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Dose response modelling of *Escherichia coli* O157 incorporating data from foodborne and environmental outbreaks

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Abstract

A human dose response model for *Escherichia coli* O157 would enable prediction of risk of infection to humans following exposure from either foodborne or environmental pathways. However, due to the severe nature of the disease, volunteer human dose response studies cannot be carried out. Surrogate models from *Shigella* fed to humans and *E. coli* O157 to rabbits have been utilised but are significantly different to one another. In addition data obtained by animal exposure may not be representative for human beings. An alternative approach to generating and validating a dose response model is to use quantitative data obtained from actual human outbreaks. This work collates outbreak data obtained from global sources and these are fitted using exponential and beta-Poisson models. The best fitting model was found to be the beta-Poisson model using a beta-binomial likelihood and the authors favour the exact version of this model. The confidence levels in this model encompass a previously published *Shigella* dose response model. The potential incorporation of this model into QMRAs is discussed together with applications of the model to help explain foodborne outbreaks.

Keywords: Dose response; *E. coli* O157; Food outbreaks; Environmental outbreaks; Risk assessment; Markov Chain Monte Carlo; Metropolis algorithm; Epidemiology

1. Introduction

Escherichia coli O157 is a widespread pathogen causing severe human infection which can be either foodborne (e.g., cooked and raw meats, dairy products, vegetables etc.), waterborne (e.g., drinking or

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swimming water), environmental (e.g., direct contact with farm animals or contaminated pasture) or by human to human transmission. The infectious dose for this organism is estimated to be low (<10 viable cells (Griffin and Tauxe, 1991) and <a few hundred (Doyle et al., 2001)) and the sequelae can be severe, particularly among children. For example it has been reported (Locking et al., 2001) that in a study of 183 *E. coli* O157 cases in Scotland, 44% were in children under 10 years of age, 77% of cases reported bloody diarrhoea, 57% were admitted to hospital and 8% developed haemolytic uraemic syndrome (HUS). This high reporting rate among children may be influenced by under reporting of adult cases. A number of large outbreaks have occurred, e.g., the Central Scotland outbreak in 1996 where the consumption of contaminated meat led to the direct death of 17 elderly people and more than 500 falling ill (Cowden et al., 2001), a hamburger outbreak in Washington State 1992–1993 where 501 cases were reported, including 151 hospitalisations, 45 cases of HUS and 3 deaths (Bell et al., 1994), and an outbreak in school-age children in Osaka, Japan, in 1996 which eventually resulted in 7966 reported cases including 3 deaths (Michino et al., 1999).

A number of dose response models have been used in quantitative microbiology to describe the relationship between the level of microbial exposure (i.e., the dose or number of organisms ingested) and the likelihood of occurrence of an adverse consequence (i.e., illness (Holcomb et al., 1999)). The most commonly used models are single hit models, where only one organism ingested is required to cause infection even though the probability of this occurring may be very small. The simplest form of this model is the exponential model (Haas et al., 1999) which assumes that the number of organisms ingested takes the form of a Poisson distribution and that each microorganism has an equal and independent survival probability of causing infection to the host which can be calculated from the binomial distribution. However, each individual host may respond differently to a given pathogen and this variation can be incorporated into the dose response model by describing the survival probability of the pathogen by a probability distribution. The most commonly used distribution used to describe this variability is a beta distribution, though it must be noted that any unimodal distribution could potentially be used (Johnson et al., 1995). This beta-Poisson dose response model can be approximated by a simple equation (see Eq. (4)) and in most cases provides a statistically significant improvement in fit over the exponential model (Crockett et al., 1996).

Fitting of these models to data is usually performed using a maximum likelihood technique with the likelihood derived from the binomial distribution. However, overdispersion can occur when the variation between replicate individuals is greater than expected. This is likely to happen in outbreaks where individuals of a wide range of susceptibilities (e.g., from relatively low susceptibility healthy adults to higher susceptibility in the elderly and infants) may be exposed to the pathogen. Haas et al., (1999) demonstrates that overdispersion can be described using a beta-binomial likelihood.

Quantitative microbiological risk assessments (QMRAs) have been performed to determine the risk of *E. coli* O157 infection both from foods (Cassin et al., 1998) and the environment (Strachan et al., 2002). These types of risk assessment are particularly useful in proposing mitigation strategies for reducing risk of infection. However, microbiological risk assessments require validated dose response models to ensure accuracy and assess uncertainty. Validation is ideally performed using data obtained from outbreaks (e.g., as developed for *Salmonella* (Fazil et al., 2001)). Surrogate dose response models have been used in *E. coli* O157 QMRAs but have yet to be fully validated with outbreak data. These include a surrogate *Shigella* beta-Poisson model based on feeding studies in humans formulated by Crockett et al. (1996) which was chosen because *Shigella* infections can be foodborne and the toxins produced are similar to those of *E. coli* O157 (Doyle et al., 2001). This model pooled experimental data from *Shigella flexneri* and *dysenteriae* strains and was shown to be statistically indistinguishable from separate dose response models of each species, suggesting its potential to represent the *Shigella* species. Haas et al. (2000) proposed a dose response model for *E. coli* O157 from rabbits inoculated through an oral catheter. The two models are considerably different with the Haas version requiring approximately 500 times as many organisms to infect 50% of animals exposed compared to the Crockett model. Strachan et al. (2001) demonstrated