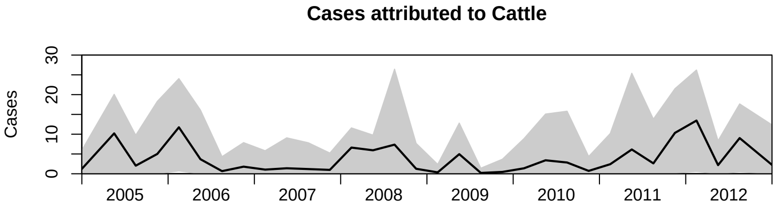
Campylobacter in the Manawatu

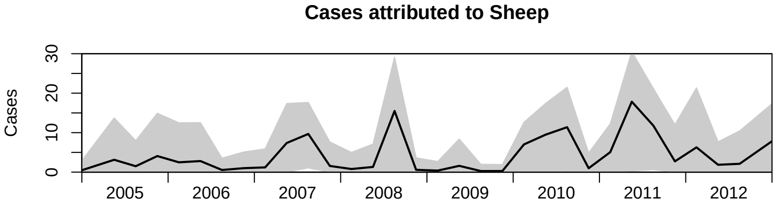


Campylobacter in the Manawatu

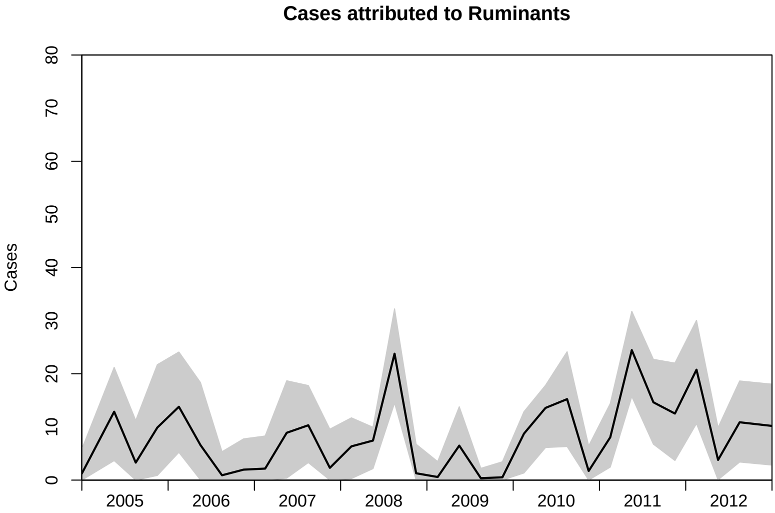


Campylobacter in the Manawatu

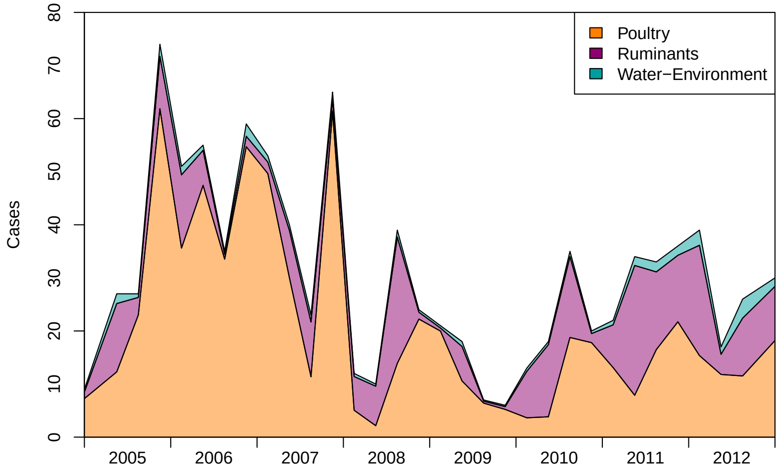




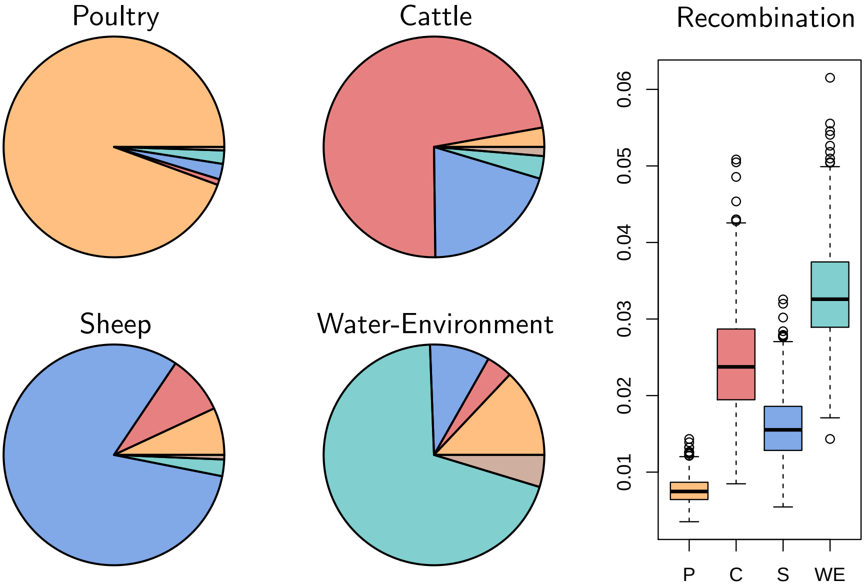
Campylobacter in the Manawatu



Campylobacter in the Manawatu



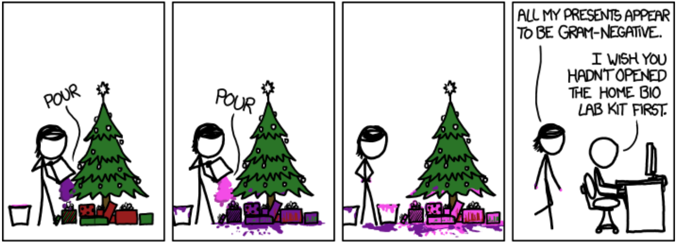
Migration, mutation, and recombination



Future work

- Improve time series model. e.g. investigate seasonality.
- Investigate the effect of intervention in poultry.
- Investigate temporal changes in ST distribution on sources.

Thanks for listening


POUR
POUR
ALL MY PRESENTS APPEAR TO BE GRAM-NEGATIVE.
I WISH YOU HADN'T OPENED THE HOME BIO LAB KIT FIRST.