Modelling of *Campylobacter* carriage and transmission between and within animal groups

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*June 2010*

prepared for
the New Zealand Food Safety Authority
and Ministry for the Environment

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1 Executive summary

The aim of this part of the CDRP-funded project: *Campylobacter* in Food and the Environment was to incorporate pathogen carriage and transmission between and within animal groups, using multi-group transmission models to capture the non-linear dynamics of infection in populations of animals and the environmental cycling of pathogens. We develop a transmission model suitable for describing a typical New Zealand dairy farm, incorporating multiple groups of animals and modelling transmission of a pathogen within and between groups via an environmental reservoir. Key features of a typical New Zealand dairy farm are incorporated, including seasonal calving and the resulting lactating and dry cycles in adult animals and variation in total animal numbers during the yearly cycle. In addition, given the evidence of small subgroups of animals being responsible for the majority of pathogen transfer (“high-shedders”) we incorporate differential shedding of animals within each management group.

We provide methods for the estimation of parameters for transmission based on a simplified simple-group model, and show how potential interventions may be assessed by simulating the model ahead in time. Two specific interventions are assessed:

- Isolating of a particular group of animals to limit between group transmission,
- Targeted active intervention on the “high-shedder” animals.

The first highlights the seasonal linkages between groups and how isolating a single management group may have carry-on effects that reduce the prevalence in all groups. The second shows that targeting “high-shedder” animals can be effective at reducing overall prevalence and environmental loading significantly even when only modest reductions in shedding are achieved.

Finally, we detail an extension to the model into a catchment framework, demonstrating how the stream network may be viewed as a pathway for between farm pathogen transmission.
2 Introduction

*Campylobacter* is a major contributor of disease notifications in New Zealand. There are a number of pathways and sources that contribute to the overall disease burden, and two important factors are the prevalence and levels of shedding of *Campylobacter* within groups of animals, and the concentration of *Campylobacter* in surface water intended for drinking or recreational use [8, 14, 15].

The motivation for this work is to extend existing ecological and environmental models by incorporate pathogen carriage and transmission between and within animals groups in order to capture the non-linear dynamics of infection in populations of animals and the environmental cycling of pathogens. The resulting multi-group model may then be used to assess the likely effects of intervention at the animal or farm level on prevalence and shedding in animals, which may then be fed into more general catchment and environmental models to assess the resulting impact on pathogen levels in environmental water, and into human exposure pathway models to assess the resulting implications for public health [7, 14, 15].

In New Zealand, the typical dairy farm uses a condensed farm management system, where there is generally a single season of calving. This results in animals being grouped into distinct age groups that are managed relatively separately. Such grouping of the animals on a farm has implication for transmission and maintenance of infectious agents – there is a lower chance of transmission between groups than there is between animals within a group. Thus, certain groups may be more important than others with respect to how infection is maintained or eliminated on a farm, as each group may have differing shedding profiles and infection rates. A multi-group model for disease transmission is therefore essential to understanding the mechanisms that maintain disease, for highlighting potential intervention points and evaluating the likely success of those interventions.

The seasonality of the New Zealand farming system also has implications for any modelling strategies: Movement of animals between groups is governed by maturation of the animals, which is dependent on date of birth of the animal and various maturation ages. Thus, any modelling system should incorporate this seasonality.
3 Semi-stochastic model

We take a semi-stochastic model from Turner et al. [23, 24] and adapt it to New Zealand conditions, incorporating the seasonal effects of calving and allowing shedding rates to vary between animals within each group.

The generic multi-group dairy herd model given by Turner assumes year-round calving with a fixed herd size, and maintains the herd size by replacing any deaths or cullings with immediate births. As a consequence of this, movement between groups is also a year-round process, and thus the stochastic model that describes the number of animals in each management group reaches its stable equilibrium quickly, and from then on is effectively static over time. This is quite different than the situation on a typical New Zealand farm, however, and thus the model needs adapting to allow seasonal variation in animal numbers in all management groups.

Our aim was to capture the major processes within a typical New Zealand dairy herd, and thus capturing this seasonal behaviour is essential. We define 3 main management groups: New born calves (C) to 2 months of age, heifers (H) to 14 months of age (first calving at 23-24 months), and adults (A). In addition, we split the adults into dry (D) and lactating (L) groups. We assume that all adult cows move between these two states each year, though they may each do so at different times. Splitting the adults in this way allows different parameters for transmission between the two groups as, in many dairy systems in New Zealand, animals during the dry cycle may be grazed on different pastures and thus have different diet than they do during lactation, which may affect transmission via the environment.

In addition to culling within the adult groups, death is expected to occur throughout the year in all groups at a certain rate, whilst births (and thus replacements) occur seasonally. Hence, the total number of animals on the farm must vary throughout the year, reaching a maximum directly after the calving season. To keep the total number of cows in the model static on the farm through time (to ensure that stochastic fadeout doesn’t occur due to death), we assume the number of replacement animals is equal to the number of deaths throughout the previous year. A separate class of animals (V) is used to hold the number of dead animals throughout the year until the birth events are sampled, so that through time, the sum of the animals in each group, including the V group is constant. Output from the model of animal numbers for a herd with approximately 300 milking cows is shown.
in Figure 1.

![Graph showing typical animal numbers from the seasonal model for a herd with approximately 300 milking cows, averaged over 10 simulation runs. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves.]

Figure 1: Typical animal numbers from the seasonal model for a herd with approximately 300 milking cows, averaged over 10 simulation runs. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves.

Within each group of animals, we further subdivide the animals into infected and susceptible animals. An infected animal is assumed to be amplifying and shedding *Campylobacter*, and we assume that upon ‘recovery’ that animal returns to the susceptible state, i.e. there is no assumed immunity gained due to prior infections. Animals may become infected either directly from other animals (via a faecal-oral route for instance) or indirectly via an environmental reservoir. We assume that *Campylobacter* may survive in the local environment (such as in water troughs, pasture, or on equipment) of each group, and that animals may become infected from the environment. This allows both an indirect transmission route within groups, and a possible pathway for infection to move between groups.

In particular, we model the local environments of each of the management groups separately (i.e. have one $E_i$ for each management group $i \in \{C, H, D, L\}$) and in addition, have an extra general environment $E_G$, representing the general farm environment. We model *Campylobacter* in the environment by specifying an “infectious unit” of bacteria as a group of one or more bacteria that when ingested are likely to cause infection. This concept of an “infectious unit” may be considered as a measure of the “av-
“average” dose required for infection, as it is used to compute the average rate of infection, rather than as a cut-off level under which no infection occurs and above which infection must occur. In this respect it may be considered analogous to the median dose for infection ($D_{50}$) on the dose-response curve. The infectious units in the local environments may migrate to the general environment, and susceptible animals in each group may then ingest infectious units from their local environment or from the general environment $E_G$, after which they are regarded as infected. This general environment, therefore, may represent farm equipment, farm personnel, shared pastures, or shared water troughs - all transmission between groups comes via this route.

In addition to this indirect transmission route, we have pseudo-vertical transmission from dam to new born during the calving season. This transmission may be of particular importance from a human health perspective, as many of those new borns are sent off as bobby calves for slaughter, and in addition, those calves that remain on the farm have been generally observed to shed at significantly higher levels than older animals [19, 20, 21].

Lastly, within the subgroups of infected and susceptibles, the model supports further subdividing into groups with differing shedding rates. This allows the observed “super-shedding” behaviour observed in both $E. coli$ [2] and $Campylobacter$ [17, 18], where certain animals persistently shed at much higher rates than other animals. Each subgroup is assumed equivalent in every way with the exception of the amount that they shed when infected. Thus, infections can occur from super-shedders to normal animals and vice-versa.

The state of the model at any time can therefore be described by the vector $(X_{ij}, Y_{ij}, E_i, E_G)$, where $X_{ij}$ is the number of susceptible animals, $Y_{ij}$ the number of infected animals, and $E_i$ the number of free-living infectious units, where $i \in \{C, H, D, L, V\}$, and $j$ is the shedding subgroup.

Since we are treating the environmental loading in terms of the number of infectious units, and since an infected animal may shed many hundreds of infectious units per day, there are essentially two time-scales in operation within the model. Events that affect the environment (shedding, natural death of infectious units, and transfer of infectious units from local to general environments) occur on a time scale of minutes or seconds. In contrast, the main events of interest, such as the infection and recovery of animals, are expected to occur on a time scale of days. A general stochastic model, where
all events are considered stochastic, therefore, would be too computationally intensive, spending almost all its time resampling environmental-level events. In addition, the rate at which the environmental-level events occur is dependent on only the overall shedding pressure of infected animals, which is constant between each animal-level event. Similarly, all the animal-level events other than the consumption of infectious units by animals are independent of the level of infectious units in the environment.

We therefore make an additional assumption that any changes in the level of infectious units in the environment between animal-level events are symmetrically distributed about zero over time. With this assumption in place, we may consider the rate at which infectious units are consumed by animals to be dependent on the level of infectious units within the environment only at the time of the last animal-level event. This allows the model to be factored into two independent portions, allowing us to model the environment-level events independently between each animal-level event. Splitting the model in this way also allows separation of the “within farm” and “between farm” transmission mechanisms within a broader catchment model. The between farm spread is modelled entirely by the environmental process, which due to the short time scale may be modelled deterministically - see Section 7.

The model therefore operates through the following Doob-Gillespie cycle [6, 11]:

1. Determine the time and type of the next animal-level event.

2. Run the deterministic model for the environments through to this time point.

3. Perform the event and update the model state.

3.1 Animal level processes

In the animal-level process, we have a mix of both seasonal events and events that occur randomly at some given rate. Careful consideration is needed, therefore, to determine which event is to be performed next at any point in time. Any event that occurs in a random fashion at a known rate is exponentially distributed, and thus has the property of being memory free. That is, the number of events that have occurred up to a given point in time has no bearing on the distribution of the time to the next event. We may therefore resample from the exponential distribution for all such events
as frequently as we wish, without altering the average rate at which those
events occur in the stochastic process. Most events in our model, such as
death, culling, infection and recovery are described by exponential random
variables. We may therefore determine the time at which the next event
occurs in the usual manner by computing the rates $r_k$ for each event $k$, and
sampling from the exponential distribution with parameter $R = \sum r_k$. The
event that should be performed at this time point is then determined by
taking a sample $u$ from the uniform distribution on $[0, 1]$, and finding the
value of $k$ that satisfies

$$ \sum_{j=1}^{k-1} r_j < u R \leq \sum_{j=1}^{k} r_j. $$

The exponentially distributed events, their associated rates, and the effect
on the model state are given in Table 1.
<table>
<thead>
<tr>
<th>Event</th>
<th>Model state</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural death of susceptible in group $i$</td>
<td>$(X_i, X_V) \rightarrow (X_i - 1, X_V + 1)$</td>
<td>$b_iX_i$</td>
</tr>
<tr>
<td>Natural death of infected in group $i$</td>
<td>$(Y_i, Y_V) \rightarrow (Y_i - 1, Y_V + 1)$</td>
<td>$b_iY_i$</td>
</tr>
<tr>
<td>Culling of susceptible in group $L$</td>
<td>$(X_L, X_V) \rightarrow (X_L - 1, X_V + 1)$</td>
<td>$mX_L$</td>
</tr>
<tr>
<td>Culling of infected in group $L$</td>
<td>$(Y_L, Y_V) \rightarrow (Y_L - 1, Y_V + 1)$</td>
<td>$mY_L$</td>
</tr>
<tr>
<td>Direct transmission within group $i$</td>
<td>$(X_i, Y_i) \rightarrow (X_i - 1, Y_i + 1)$</td>
<td>$\beta_iX_iY_i$</td>
</tr>
<tr>
<td>Consumption of local infectious unit by susceptible in group $i$</td>
<td>$(X_i, Y_i, E_i) \rightarrow (X_i - 1, Y_i + 1, E_i - 1)$</td>
<td>$z_iX_iE_i$</td>
</tr>
<tr>
<td>Consumption of infectious unit from general environment by susceptible in group $i$</td>
<td>$(X_i, Y_i, E_G) \rightarrow (X_i - 1, Y_i + 1, E_G - 1)$</td>
<td>$s_iX_iE_S$</td>
</tr>
<tr>
<td>Consumption of local infectious unit by infected in group $i$</td>
<td>$(E_i) \rightarrow (E_i - 1)$</td>
<td>$z_iY_iE_i$</td>
</tr>
<tr>
<td>Consumption of infectious unit from general environment by infected in group $i$</td>
<td>$(E_G) \rightarrow (E_G - 1)$</td>
<td>$s_iY_iE_G$</td>
</tr>
<tr>
<td>Recovery of infected in group $i$</td>
<td>$(X_i, Y_i) \rightarrow (X_i + 1, Y_i - 1)$</td>
<td>$\gamma Y_i$</td>
</tr>
</tbody>
</table>

where $i \in \{C, H, D, L\}$

Table 1: Definition of the stochastic model.
The remainder of the animal-level events such as births, maturation, and the dry-off period for each adult cow, are seasonal and thus cannot be described by an exponential distribution. We must therefore fix these events in time, and sample them only once, as their distributions will not be memory-free. We note that the event times are independent of the state of the herd (susceptible versus infected) and the levels in the environment, and that each event is essentially tied to a birth event. Once we know when an adult cow should give birth, we may infer when the dry-off period should begin prior to the next calving season, and we can also infer the maturation events for the calf. As births occur each year, we have a specific annual event, timed to occur before the calving season begins which is used as a trigger for creating a queue of all seasonal events up to and including the trigger event for the following year. We assume that all adult cows in the herd will be in calf, and that these are distributed throughout the calving season by some given distribution. For each birth event, we thus sample the date of dry-off for the adult in the following year. The majority of these calves will go to the bobby calf trade, and only enough calves to serve as replacements for cows that were removed from the herd over the last 12 months will remain. These calves are chosen by random sample, and for each calf we then sample the maturation events (calf to heifer, and heifer to adult).

All the seasonal events are thus described by the date at which they occur and the type of event that should be performed. These are then placed into a sorted event queue to be processed throughout the year at the appropriate time point.

The distributions used for sampling, based on a typical New Zealand dairy farm [16] are given in Table 2.

<table>
<thead>
<tr>
<th>Event</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Births</td>
<td>Normal with mean 30th June, variance 100 days</td>
</tr>
<tr>
<td>Calf to Heifer</td>
<td>Normal with mean 60 days, variance 10 days from birth</td>
</tr>
<tr>
<td>Heifer to Adult</td>
<td>Normal with mean 365 days, variance 10 days from calf to heifer time</td>
</tr>
<tr>
<td>Drying off of Adult</td>
<td>Normal with mean 300 days, variance 10 days from last birth or maturation of heifer</td>
</tr>
</tbody>
</table>

Table 2: Distributions used for sampling the seasonal events.
3.2 Modelling the local environments

For the environmental-level events, we model the number of free-living infectious units in each of the local and general environments deterministically. Between any of the animal-level events listed above, we have a static shedding pressure from each of the groups, and no consumption events. Thus, there are just 3 events to consider that affect the number of infectious units in the environment:

- Shedding of an infectious unit by an infected animal.
- Death or inactivation of an infectious unit.
- Movement of an infectious unit from local to general environments.

Let $\eta_{ij}$ denote the shedding rate of an individual in shedding group $j$ of group $i$, $p_i$ the transfer rate from the local to general environment, and $q_i$ the death rate in environment $i$. We then have the following system of differential equations governing the population of free-living infectious units.

$$
\frac{dE_i}{dt} = \sum_j \eta_{ij} Y_{ij} - (p_i + q_i)E_i, \quad \text{for } i \in \{C, H, D, L\},
$$

$$
\frac{dE_G}{dt} = -q_G E_G + \sum_i p_i E_i.
$$

We note that the differential shedding is effectively evaluated in the $\sum_j \eta_{ij} Y_{ij}$ term, and that this denotes the total shedding pressure from group $i$ across all infected individuals. Thus, the model supports an arbitrary number of different shedding profiles by placing the animals into subgroups. This could be extended as far as allowing each animal to have a different shedding profile, and also allows that shedding profile to change through time. The only restriction of the model is that between animal-level events the total shedding pressure is kept at a constant level. Evidence of differing levels of shedding in *E. coli* both between animals and in the same animal over time has been observed by Robinson et al. [19] as seen in Figure 2, and similar results have been observed for *Campylobacter* [18, 17].
The above equations may be solved analytically, yielding the solution

\[
E_i(t) = \frac{b_i}{p_i + q_i} + e^{-(p_i + q_i)t} \left[ E_i(0) - \frac{b_i}{p_i + q_i} \right], \quad \text{for } i \in \{C, H, D, L\}
\]

\[
E_G(t) = \sum_{i=1}^{4} p_i \left\{ \frac{b_i}{q_G(p_i + q_i)} (1 - e^{-q_G t}) + \frac{E_i(0) - \frac{b_i}{p_i + q_i}}{q_G - (p_i + q_i)} \left[ e^{-(p_i + q_i)t} - e^{-q_G t} \right] \right\} + G(0)e^{-q_G t},
\]

where \( b_i \) is the shedding pressure \( b_i = \sum_j \eta_{ij} Y_{ij} \).

Combining these with the exponential and seasonal animal-level events allows us to model the on-farm dynamics as follows:

1. Initialize the model state at time 0 with a suitable number of animals in each group and subgroup.
2. Sample the annual “trigger” event and place in the sorted event queue.
3. Sample the next exponential event and place in the sorted event queue.
4. Run the deterministic model of the environments through to the next time in the event queue.
5. Perform the event, updating the model state.
6. If the event is the annual “trigger” event:
   
   (a) Sample a birth event for each adult cow.
   (b) Sample the dry-off event for each adult cow.
   (c) Sample replacement birth events for each cow in group V from the birth events generated in (a).
   (d) Sample maturation events for each birth chosen in (c).
   (e) Sort the events into the event queue.
   (f) Add the “trigger” event for the following year to the event queue.

7. Repeat from step 3 until a suitable time period has been covered.

4 Running the model

The model is implemented in R and C/C++, which interacts with a Microsoft Excel spreadsheet for setting parameters using the xlsReadWrite package for R[12]. The model thus consists of 3 files:

- multigroup.R (the R script that performs the modelling),
- exp_samp.dll (a dll that handles sampling the exponential rates and determining the next event),
- MultiGroupParameters.xls (the Excel spreadsheet giving the parameters for the model).

A typical model run is as follows:

1. Load the Excel spreadsheet and alter parameter values as needed.
2. Optionally save the spreadsheet to a separate file.
3. Load R and set the working directory to the folder containing the model files.
4. Enter `source("multigroup.R")` to load the model script.
5. Enter `multigroup(100,"MyParameters.xls")` to run the model for 100 iterations using the supplied Excel sheet of parameters.
The model will then be simulated the given number of times, and summary output and graphs are produced. An example of typical model output is given in Figure 3 and Table 3. Note that the variation in prevalence between simulation runs (indicated by the point-wise 2.5% and 97.5% percentiles) in the smaller groups such as the Heifers can be quite large, which is a typical feature of stochastic models, particularly with a relative small population at risk (in the case of the Heifer group, 55 animals). The resulting environmental loading also exhibits this behaviour.
Figure 3: Typical output from the model, with 50 simulation runs. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves. Dotted lines are point-wise 2.5% and 97.5% percentiles.
<table>
<thead>
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<th>Simulation</th>
<th>Time</th>
<th>X_C</th>
<th>X_H</th>
<th>X_L</th>
<th>Y_C</th>
<th>Y_H</th>
<th>Y_D</th>
<th>Y_L</th>
<th>E_C</th>
<th>E_H</th>
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<td>47</td>
<td>0</td>
<td>228</td>
<td>0</td>
<td>18</td>
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<td>17</td>
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<td>0</td>
<td>231</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>55</td>
<td>0</td>
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<td>7619680</td>
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<tr>
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<td>46</td>
<td>0</td>
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<td>0</td>
<td>19</td>
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<td>56</td>
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<td>112793585</td>
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<td>76294553</td>
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<tr>
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<td>20.5</td>
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<td>0</td>
<td>228</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>58</td>
<td>0</td>
<td>119498857</td>
<td>0</td>
<td>75965007</td>
</tr>
</tbody>
</table>

Table 3: Sample output from the stochastic model.
5 Parameter estimation

The multi-group model necessarily has many parameters associated with it, and many of these are difficult to estimate reliably. Table 4 gives a list of the stochastic parameters with their “base-line” values, along with notes with references as to where these were derived where available.

While the many parameters present in the multi-group model gives flexibility in what intervention strategies the model can evaluate, this comes at the expense of having to estimate those parameters to produce reasonable output. Given the sparsity of data on Campylobacter prevalence and counts in the New Zealand context (and more generally, worldwide) this is very difficult to achieve, particularly for the transmission parameters $b_i$, $s_i$, and $z_i$, and the environmental transfer parameter $p_i$. With multiple transmission routes, infection may be maintained at the same prevalence levels with many differing parameter sets. For example, one may reduce $b_i$ controlling the ‘animal to animal’ transmission route, whilst increasing those that control the ‘environment to animal’ transmission route ($s_i$, $z_i$, and shedding rates) and still maintain the same overall level of infection. Similarly, one can obtain the same overall prevalence by increasing the infection rates of one animal group while reducing the infection rates of other groups. The linkages between the interacting parameters makes parameter estimation difficult, and thus leaves a great deal of uncertainty about which transmission routes are driving the maintenance of the infection. We can, however, make progress by considering a simple model to assess the relative effect of each parameter.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>References and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>( m_i )</td>
<td>Culling rate</td>
<td>0.0004 for ( i = D )</td>
<td>Assumed only culling during dry-off [16]</td>
</tr>
<tr>
<td>( b_i )</td>
<td>Death rate</td>
<td>0.000137 for ( i = C )</td>
<td>Busato et al. [1]</td>
</tr>
<tr>
<td>( b_i )</td>
<td></td>
<td>0.000023 for ( i = H )</td>
<td>Gardner et al. [10]</td>
</tr>
<tr>
<td>( b_i )</td>
<td></td>
<td>0.0004 for ( i \in { D, L } )</td>
<td>LIC and DiaryNZ [16]</td>
</tr>
<tr>
<td>( \beta_i )</td>
<td>Direct infection rate</td>
<td>0.004 for ( i = C )</td>
<td>Back-computed from prevalence</td>
</tr>
<tr>
<td>( \beta_i )</td>
<td></td>
<td>0.0005 for ( i = H )</td>
<td></td>
</tr>
<tr>
<td>( \beta_i )</td>
<td></td>
<td>0.0001 for ( i \in { D, L } )</td>
<td></td>
</tr>
<tr>
<td>( \gamma_i )</td>
<td>Recovery rate</td>
<td>0.05</td>
<td>Discussion between G.McBride and B.Gilpin (value assumes no further exposure)</td>
</tr>
<tr>
<td>( k_i )</td>
<td>Concentration in faeces (cfu/g)</td>
<td>( 10^6 ) for ( i = C )</td>
<td>Rapp and Ross [17], Rapp et al. [18], Stanley et al. [21]</td>
</tr>
<tr>
<td>( k_i )</td>
<td></td>
<td>( 10^4 ) for ( i = H )</td>
<td></td>
</tr>
<tr>
<td>( k_i )</td>
<td></td>
<td>( 10^3 ) for ( i \in { D, L } )</td>
<td></td>
</tr>
<tr>
<td>( f_i )</td>
<td>Defaecation rate (kg/day)</td>
<td>6 for ( i = C )</td>
<td>Turner et al. [24], Donnison et al. [5]</td>
</tr>
<tr>
<td>( f_i )</td>
<td></td>
<td>20 for ( i = H )</td>
<td></td>
</tr>
<tr>
<td>( f_i )</td>
<td></td>
<td>26 for ( i \in { D, L } )</td>
<td></td>
</tr>
<tr>
<td>( q_i )</td>
<td>Deactivation rate in local environments</td>
<td>0.138</td>
<td>Half the rate found in gravel by Close et al. [3] and in some soils in Donnison and Ross [4]</td>
</tr>
<tr>
<td>( p_i )</td>
<td>Transfer rate from local to global environment</td>
<td>0.05</td>
<td>Back-computed from prevalence</td>
</tr>
<tr>
<td>( z_i )</td>
<td>Consumption rate of infectious units in local environment (per animal per day)</td>
<td>( 2 \times 10^{-10} ) for ( i \in { C, H } )</td>
<td>Back-computed from prevalence</td>
</tr>
<tr>
<td>( s_i )</td>
<td>Consumption rate of infectious units in global environment (per animal per day)</td>
<td>( 2 \times 10^{-10} ) for ( i \in { C, H } )</td>
<td></td>
</tr>
<tr>
<td>( \rho )</td>
<td>Pseudo-vertical transmission</td>
<td>0.46</td>
<td>Gannon et al. [9]</td>
</tr>
<tr>
<td>( u )</td>
<td>Average number of viable bacteria in an infectious unit</td>
<td>100</td>
<td>Estimated median dose for cattle, based on typical human value of 900 [22], and assumed lower defenses due to no resulting disease</td>
</tr>
<tr>
<td>( q_G )</td>
<td>Deactivation rate in global environment</td>
<td>0.138</td>
<td>See ( q_i ) above</td>
</tr>
<tr>
<td>( h_P )</td>
<td>Proportion of high shedders</td>
<td>0.1</td>
<td>Estimate based on Rapp and Ross [17]</td>
</tr>
<tr>
<td>( h_F )</td>
<td>High shedding multiplier</td>
<td>100</td>
<td>Estimate based on Rapp and Ross [17]</td>
</tr>
<tr>
<td>( \eta_i )</td>
<td>Shedding in infectious units per animal</td>
<td>( \eta_i = f_i k_i 1000 / u )</td>
<td>Directly computed</td>
</tr>
<tr>
<td>( n_i )</td>
<td>Number of animals</td>
<td>( \sum n_i = 400 )</td>
<td>Averages as per LIC and DiaryNZ [16]</td>
</tr>
</tbody>
</table>

where \( i \in \{ C, H, D, L \} \)

Table 4: Parameters for the multi-group model.
5.1 Simple model assessing exposure to the Environment

In order to investigate the relative contribution of direct animal to animal transmission in comparison to environmental transmission, we develop a simple deterministic single group farm based model, where we have just two transmission paths - direct animal to animal transmission, and indirect transmission via the environment.

Let $N$ be the number of animals on the farm, $I$ the number infected, and let $E$ be the number of infectious units in the environment. Then we have the system of differential equations

\[
\frac{dI}{dt} = \beta I (1 - \frac{I}{N}) - \gamma I + zE(N - I),
\]

\[
\frac{dE}{dt} = \eta I - zEN - qE
\]

where $\beta$ is the direct transmission rate, $\gamma$ is the recovery rate, $z$ is the consumption rate of infectious units in the environment, $\eta$ is the shedding rate, and $q$ is the inactivation rate in the environment. It should be noted that the direct transmission rate here is on the same scale as the recovery rate due to the divisor of the total number of animals, whereas in the full stochastic model the rate has no such divisor.

The question of the relative importance of each transmission route can be answered by an analysis of the parameters that yield to stable equilibria. The equilibria for this system are $(I, E) = \{(0, 0), (I^*, \frac{\eta}{zN + \eta} I^*)\},$ where

\[I^* = N \left[1 - \frac{\gamma}{\beta + \beta_E}\right],\]

and

\[\beta_E = \frac{\eta}{1 + \frac{q}{zN}}.\]

The trivial equilibrium point $(I = 0, E = 0)$ is unstable, thus occurs only if the initial values permit it or if the alternate equilibrium point is infeasible. The non-trivial equilibrium point is stable and permissible only if $\gamma < \beta + \beta_E$. Thus, the system permits a non-trivial infected equilibrium under the conditions that the rate of recovery is less than the combined rate of infection, and that the initial conditions allow at least one infected individual. If the rate of recovery exceeds that of infection, then the disease dies out.
The relative size of $\beta$ compared with $\beta_E$, therefore, determines which transmission route is more important in maintaining the infection. If $\beta > \beta_E$ then direct transmission is the dominant source of infection, whereas if $\beta < \beta_E$ then the environment plays a more dominant role. Given that the transmission parameters are the most problematic to estimate, one way forward is to use data for long term herd prevalence combined with known estimates of recovery, deactivation, and shedding rates to infer a likely overall transmission rate $\beta + \beta_E$. The direct and indirect rates may then be apportioned in different ratios to make up that overall transmission rate, and thus inform the parameters of the larger model. The computations are available on the MultiGroupParameters.xls spreadsheet so that the expected long-term prevalence for each group may be checked when altering model parameters.

Once estimates of direct and indirect transmission based on a single-group model are found, we can extend this to the multi-group model by apportioning the indirect rates between the local and general environments based on how much between-group transmission is expected to occur. The multi-group model outputs the number of direct, indirect, and between-group infections that occur so that these parameters may be tuned.

## 6 Assessing Interventions

In this section we assess two particular intervention scenarios aimed at reducing or eliminating on-farm infection. The scenarios and potential interventions are given in Table 5.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection driven by young stock</td>
<td>Isolation of calves</td>
</tr>
<tr>
<td></td>
<td>Isolation of heifers</td>
</tr>
<tr>
<td></td>
<td>Isolation of adults</td>
</tr>
<tr>
<td>Infection driven by “high-shedders”</td>
<td>Targetted treatment to reduce shedding</td>
</tr>
</tbody>
</table>

Table 5: Scenarios and interventions assessed using the multi-group model.
6.1 Infection driven by young stock

It has been observed that young stock infected with *E. coli* or *Campylobacter* exhibit higher shedding than adult animals, and a higher prevalence than older animals [18, 20, 2, 24, 19]. We therefore hypothesize that the infection across a farm could feasibly be maintained at a higher level solely by the younger stock, with adult stock becoming infected via cross-contamination. Under this scenario, a suitable intervention would be to attempt to reduce the cross-contamination by isolating particular groups of animals. Without the possibility for cross-contamination, the prevalence in the adult groups may be reduced. Once the prevalence is reduced in the adults, it will necessarily be reduced in the young stock of the next generation, assuming no other external source of infection is available.

To assess this scenario, we use the standard parameter values as given in Table 4 with the direct transmission parameters reduced slightly to \( \beta_C = 0.004, \beta_H = 0.0001, \beta_D = \beta_L = 0.00003 \), so that the majority of the transmission is via the environment. The parameter changes to test the 3 interventions are given in Table 6.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Changes to Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation of calves</td>
<td>( s_C = 0, p_C = 0, k_C = 10000 )</td>
</tr>
<tr>
<td>Isolation of heifers</td>
<td>( s_H = 0, p_H = 0 )</td>
</tr>
<tr>
<td>Isolation of adults</td>
<td>( s_i = 0, p_i = 0 ) for ( i \in {D, L} )</td>
</tr>
</tbody>
</table>

Table 6: Parameter variation in for interventions in the young stock scenario.

The model was run for 100 iterations for each intervention, and the prevalence through time for the baseline and interventions is given in Figure 4, with summary data in Table 7. As can be seen, each of the interventions has around the same effect on each group overall. Isolation of calves (and the reduction in shedding) reduces the prevalence in calves and, while they are isolated, as they mature this transfers into a higher initial prevalence in the heifers. The prevalence in adults however does not increase significantly during the calving period. Isolation of heifers or adults appear equally as effective overall, differing only in how the cross contamination from the young stock effect prevalence in each group.
Table 7: Prevalence in each of the management groups in year 5 following intervention, and overall prevalence and total farm shedding ($\times 10^9$ cfu/day) with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Isolate calves</th>
<th>Isolate heifers</th>
<th>Isolate adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves</td>
<td>0.2(0.16, 0.24)</td>
<td>0.14(0.06, 0.19)</td>
<td>0.18(0.12, 0.24)</td>
<td>0.19(0.14, 0.23)</td>
</tr>
<tr>
<td>Heifers</td>
<td>0.65(0.45, 0.78)</td>
<td>0.6(0.26, 0.75)</td>
<td>0.65(0.3, 0.77)</td>
<td>0.59(0.22, 0.75)</td>
</tr>
<tr>
<td>Adults</td>
<td>0.51(0.41, 0.59)</td>
<td>0.46(0.29, 0.55)</td>
<td>0.41(0.3, 0.49)</td>
<td>0.39(0.25, 0.49)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.54(0.44, 0.62)</td>
<td>0.48(0.3, 0.58)</td>
<td>0.46(0.33, 0.53)</td>
<td>0.43(0.31, 0.52)</td>
</tr>
</tbody>
</table>

Shedding 1.22(0.95, 1.41) 0.76(0.42, 0.92) 1.1(0.76, 1.27) 1.06(0.75, 1.25)
Figure 4: Prevalence under the scenario where most of the on-farm infection is being maintained by the young stock. Interventions from top to bottom, baseline, isolation of calves, heifers, and adults. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves. Dotted lines are point-wise 2.5% and 97.5% percentiles.
6.2 Infection driven by high shedders

There has been several indications in the literature of infection being driven by “high-shedders”, a small subset of animals that shed unusually high amounts of bacteria compared with other stock [24, 19, 17, 18]. An obvious intervention strategy in the presence of high-shedding animals is to focus on reducing the amount of shedding in those animals. This involves firstly identifying risk factors associated with high shedding, and then isolating which of these risk factors can be reduced, or which “active” interventions can be put in place targeting those animals.

We may evaluate the efficacy of such an intervention by running the model with the high-shedders present, and then with the amount that they shed reduced by set amounts, comparing the resulting prevalences. Given the ranges observed in Rapp and Ross [17], we designate 10% of animals as high-shedders, and run 3 scenarios where those animals shed at 10, 30, or 100 times that of other animals. The base-line values used are the same as in Table 4, and we necessarily decrease the amount of shedding by low-shedding animals in these scenarios in order to keep the total shedding pressure constant, thus allowing comparisons between the different scenarios. For each of these 3 scenarios we then introduce an intervention targeted to the high-shedders, which results in a reduction in their shedding by factors of 2, 5, or 10 respectively. Thus, we have 3 scenarios, each with a baseline and 3 levels of intervention. The models were each run for 100 iterations, and results are given in Figures 5-7. As expected, the intervention is more effective in the scenarios where the high-shedders contribute more of the overall shedding. Of particular note is that the required decrease in shedding amounts need not be all that large, with a 1 log decrease dramatically reducing total prevalence even in the case where high-shedders shed only 1 log higher than normal animals initially. Table 8 summarises the effect of each intervention on prevalence and shedding at the 5 year mark. Note that, due to the fact that total shedding pressure is kept constant, the baseline conditions are essentially the same across all scenarios, with more variation present in the case where high-shedding animals account for a greater proportion of the total shedding. In addition, Table 9 shows the proportion of simulations where the disease was eliminated, and (where possible) the Kaplan-Meier estimate of median time to sterility in days[13].
Table 8: Prevalence (upper) and shedding ($\times 10^9$ cfu/day) (lower) in year 5 following intervention for three high-shedder scenarios. Numbers in brackets are 95% confidence intervals.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline</th>
<th>Reduce by 2</th>
<th>Reduce by 5</th>
<th>Reduce by 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.6(0.53, 0.65)</td>
<td>0.51(0.46, 0.55)</td>
<td>0.43(0.4, 0.46)</td>
<td>0.4(0.37, 0.43)</td>
</tr>
<tr>
<td></td>
<td>15.46(13.29, 17.43)</td>
<td>10.09(8.69, 11.35)</td>
<td>7.14(6.32, 7.86)</td>
<td>6.11(5.04, 6.82)</td>
</tr>
<tr>
<td>30</td>
<td>0.59(0.49, 0.66)</td>
<td>0.45(0.36, 0.52)</td>
<td>0.28(0.19, 0.34)</td>
<td>0.19(0.01, 0.26)</td>
</tr>
<tr>
<td></td>
<td>15.27(12.2, 17.41)</td>
<td>7.63(5.83, 9.26)</td>
<td>3.39(1.72, 4.37)</td>
<td>1.94(0.03, 2.9)</td>
</tr>
<tr>
<td>100</td>
<td>0.58(0.44, 0.67)</td>
<td>0.36(0.08, 0.49)</td>
<td>0.05(0, 0.23)</td>
<td>0(0, 0)</td>
</tr>
<tr>
<td></td>
<td>15.06(10.58, 18.02)</td>
<td>5.49(0.81, 7.66)</td>
<td>0.42(0, 2.23)</td>
<td>0(0, 0)</td>
</tr>
</tbody>
</table>

Table 9: Proportion of simulations where sterility occurred by year 5 as a result of reducing the high shedding factor, and in those cases where at least 50% of simulations resulted in sterility, the median number of days to sterility with 95% confidence intervals.

<table>
<thead>
<tr>
<th>High shedder reduction</th>
<th>Probability of sterility</th>
<th>Median days to sterility</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 3</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>100 to 50</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>100 to 20</td>
<td>0.72</td>
<td>553(467, 717)</td>
</tr>
<tr>
<td>100 to 10</td>
<td>1.00</td>
<td>257(198, 293)</td>
</tr>
</tbody>
</table>
Figure 5: Prevalence under the scenario where most of the on-farm infection is being maintained by 10% of stock that shed 10 times higher than the rest of the stock. Interventions from top to bottom, baseline, 2-fold, 5-fold, and 10-fold reductions in shedding in the high-shedding group. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves. Dotted lines are point-wise 2.5% and 97.5% percentiles.
Figure 6: Prevalence under the scenario where most of the on-farm infection is being maintained by 10% of stock that shed 30 times higher than the rest of the stock. Interventions from top to bottom, baseline, 2-fold, 5-fold, and 10-fold reductions in shedding in the high-shedding group. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves. Dotted lines are point-wise 2.5% and 97.5% percentiles.
Figure 7: Prevalence under the scenario where most of the on-farm infection is being maintained by 10% of stock that shed 100 times higher than the rest of the stock. Interventions from top to bottom, baseline, 2-fold, 5-fold, and 10-fold reductions in shedding in the high-shedding group. The cyan line is lactating animals, red is dry adults, green is heifers, and blue is calves. Dotted lines are point-wise 2.5% and 97.5% percentiles.
7 Catchment level modelling

The above model is amenable to inclusion within a higher level catchment model, where we consider a stream as the primary method of transmission between farms within the catchment. Each farm adjacent to the stream can potentially contribute to the concentration of infectious units in the stream, either by direct defaecation from animals, or from indirect runoff from the environments. Similarly, animals may have direct access to drink from the stream or farms may pump stream water into troughs for animals, and hence animals may become infected from the stream.

7.1 The basic stream model

The stream may be modelled as a tree structure of stream reaches, with water flowing from the upstream leaf nodes of the tree down towards the trunk of the tree. This gives the facility for upstream farms to pass infection to downstream farms, and also allows all farms to contribute to the total concentration of pathogen at the lower end of the stream, which may be a useful estimate in terms of water quality.

The counts of bacteria in the stream may be modelled by the system of equations

\[ \frac{dS_i}{dt} = \sum \beta_j(t) + \sum \frac{Q_k(t)}{V_k(t)} S_k(t) - \frac{Q_i(t)}{V_i(t)} S_i(t) - q_S S_i(t), \]

where \( Q_i(t) \) is the flow, and \( V_i(t) \) is the volume in reach \( i \). The first sum captures the movement of infectious units from farms \( j \) adjacent to the stream, the second captures the movement of infectious units from upstream \( (k \) directly upstream from \( i \)), the third term is loss downstream, and the last is loss due to deactivation.

If we solve these equations at the same time as we solve the environmental equations, then the \( \beta_j(t) \) terms are known in advance: they represent the number of infectious units moving into the stream reach from each farm. A simple method of modelling this term would be to treat the stream as a way for infectious units to spread between the general environments \( E_G \) on each farm, so that \( \beta_j(t) \propto E_G(t) \). More complex modelling would add a delay to this term (allowing for a percolation effect for instance), or allow the term to alter based on rainfall information, thus incorporating some simple
hydrological information about the area to affect the rate at which infectious units reach the stream.

Rainfall, of course, will also affect the flow rate and volumes in each stream reach, and thus the time period over which we need to solve the above equations will need considering. The time period will be determined by the length of time between animal-level events across all farms: only between animal events is $E_G(t)$ known. We expect animal-level events on a single farm to be on the order of a day or so, and it is clear that number of events per day would grow with the number of farms. We thus expect the time period over which we are required to solve the flow equations for the stream to be on the order of a few hours, and hence treat the flow and volumes as constant between animal-level events. We may then solve the equations directly by starting at the head waters and proceeding downstream.

Since the flow into each reach is dependent only on the flow out of the reaches directly above it, the system may be solved analytically to yield solutions of the form

$$S_i(t) = A_i + \sum_{j} B_{ij} e^{-C_{ij} t}$$

where the constants $A_i, B_{ij}, C_{ij}$, and $n_i$ may be determined from the recurrence relations

$$A_i = S_i(0) + \sum_j p_j E_j + \frac{Q_{k1}}{V_{k1}} A_{k1} + \frac{Q_{k2}}{V_{k2}} A_{k2}$$

$$n_i = n_{k1} + n_{k2} + 1$$

$$C_{ij} = \begin{cases} C_{k1,j} & j \leq n_{k1} \\ C_{k2,j} & n_{k1} < j \leq n_{k2} \\ \gamma + \frac{Q_{j}}{V_{j}} & j = n_j \end{cases}$$

$$B_{ij} = \begin{cases} \frac{Q_{k1} B_{k1,j}}{V_{k1}(C_{ij} - C_{k1,j})} & j \leq n_{k1} \\ \frac{Q_{k2} B_{k2,j}}{V_{k2}(C_{ij} - C_{k2,j})} & n_{k1} < j \leq n_{k2} \\ E_i(0) - A_i - \sum_{d=0}^{n_i-1} B_{id} & j = n_j \end{cases}$$

Note that we have assumed at most two reaches ($k_1$ and $k_2$) directly feeding reach $i$. This assumption may be lifted, though a simple rearrangement of the tree representing the stream will allow this to hold in general.

Example output from the model is given in Figure 8, where we seed infection
on a farm at the top end of the Toenepi catchment in Waikato, New Zealand. This is a typical New Zealand dairy catchment with 24 farms spread over a single stream system consisting of 91 stream reaches. It is assumed all farms are of the same size, with animal numbers similar to that of Figure 1. It is further assumed that the stream system is at its long term average in terms of flows and volumes, and that these are constant. Thus, it represents base flow conditions.

Figure 8: Output from the full catchment model run over a 45 day period. Green areas are uninfected farms, while yellow through red indicate infected farms. The more red present, the more infection the farm has.

7.2 Variable flow and volume

The assumption of constant flow and volume in each stream reach during the period over which the differential equations are solved does not preclude variable flow and volume, due to rainfall, from one time period to the next. While the above formulation deals quite well in base flow situations, during storm events we’d expect that flows and volumes will vary a great deal, and thus we develop some simple flow routing based on the work of Elliott and Harper [7]. For a particular reach, simple mass conservation of water
requires
\[ \frac{dV}{dt} = I - Q, \]
where \( V \) is the volume of water in the reach, \( I \) is the inflow to the reach, and \( Q \) is the outflow. Under the assumption that each stream reach may be considered as an ideal rectangular channel, \( V = AL \) where \( A \) is the cross-sectional area, and \( L \) is the channel length. This yields
\[ \frac{dA}{dt} = \frac{I - Q}{L}. \]
Manning’s equation for uniform flow is used to relate the flow and cross-sectional area
\[ Q = \frac{A^{5/3}}{n} S_0^{0.5} P^{-2/3} \]
where \( S_0 \) is the slope of the channel bed, \( n \) is Manning’s roughness constant, and \( P \) is the wetted perimeter. For our rectangular channel, \( P = 2A/W + W \) where \( W \) is the channel width, so that
\[ Q = \frac{S_0^{0.5}}{n} A^{5/3}(2A/W + W)^{-2/3}. \]
Noting the relationship between \( Q \) and \( A \) is approximately linear, we may linearize \( Q \) in terms of \( A \) using
\[ Q = Q_0 + k(A - A_0) \]
where \( A_0 \) and \( Q_0 \) are the area and flow at the start of the period, and \( k \) is a constant, that may be found directly by differentiating Manning’s equation at the start of the time step. The differential equation reduces to
\[ \frac{dA}{dt} = \frac{I - Q_0}{L} - \frac{k}{L}(A - A_0) \]
which has solution
\[ A(t) = A_0 + \frac{I - Q_0}{k}(1 - e^{-kt}). \]
Multiplying through by \( L \) gives the volume in the stream at the next time point, and using the mass balance gives us the outflow \( Q \).

Using this we can input rain and runoff into the system via the inflow \( I \) at the headwaters, and then solve each stream segment as we go down the stream, adding both rain and runoff in addition to the outflow from the
upper stream reaches as inflow to the next reach. This allows us to model the flow of water through the system as it varies with rainfall.

Lastly, as noted above, in addition to allowing movement of infectious units between farms, this same model gives a measure of the number of infectious units at the outflow of the catchment, which may be useful from a water quality perspective. It is also a key variable to use for validation of the model against data, as it provides an easy to measure quantity to test against. It is clear, however, that more data will be required if we are to resolve many of the parameters contributing to the model. Good longitudinal data on shedding at the animal level and at the farm level is essential.

8 Concluding remarks

We have detailed a multi-group model for the transmission of Campylobacter within New Zealand dairy herds, and shown how the model may be used to assess the effects of potential interventions on the overall prevalence and shedding on the farm. In particular, we have highlighted the important role that high-shedding animals play in the maintenance and transmission of the pathogen, and how even modest reductions in the shedding from these animals may have a large impact on prevalence and environmental loading.

The modelling process has highlighted a number of areas in which further work is required. In particular, many of the key transmission parameters in the model are unknown, and a lack of good data surrounding Campylobacter shedding and prevalence in New Zealand dairy herds makes estimating these parameters difficult. Detailed longitudinal studies are needed to collect data on the shedding behaviour of animals within each management group through time and across regions in order to refine parameter estimates and verify model behaviour. In addition, studies on the levels and survival rates of Campylobacter in the immediate environment on farms would be useful in determining the proportion of direct and indirect transmission of pathogen between animals.

In addition to assessing the immediate effect of farm-level interventions to the prevalence of Campylobacter within animals, the changes in environmental loading predicted by the model may be used as input within wider catchment and environmental water models, thus estimating the resulting effect on water quality [7]. These may in turn inform human exposure path-
way models, thus allowing those interventions to be assessed in terms of the potential benefit to public health [14, 15].

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References


