A RESEARCH PLAN FOR ENTERIC ZOONOSES: MODELLING THE LINK BETWEEN HUMAN HEALTH AND THE ENVIRONMENT; IDENTIFYING EFFECTIVE INTERVENTIONS

Prepared by the Enteric Zoonotic Disease Modelling Group, August 2006

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Contents

INTRODUCTION

This report concerns a three-year research programme for modelling the risks of enteric zoonoses in New Zealand. The need for such a programme is described, and the key components and beneficial outcomes are identified. The emphasis in this work will be on campylobacteriosis, given its dominance in New Zealand's reported zoonoses. However, the underlying approach is applicable to other zoonotic pathogens.

Some of the work identified should be carried out by the Modelling Group, combining their knowledge and skills to provide a global view of the ecology and risk factors of zoonotic pathogens. Other aspects lie in the expertise of particular groups (for example genotyping studies, which have the potential to greatly enhance the understanding of sources and transmission of zoonotic pathogens). Modelling is proposed as a holistic framework to guide future management actions and research efforts.

The following sections of this report give the background to the issues, a summary of current understandings, and then identify a research plan.

WHAT ARE THE ISSUES?

Economic cost

The impact of enteric zoonoses in New Zealand in terms of human illness has not been specifically determined. Nevertheless, a useful guide is the impact of infectious intestinal disease, which has been estimated as between approximately 340,000 and 800,000 cases per year (Lake *et al*. 2000, and pers. comm.).[1] The economic cost of these illnesses was estimated in 2000 as between approximately $120 and $220 million (Scott *et al*. 2000). The majority of these cases were caused by enteric zoonotic pathogens.[2]

It is reasonable to consider this cost as an underestimate, as it only includes direct medical costs, the value of lost production (paid and unpaid), and the value of lives lost. The considerable medical costs involved in the long term consequences of infectious intestinal disease (e.g. Guillain Barré syndrome, reactive arthritis, haemolytic uraemic syndrome) were not included; neither was loss of quality of life from these conditions. These costs have been a major component of overseas estimates of the same burden of illness (e.g., for the USA—Buzby *et al.* 1996). There have also been reports of significantly increased risk of mortality for up to one year following illness caused by some enteric zoonoses (Helms *et al.* 2003).

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[1] These figures will be improved in 2007, under ESR's Acute Gastrointestinal Illness Study.
[2] The major exception is norovirus, which causes large numbers of cases (approximately 25% of the total) but has less economic impact (approximately 7% of the total), being a milder illness.

Campylobacteriosis

The most significant enteric zoonosis in terms of human illness is campylobacteriosis, which causes over 60% of the infectious illness cases above, and contributes over 70% of their cost of illness. Campylobacteriosis was also ranked highly as an issue during a risk ranking exercise (Cressey & Lake 2005). Recently, Baker *et al*. (2006) have noted, in respect of campylobacteriosis, that "… further research and intervention studies should be public health priorities in this country".

Much of the risk for campylobacteriosis is associated with foodborne transmission (Lake *et al.* 2005). However, a focus on food-related interventions may miss important aspects of the issue. One is that the potential benefits from interventions must been seen in context with other exposures (McBride *et al.* 2005), including drinking water, recreational water and occupational contact with animals or animal wastes. Another is the pathogen's "delivery chain" from animals to humans. This is defined as the sequence of steps leading to human exposure, which will include not just infection or contamination of the food, but the source(s) of that infection or contamination. Transmission of zoonotic pathogens through the environment will play an important role. A general schematic is shown in Figure 1.

Effective control measures are therefore likely to involve some combination of environmental interventions (reviewed by Collins 2005a) and food preparation/processing interventions (Lake 2005), the balance of the two having to do with the strength of the link between enteric zoonoses and environmental contamination that this project seeks to address.

We propose that this research package should be focused on *Campylobacter*, for the following reasons.

- New Zealand's reported rate of campylobacteriosis is the highest among all countries that report its incidence, and it has shown a strong and continuing tendency to rise (Till & McBride 2003). The current reported rate has exceeded 400 cases per 100,000 people (for the 12 month period to May 2006).
- Environmental surveys have found it to be present to a surprising degree, even in recreational waters (McBride *et al.* 2002)—in contrast to other zoonotic pathogens. The implication is that this prevalence somewhat simplifies research studies, because it is so often present in environmental sampling.
- We have more detailed understandings and more data concerning the role of *Campylobacter* in the environment than is the case for other zoonotic pathogens.
- Comprehensive summaries of pertinent aetiological issues are available (Wilson 2005, Lake 2005).
- Most importantly, effective environmental interventions for *Campylobacter* can be expected to cause the loading of other zoonotic pathogens onto the environment to also be reduced.

Why should this work be done?

While the numbers of cases and economic burden of enteric zoonoses as outlined above may be less than public health problems such as obesity and diabetes, they are substantial, and increasing. But enteric zoonoses are also important for other reasons, including potential impacts on New Zealand's agricultural produce and our "clean, green" environmental image. Human illness with enteric zoonotic pathogens occurs as a result of contamination of our environment, animals, water and food with faecal material. More effective controls are needed.

Furthermore, results from modelling studies can modify our understandings. For example, a preliminary risk assessment for campylobacteriosis (McBride *et al*. 2005) identified cross-contamination (e.g., from chicken to salad) as the most important exposure, whereas that route had not been identified in an earlier epidemiological study (Eberhardt-Phillips *et al.* 1997).[3] That preliminary analysis also indicated new possible transmission routes and the need to better quantify the animal contact route.

Results of modelling studies can also directly inform public policy. For example, a quantitative risk analysis for direct exposure of swimmers with water contamination (by *Campylobacter*) now forms the basis of New Zealand's water quality guidelines for freshwater recreational areas (MfE/MoH 2003).

Modelling offers the best hope of effectively tackling the difficult problem of identifying effective interventions—Lake (2005) notes in respect of poultry that "Despite considerable research by the industry and scientific community into on-farm and processing options, a "magic bullet" has yet to be found". This is in contrast to effective control of *Salmonella*, for which presence in poultry in New Zealand retail product has been reduced to amongst the lowest in the world. Modelling research may show certain interventions to be both practicable and effective. In its absence, the existence and effectiveness of that intervention may not be discovered.

The role of modelling

Scientific endeavour is focused, one way or another, on modelling. This can take the form of a conceptual diagram or a detailed set of mathematical equations and associated computer software. A conceptual diagram we have been using for campylobacteriosis is shown in Figure 1. It is in essence a holistic approach, whereby the delivery chains, exposure locations, research gaps, and effective interventions and their impacts on disease burden can be considered simultaneously. This integrates a number of focused research efforts into a broader picture. It sets various components in context, e.g., the relative importance of environmental contamination versus food processing, or the relative contribution of dairying versus other farming activities to the environmental loading of zoonotic pathogens.[4] It is always beneficial to pose models at the start of major research programmes, and modify them as necessary as the work proceeds and more information becomes available.

Once tested to a point where some confidence can be had in their results, models can perform many "what if" calculations, e.g., trading off the consequences of three categories of interventions: deliberate environmental interventions (e.g., on-farm "Best Management Practices", pathogen-specific vaccinations), natural interventions

[3] The preliminary relative risk assessment also indicated that occupational contact, poultry meat and untreated drinking water are important risk factors.

[4] A national survey of freshwater recreational sites has indicated that catchments dominated by sheep farming may be contributing similar (if not greater) quantities of *Campylobacter* (McBride *et al*. 2002).

(e.g., floods) and human consumption interventions (e.g., disinfection or freezing of poultry meat).

Models also inform surveillance and forecasting. A major advantage of risk some forms of models, e.g., the Bayesian risk model of Hald 2005, is that they are able to be updated on a yearly basis and therefore can be used as a tool to inform surveillance and forecasting.

Modelling is also accumulative, building on the results of previous studies, such as in the preliminary relative risk assessment for campylobacteriosis McBride *et al*. (2005).

Ability of the Modelling Group to deliver useful results

All members of the Modelling Group have a track record of delivery in many aspects of risk analysis, microbiology and environmental modelling. Furthermore, all the major disciplines necessary for a holistic analysis are represented on the Group.

Full account will be taken of all current understandings concerning *Campylobacter* sources, routes, transmissions and health effects, as summarized in the Appendix.

RESEARCH PLAN

As mentioned in the introduction, some of the work identified should be carried out by the Modelling Group, combining their knowledge and skills to provide a global view of the ecology and risk factors of zoonotic pathogens. Other aspects lie in the expertise of particular groups (for example typing studies, which have the potential to greatly enhance the understanding of sources and transmission of zoonotic pathogens).[5] The Modelling Group proposes to update existing models with recently available information (e.g., as given by Collins *et al*. 2005), and to develop new models.

Evaluation of progress will be made at regular intervals, in association with the Enteric Zoonotic Disease Steering Committee.

The Plan is aimed at synthesizing all the work done to date, with new findings, to reap the full benefit in investments made. The following priorities are deemed appropriate to achieve this goal as soon as possible.

Priority 1 **Update existing models** with information that has recently become available; for example, ESR's poultry model, CDRP-funded project on environmental pathogens in the environment (Collins *et al*. 2005a), ESR's Ambassadors for Sustainability project (Gilpin 2006), NIWA's SPARROW modelling (Alexander *et al*. in prep.). Much work has been done in recent years. It is important that all this work is now collated and its implications assessed. This will enable best use of research done to

[5] Although the simple concept of "sources" may not adequately describe the complex feedback cycles of campylobacter ecology, breaking the key components of such cycles is a key to identifying effective intervention measures.

date, prevent duplication, pose new research questions or amend current ones and thus guide priorities for research.

Priority 2 **Revise the preliminary ranking of sources and reservoirs** (McBride *et al*. 2005) of *Campylobacter* and their probable relative contribution to cases of human campylobacteriosis.

Priority 3 **Develop new models of** *Campylobacter* cycles in the environment, update the ranking of sources and reservoirs, and identify effective interventions.

Priority 4 **Develop economic models** to establish the most cost-effective ways in which a lower incidence of campylobacteriosis can be established.

Objective and scope

The objective will be to identify the key campylobacteriosis delivery chains and so identify effective mitigation measures.

This will include the investigation of the many possible pathways that lead to human infection and disease, including both the environment and food. The wide scope of this project is appropriate since only a comprehensive study will be able to identify adequately the impact of the various risk factors and the opportunities for reduction of the campylobacteriosis disease burden of the New Zealand population.

Approach

The modelling will comprise three components: *Attribution (human exposure*), *ecological/environmental,* and *Linkages*.

Attribution models have to do with exposures and their effects. This will include new work on Bayesian typing for source assessments,[6] and improvements to existing comparative exposure work (using Monte Carlo techniques) on relative risk modelling for process pathways.[7] New genotyping methods are offering powerful new methods for source tracking of bacteria. Phenomenological approaches will be incorporated wherever possible. For example, building on new understandings of how differential immunity between ages and population groups (McBride & French 2006).

The Ecological modelling is concerned with explaining how pathogenic *Campylobacter* get from animals to the point of human exposure. This will use a number of existing catchment modelling approaches, especially those to be embedded in the "CLUES" package,[8] and advances in catchment bacteria modelling (Collins & Rutherford 2004; Muirhead *et al*. 2004; Kay *et al*. 2005, Wilkinson *et al.* 2006). It will include new modelling approaches for the effect and efficacy of natural interventions and artificial interventions, and for animal re-infection.

[6] Based on Danish Salmonella model (Hald *et al*. 2004).
[7] McBride *et al*. (2005).
[8] CLUES – Catchment Land Use for Environmental Sustainability (Woods *et al.* 2006). This model includes the SPARROW national model (Elliott *et al*. 2005), recently calibrated for *E. coli* and *Campylobacter* over the whole New Zealand landscape at 30 m resolution (Alexander *et al.*, in prep.).

The Linkages modelling will seek to tie these two strands together.

Full details of the work proposed for each component are given on Tables 1–3. Figure 2 indicates the interactions between them.

Final product

This Modelling Group will draw on existing and needed work identified in Tables 1-3 to develop a set of linked ecologic models, each devoted to an area of importance in zoonotic transmission, with over-arching models concerning attribution. A single stand-alone model is not desirable. The output therefore will comprise reports from the Modelling Group, informed by the application and output of these models. There will need to be regular liaison with industry and regulators in refining the research questions and approaches, as indicated on Figure 2.

Some of the items shown in Tables 1–3 should be undertaken by individual group members or organisations, and others by the group as a whole. Allocations for these tasks and associated funding would require further consultation, including the Enteric Zoonotic Disease Steering Committee, once overall funding has been obtained.

Research team members

All team members bring unique skills to this project, including:

- statistics
- mathematics
- molecular epidemiology
- health surveillance
- risk modelling
- environmental modelling (transmission over the landscape)
- microbiology
- veterinary science
- food safety
- ecological studies (interactions between animals and humans and their environment, e.g., for animal re-infection patterns)

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Table 1: Attribution models

Component	Methodology	Relevant projects	New projects
Occupational contact	• Studies of workers in high risk occupations. • MLST of human cases with putative occupational exposure. • Improve animal contact module with data on farm type, size of populations exposed, prevalence of animal carriage.	• Pulford *et al.* (2005). • ESR project on quantity of water ingested by recreational pursuits, drinking water.	• Extend Bayesian models to occupational exposure. • Assess size of populations exposed. • Refine mechanistic exposure models. • Use approach of Dutch divers infection study (Schijven & de Roda Husman 2006).
Other exposures	Use information on overseas travel, pets (especially for toxoplasma); shellfish, swimming, drinking water, birds.	• Massey genotyping thesis. • Donnison *et al*. (1999). • Donnison (2006). • Schönberg-Norio *et al*. (2004). • French *et al.* (2005).	• Carriage by pets (overseas studies variable). • Shellfish surveys.
Red meat & poultry	New data and model on retail to consumption exposure.	NZFSA-ESR project for 2006/7 Incorporation of risk models for *Campylobacter*.	None needed?
Person-person transmission	Follow giardiasis work leads.	?	• Re-examine MAGIC data. • Use UK DoD smallpox modelling example (Gani & Leach 2001).
Campylobacter strain typing	MLST and PFGE of strains from human clinical cases, poultry, red meat and the environment (and pets?).	• ESR HRC proposal (exposure and clusters). • Massey Manawatu sentinel study, including demographics. • ESR typing, Ashburton results (Devane *et al*. 2005).	• Type the FMRP data versus catchment category? • Strain genotype versus age study.
Considering differential immunity	Build exact analytical and numerical approximation models.	• McBride & French (2006). • ESR study of case rates as a function of occupational groups, using EpiSurv.	Extend model to temporal (as well as age); parameter sensitivities; cross-strain. immunity; collaboration with Havelaar & Strachan (Miller *et al.* 2005).
Food handling / preparation	Under consideration.	List being compiled.	Identifying exposures through food service channel (focus on restaurants?).

Table 2: Ecological models

Component	Methodology	Relevant projects	New projects
Include sheep and poultry farms, and wildlife	Extending existing models (including SPARROW approaches) to include a distribution of farm and landscape types.	• CLUES (Woods *et al*. 2006). • NIWA ESR subcontract for Toenipi catchment *E. coli*/*Campylobacter* modelling (Wilcock *et al.* 2006). • SPARROW (Elliott *et al*. 2005). • Models of dairy herd transmission dynamics (Xiao *et al.* 2005). • ESR/Massey work on persistence in cowpats (Gilpin 2006).	• Extend SPARROW to do seasonal concentrations. • Add intervention overlay to SPARROW. • Integrate with (inform with?) within-farm and between-farm transmission models.
Catchment dynamics	Extend catchment modelling techniques. Compare with Sydney studies (Ferguson *et al*. 2003).	• *Campylobacter* attenuation studies (Collins *et al*. 2004, Ross & Donnison 2003). • French *et al.* (2005).	• Extend models to diverse landscapes.
Impact of animal litter disposal	Incorporation of poultry litter disposal and other animal wastes into risk models.	• Data on use on-farm? Home use? • ESR study of poultry on-farm factors (*Campy* & *Salmonella*).	• Survey of use and disposal.
Disturbance events	Incorporation of spatial events (e.g., flooding, sediment stirring) into risk models (particularly for coastal effects).	• NIWA/Agresearch studies (Muirhead *et al*. 2004). • Freshwater mussel *Campylobacter* data (Donnison & Ross 1999).	• Extend to different streams, including larger rivers? • Survey pathogens in marine shellfish.
Pathogen transmission between & within animal groups	Studies of inter and intra-management group transmission, multi-group mathematical modelling.	• Turner *et al*. (2003). • Matthews *et al.* (2006). • French *et al.* (2005). • Turner *et al*. (2006).	• Extend models to between-farms, between-animals. • Expand from dairy to other animals (ambitious).
Carriage rates	Simple incorporation.	• Gilpin (2006). • Clough *et al*. (2003). • Turner *et al*. (2003, 2006).	• Shedding rates and patterns (over: age groups, time, different species). • Distinguish animal from herd prevalence.
Sewage, biosolids/septic tanks	Simple incorporation.	• ESR surveys(Leonard). • Mangere Wastewater Treatment Plant data.	• Keep under review. Can be human → environment → human?

Table 3: Linkages model

Component	Methodology	Relevant projects	New projects
Incorporating all modelling	• Integrating farm environmental and human illness models. • Using environmental aspects to predict changes in exposure model. • Extrapolate to *relative* changes in disease burden.	None!	• Incorporating and communicating model uncertainty. • Consider illness vs. infection argument. When does it matter? • How to interface with risk management. • Use-based metrics (ALOP → FSO, Performance Objective, Performance Criteria)—how do models inform them? (Havelaar *et al.* 2004)

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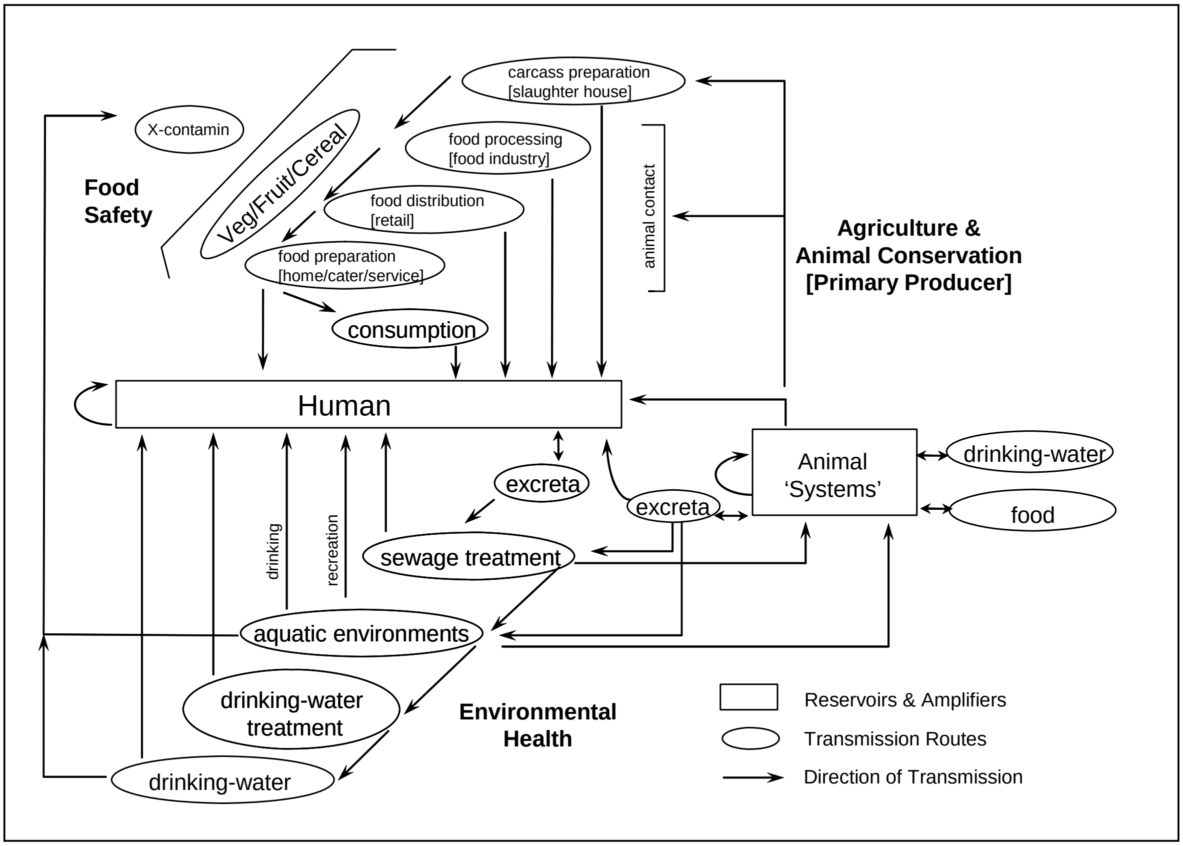

Figure 1: Transmission diagram for *Campylobacter* ecology: reservoirs, amplifiers and transmission routes.

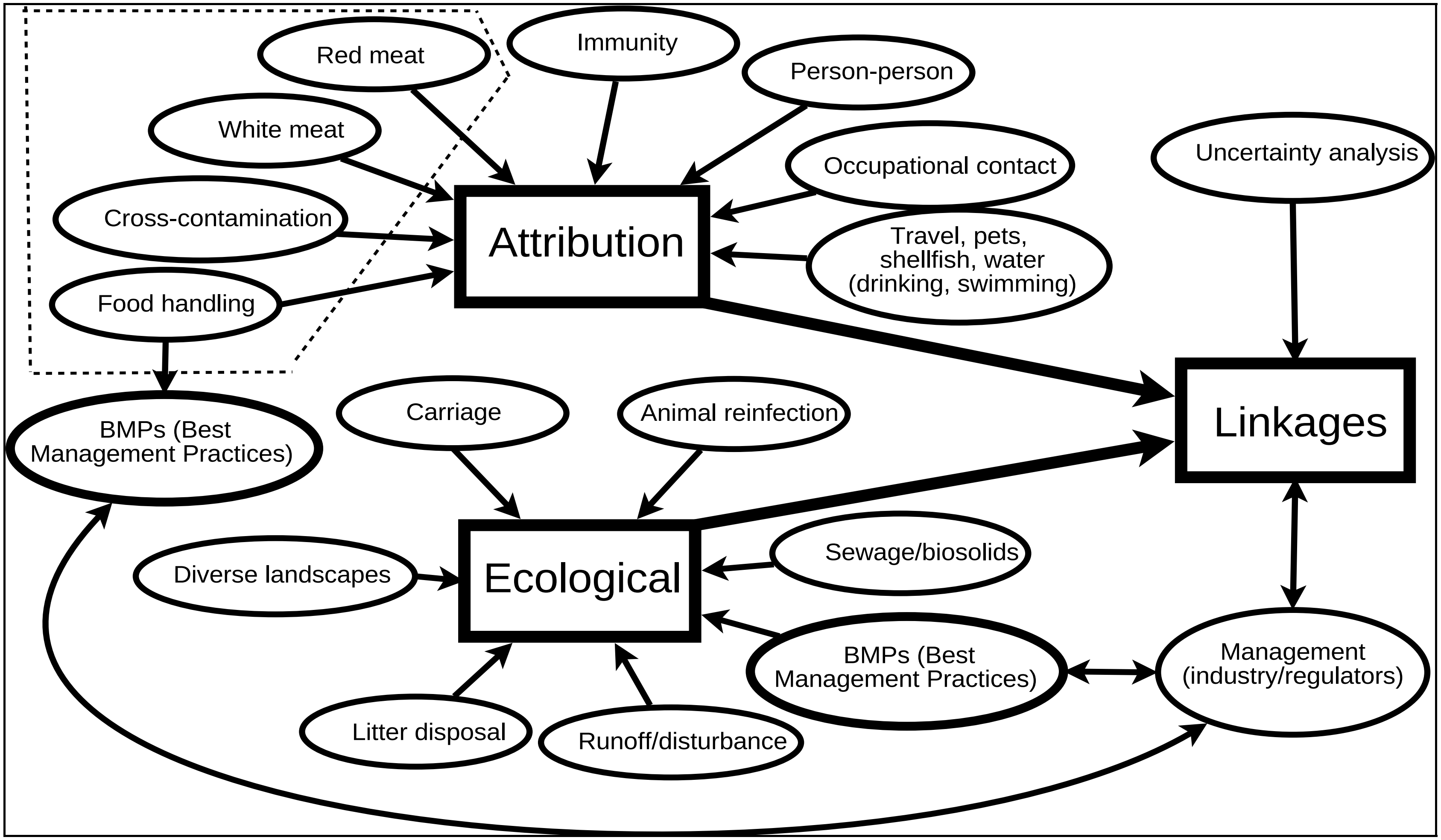

Figure 2: Campylobacteriosis influence diagram for inputs and relationships between the Attribution (Human Health), Ecological and Linkages models. Boxes depict modelling efforts, ellipses are key influences, and arrows are information flows.

APPENDIX: CURRENT UNDERSTANDINGS

Aetiology

A detailed review of the aetiology of campylobacteriosis has identified that there appears to be "sufficient evidence for contaminated food having a causal relationship with campylobacteriosis in the New Zealand setting" (Wilson 2005). A more detailed consideration of many factors by Lake (2005) indicates that poultry consumption is the key food-related risk factor, while overseas travel and animal contact have important but lesser roles. He also found that the "presence of *Campylobacter* in environmental waters (and the environment generally) is likely to play an important role in the cycling of the bacterium in animals, causing infection in cows, pigs and sheep, and possibly poultry." Data on the prevalence of *Campylobacter* in farm animals is sparse, but such data as we have indicate that it may be on the order of 50%.

ESR's *Public Health Observatory*[17] contains full summaries of relevant human health statistics (including the unexplained feature that reported campylobacteriosis rates are higher among males than females, as is true also in overseas jurisdictions).

The aetiology of other zoonoses is less well-known. For example, Learmonth *et al.* (2004) have noted that little is known about the genetic characteristics, distribution and transmission cycles of *Cryptosporidium* species in New Zealand, apart from the well-recorded seasonality of cryptosporidiosis in rural regions (Hood 2003).

Reservoirs

By "reservoir" we mean a source, characterized by long-term survival or growth of the zoonotic pathogen. The current information on this topic for livestock, humans, cowpats, sediments, water, soil (to a limited extent), wildlife, birds and pets is summarized by Gilpin (2005). Skelly 2002 (in constructing the "Water Simple" model) found that cattle were the largest reservoir (although chickens were not included in the analysis). Further data is given by Skelly & Weinstein (2003).

Devane *et al.* (2005), using PFGE techniques, have reported *C. jejuni* serotypes in 12 matrices in the Ashburton area, indicating that cattle may act as a significant reservoir of *C. jejuni* subtypes capable of causing human campylobacteriosis and that some subtypes may be associated with particular environmental reservoirs.

Adhikari *et al*. (2004), also using PFGE techniques, found that cattle, sparrows, rodents, and flies are potential reservoirs for *C. jejuni* on dairy farms.[18] Identical clones of *C. jejuni* carried by these four groups probably indicate a common source of infection (or transmission between these animals).

Deposition

Some data on deposition rates and persistence in cowpats are now available (Gilpin 2005). Data appear to be lacking on the disposal and effect of poultry litter.

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[17] http://www.nzpho.org.nz/view_data.asp

[18] Ekdahl *et al*. (2005) and Nichols (2005) consider that flies could be an important vector of *Campylobacter*.

Little is known about the age-dependency of animal shedding, yet it may be an important model input regarding seasonality (Hearnden *et al*. 2003).

Other data suggest that we can have negative sheep flocks, but not negative cattle herds (Dr Andrea Donnison, Agresearch, Ruakura, pers. comm.)

Environmental transmission routes

The following observations may be made.

- There is a surprisingly high degree of occurrence of *Campylobacter* in freshwater (McBride *et al.* 2002). One study, for the Taieri River reported an apparent association between concentrations of *Campylobacter* at the main river bathing site, and local reported rates of campylobacteriosis (Eyles *et al*. 2003).
- Zoonoses can be associated with poor drinking water quality (Fraser & Cooke 1991, Duncanson *et al*. 2000, Close *et al.* submitted).
- Farmed land tends to be more contaminated than arable/forest lands.
- The urban stormwater content of zoonotic pathogens is unknown.
- Beach sand can be substantially contaminated with *Campylobacter* spp. (Bolton *et al*. 1999).
- Roof water for drinking supply can be contaminated with zoonotic pathogens (Simmons *et al.* 2000, Savill *et al*. 2001).
- Sheep/goats may contribute disproportionately to their reservoir size (cf. cattle), because they tend to be farmed on steeper land than cattle (Collins *et al.* 2005b)
- *E. coli* and *Campylobacter* can be stored in stream sediments for long periods, and released during higher flows (Muirhead *et al*. 2004). However, these two groups behave differently under flood conditions, with the peak *E. coli* concentration always preceding the peak *Campylobacter* concentration, suggesting that instream-concentration of *Campylobacter* are more predominantly derived from runoff, cf. channel storage (Donnison *et al.* 2006)
- We are starting to get strain-type information to identify common-source outbreaks (e.g., Devane *et al.* 2005; Gilpin *et al*. in press).

Food processing and preparation

ESR has carried out various projects, as commissioned by NZFSA, that relate to *Campylobacter*, including:

Risk profiles*: Campylobacter jejuni/coli* in poultry; *Campylobacter* on red meat and poultry offal (under preparation); *Campylobacter* on uncooked bovine, ovine and porcine meat (under preparation).

Campylobacter risk models: *Campylobacter* spp. in the poultry food chain; C*ampylobacter* in red meat (paper submitted to NZFSA).

Other *Campylobacter*-related projects: *Campylobacter* pathways discussion document; Microbiology of uncooked retail meat products: *Campylobacter*; Undercooked chicken livers as a vehicle for campylobacteriosis; Pathogen loading on freshly slaughtered chickens; The effect of refrigeration on *Campylobacter* survival on poultry meat; Temperature control at retail level; Assessment of domestic food handling practices; National typing database.

Consequently much work has been done so far in this area. Further projects are currently being developed by ESR and NZFSA.

Human exposures

Available data includes:

- National nutrition survey for foods (Russell *et al.* 1999) and Child Nutrition Survey.
- Both NZFSA and ESR are evaluating options for dietary modelling.
- Water consumption and contact recreation exposure (McBride *et al*. 2002).
- One approach that is being piloted is risk factor ranking. A comprehensive list of detailed campylobacteriosis risk factors has been compiled by ESR. These have been ranked into seven categories (from no risk to very high risk) by an expert panel comprising food and water scientists, HPOs and a MOH using a modification of the Delphi method. The data is scheduled be collected next year using a supplementary case questionnaire, from which attributed risks will be estimated for the risk factor groups (ie. food, drinking-water, animal, person-to-person, recreational water etc).
- The MAGIC study (multi-centre case-control study for campylobacteriosis, Eberhardt-Phillips *et al*. 1997) elucidated many exposures, particularly for undercooked chicken.
- A Manawatu MLST pilot study has assessed human exposure to *Campylobacter* from several sources (P. Mullner, Massey University, pers. comm.)

Potential mitigation measures

A number of potential mitigation measures have been identified to reduce the *Campylobacter* load to the environment:

- Farm runoff can be reduced –standoff pads, delayed irrigation, fencing, bridges (animal crossings), riparian retirement, water treatment for animals, DNA vaccines, phage therapy.
- Waste treatment—including collection and disposal.
- Composting.
- Primary processing options.
- Management of poultry contamination, drawing on experience in Sweden, Iceland and Belgium in risk reduction (freeze all chicken; disinfection pads,…).
- Better kitchen food handling practices.
- Animal exposures.
- Water treatment.
- Animal movement.

Such options are discussed in a recent authoritative text (Cotruvo *et al*. 2004).