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Dose-response relationships for foot and mouth disease in cattle and sheep

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SUMMARY

The relationships between the inhaled dose of foot and mouth disease virus and the outcomes of infection and disease were examined by fitting dose-response models to experimental data. The parameters for both the exponential and beta-poisson models were estimated using maximum likelihood and Bayesian methods. The median probability of infection given a single inhaled $TCID_{50}$ was estimated to be 0·031 with 95% Bayesian credibility intervals (CI) of 0·018–0·052 for cattle, and 0·045 (CI = 0·024–0·080) for sheep. These estimates were used to construct dose-response curves and uncertainty distributions for use in quantitative risk assessments.

INTRODUCTION

An understanding of the relationship between dose, infection and disease is an essential component of quantitative microbial risk assessments (MRAs). Indeed, in the area of food safety MRA, there has recently been an extensive amount of research which focuses on how best to represent this relationship mathematically. Such research has resulted in the production of guidelines which outline key theoretical features of dose response modelling (WHO/FAO Guidelines on hazard characterization for pathogens in food and water. Available at http://www.fao.org/ES/esn/pagerisk/mra006.pdf). These features are applicable to any area of risk assessment where infection or disease is the required end-point.

The relationship between virus dose and the likelihood of infection has often been referred to in publications on foot and mouth disease (FMD) [1–3].

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In common with other viruses, the amount of FMD virus in a sample is frequently measured in units of ID_{50} (infectious dose 50). A single tissue culture ID_{50} ($TCID_{50}$) is the amount of virus that will infect 50% of tissue cultures, whereas a single mouse ID_{50} (MID_{50}) will infect 50% of inoculated mice. Both are assumed to be directly proportional to the number of infectious virus particles in the sample. A frequently used concept is that of the minimum infectious dose (often given in ID_{50}s) often defined as the minimum amount of virus required to cause disease. By implication, exposure to doses below this quantity will not result in disease, whereas doses above this will, with increasing probability, result in infection and disease [1, 4]. However, the experiments used to determine the putative minimum infectious dose are often carried out on small numbers of animals [5, 6]. The probability of at least one animal in a group becoming infected is not only dependent on the virus dose, but also on the sample size; the larger the sample size, the greater the probability that at least

one animal will become infected. It is highly likely, therefore, that the minimum infectious doses reported in the literature, refer to doses with a low probability of causing infection and/or disease and it is likely that even smaller doses could result in infection in larger populations.

The relationship between dose and response for FMD was further developed by Sutmoller and Vose [3] and Cannon and Garner [7] who proposed deterministic models of the relationship between dose and infection based on probabilistic arguments and 'single hit theory' models of dose-response. Their models are deterministic in that they do not include a description of the uncertainty associated with the dose-response parameters. In reality, however, these parameters are likely to be uncertain, as a result of, for example, the small sample sizes used to obtain the experimental data. In this paper we consider the importance of uncertainty by extending the work of these authors. In particular, we fit stochastic models to data published in the literature with the aim of parameterising a dose-response curve for FMD in cattle and sheep exposed by inhalation. The recent major epidemic of FMD in the UK underlined the need for appropriately parameterised models to aid decision making and guide policy; an understanding of the relationship between exposure dose and the probability of infection and disease is an important contribution to model-based risk assessments.

METHODS

Raw data on the relationship between virus dose (measured in $TCID_{50}$s) and infection and disease were taken from the papers by Donaldson et al. [5] and Gibson and Donaldson [6]. In the study by Donaldson et al. [5], 33 calves in two separate experiments were exposed to natural and artificial aerosols of two strains of FMD virus (O_1 BFS 1860 and SAT 2 SAR 3/79) and the dose received by each calf was estimated. In the study by Gibson and Donaldson [6], 24 sheep were exposed to aerosols of FMD virus strain O_1 BFS 1860. An animal was defined as 'infected' if it either sero-converted or virus was recovered in oesophageal-pharyngeal fluid. We have defined an animal as 'diseased' if it became viraemic and/or developed lesions.

The dose–response relationship was explored by fitting two models; the exponential and beta-poisson models [8, 9].

Exponential model:

$$P_{\text{inf/dis}}(D; r) = 1 - e^{-rD} \tag{1}$$

Where $1 - e^{-r}$ is the probability of infection or disease, $P_{\text{inf/dis}}$, given a single unit ($TCID_{50}$) of infection and D is the dose. This is the most commonly used 'single-hit' dose-response model which assumes that all organisms are independent and have the same probability of initiating infection/disease.

Beta poisson model:

$$P_{\text{inf/dis}}(D; \alpha, \beta) = 1 - \left(1 + \frac{D}{\beta}\right)^{-\alpha} \tag{2}$$

Where α and β are parameters of the beta distribution which describes the assumed heterogeneity in the probability of any individual organism initiating infection/disease in any host.

Two methods were used to fit the models and estimate parameters: Maximum likelihood and Bayesian methods (see Appendix for details). The latter provides posterior distributions of the parameters r, α and β. The prior used for the parameter 'r' in the exponential model was an exponential (parameter = 1) distribution.

RESULTS

Dose and infection in cattle

The parameter 'r' in the exponential model was estimated to be 0·030 using maximum likelihood methods and the median of the Bayesian posterior distribution was 0·032 with 95% credibility intervals (CI) of 0·018 to 0·054 (Table 1). Thus the probability of infection given a single $TCID_{50}$ ($1 - e^{-r}$) was estimated to be 0·031 (95% CI = 0·018–0·052). The posterior distribution for the parameter is described well by a shifted gamma distribution with a shape parameter of 9·33, a scale parameter of 0·0030 and a shift of 0·0053 (Fig. 1). The predicted dose-response curve for model 1 with 95% credibility intervals is given in Figure 2. The maximum likelihood estimates of the parameters for the beta-poisson model were $\alpha = 9{\cdot}4$ and $\beta = 288$ giving an estimated probability of infection given a single $TCID_{50}$ of 0·03. However, a plot of the likelihood as a function of α and β reveals a long ridge, the top of which is almost level. This means that a wide range of (α, β) values, along the top of this ridge, have likelihood values almost indentical to that of the maximum likelihood estimates, and so

Table 1. *The maximum likelihood and Bayesian estimates of the parameter* 'r' *in the exponential dose-response model for Foot and Mouth Disease in cattle and sheep*

Model	Maximum likelihood estimate	Bayesian posterior median	95% Bayesian credibility interval
Cattle: dose-infection	0·0301	0·0321	0·0183–0·0539
Cattle: dose-disease	0·00078	0·00082	0·00047–0·0013
Sheep: dose-infection/disease	0·0422	0·0465	0·0240–0·0839

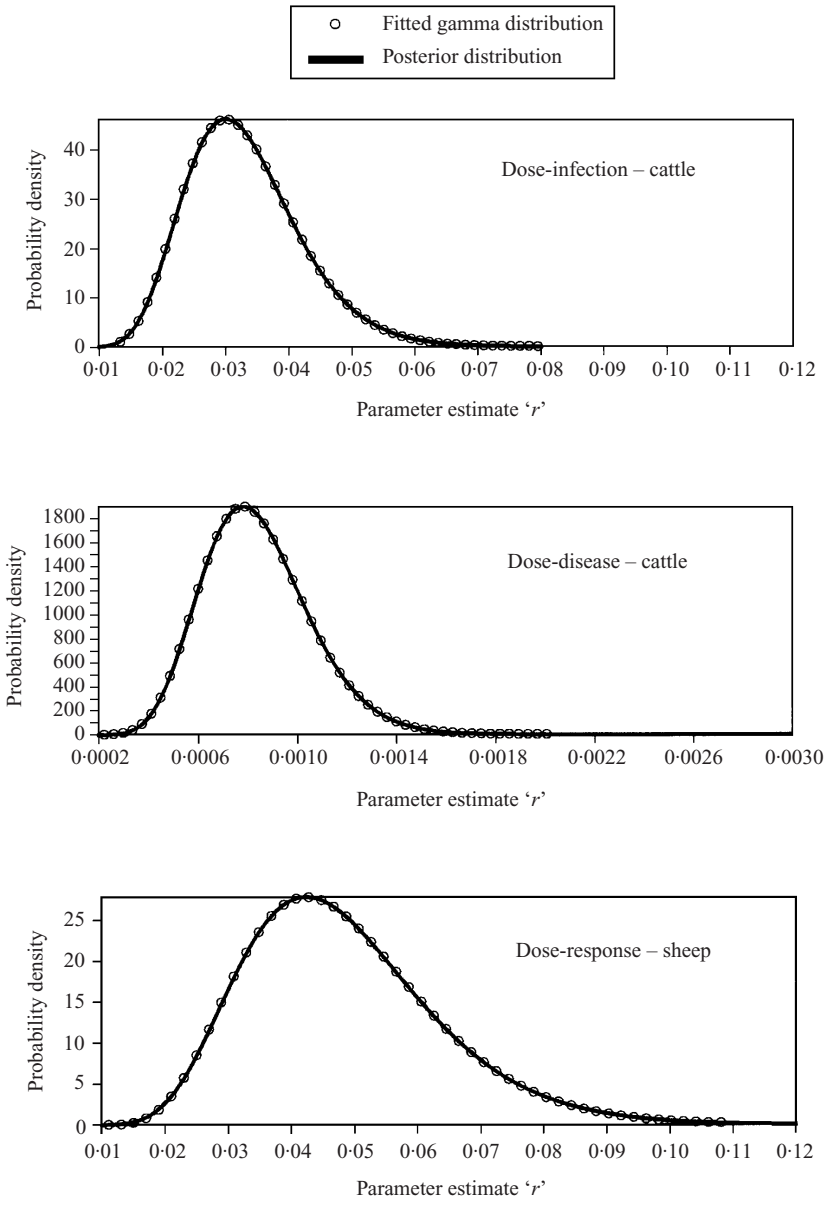

Fig. 1. Posterior distributions for the parameter '*r*' (the probabilities of infection and disease given exposure to a single $TCID_{50}$) for cattle and sheep.

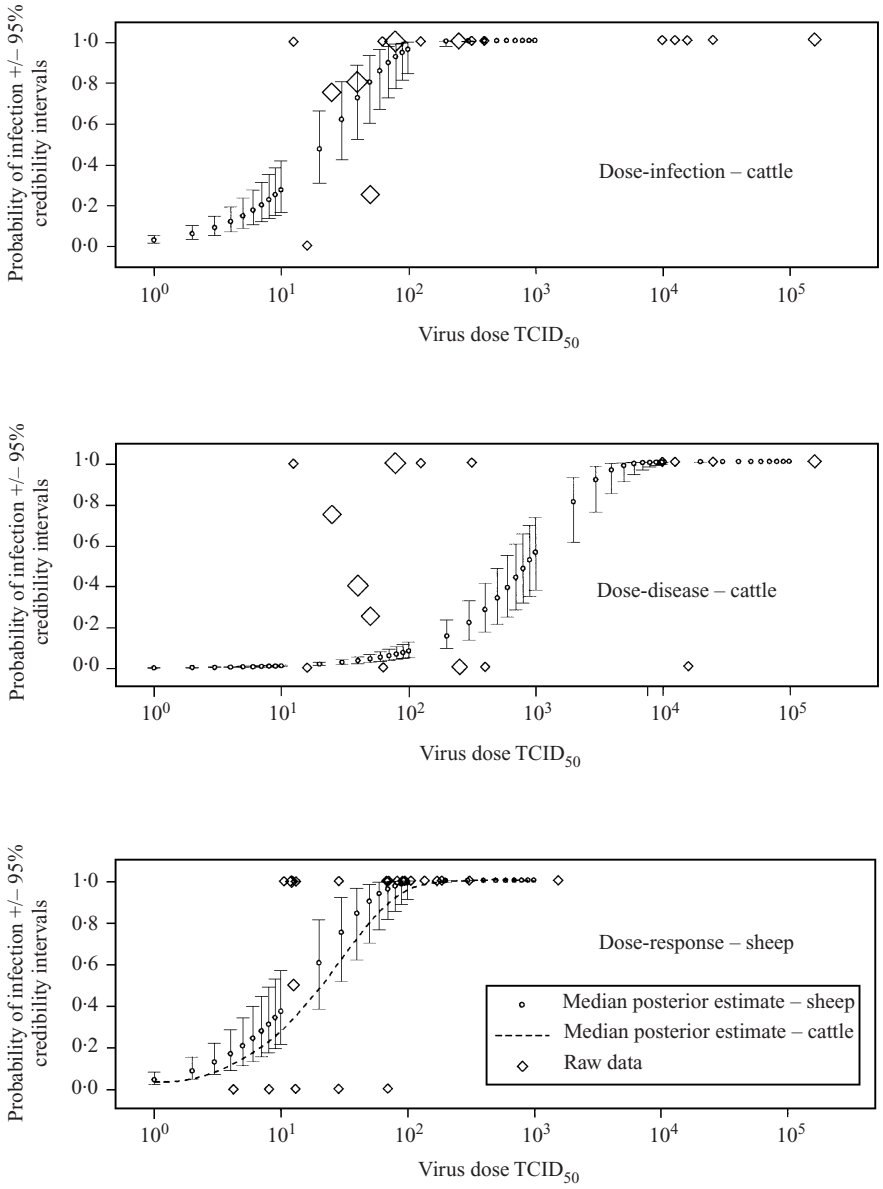

Fig. 2. The relationship between dose and response (infection and disease) in cattle and sheep for inhalation of FMD from an exponential model. The plots show the Bayesian posterior estimate with 95% credibility intervals. The diamonds show the raw data with the symbol size varying according to the number of animals exposed to each dose (range 1–5).

are almost as plausible as parameter estimates. Thus there is a great deal of uncertainty associated with the parameter estimates, and credibility intervals would be very wide. In fact, when trying to fit this model to the data by Markov chain Monte Carlo methods in order to compute credibility intervals, the algorithm failed to converge. On the other hand, the likelihood ridge is aligned in the direction in which α/β is constant, which means that although neither α nor β can be estimated with any great precision, we can be more confident of our estimate of the ratio α/β, the maximum likelihood estimate being $\alpha/\beta = 0{\cdot}03$. As a first order approximation, the probability of infection given a single $TCID_{50}$ for the beta-poisson model is given by precisely this ratio.

Dose and disease in cattle

The parameter 'r' in the exponential model was estimated to be $7{\cdot}8 \times 10^{-4}$ using maximum likelihood methods and the median of the Bayesian posterior distribution was $8{\cdot}2 \times 10^{-4}$ with 95% CI of $4{\cdot}7 \times 10^{-4}$–$1{\cdot}3 \times 10^{-3}$ (Table 1). The posterior distribution was well described by a shifted gamma distribution with a shape parameter of 14·8, a scale parameter of $5{\cdot}6 \times 10^{-5}$ and a shift of $7{\cdot}3 \times 10^{-6}$ (Fig.

1). Given the low value of 'r' this is equivalent to the probability of disease given exposure to a single $TCID_{50}$ (i.e. $r \sim 1-e^{-r}$). The estimated dose-response curve is shown in Figure 2. On inspection the model seemed to provide a poor fit to the data; the relatively high probability of disease for low doses was not well described by the exponential model. The maximum likelihood estimates of the parameters for the beta-poisson model were $\alpha = 0{\cdot}097$ and $\beta = 0{\cdot}02$ giving an estimated probability of infection given a single $TCID_{50}$ of 0·32. However, as in the case of the dose-infection data, the likelihood surface consists of a long ridge of almost equally plausible (α, β) values, and in this case the ridge is not aligned in the direction in which α/β remains constant. Thus not only are the estimates of α and β separately likely to be unreliable, but so is the estimate of their ratio, and hence of the probability of infection given a single $TCID_{50}$. The estimate of this probability also seems biologically inconsistent because it is 10 times greater than the probability of infection given a single dose.

Dose response (*infection and disease*) *in sheep*

In this study 24 sheep were exposed to varying doses of virus, of which all infected animals became diseased. It was therefore not possible to distinguish between infection and disease in this species. The parameter 'r' in the exponential model was estimated to be 0·042 using maximum likelihood methods and the median of the Bayesian posterior distribution was 0·047 with 95% credibility intervals (CI) of 0·024 to 0·084 (Table 1). The equivalent estimate for the probability of infection and disease given a single $TCID_{50}$ was therefore 0·045 (95% CI = 0·024–0·080). The posterior distribution was well described by a shifted gamma distribution with a shape parameter of 6·86, a scale parameter of 0·0058 and a shift of 0·0081 (Fig. 1). The estimated dose-response curve is shown in Figure 2. As with the cattle data, fitting the beta-poisson model to these data results in a likelihood surface with a wide range of almost equally plausible (α, β) values, so that maximum likelihood estimates cannot be relied upon and any estimate of the probability of infection given a single $TCID_{50}$ will have a great deal of uncertainty associated with it.

DISCUSSION

The relationship between the dose of FMD virus and the response, in terms of infection and disease, is an important component of many model-based risk assessments of the spread of this disease in animal populations [1, 7, 10, 11]. Frequently, single estimates of the 'minimum infectious dose' are used to determine cut-off points for infection and disease, with the implication that infection will not occur at a lower dose. This approach was challenged by Sutmoller and Vose [3] who used a more probabilistic argument to determine the relationship between oral dose of FMDV and infection in pigs. Likewise Cannon and Garner [7] used a similar method to estimate the response to inhaled FMDV in cattle and sheep. In these studies 'single hit' models were used to calculate the probability that a single infectious unit would initiate an infection. From these estimates the authors calculated the probability that at least one animal in a group would be infected by a given dose. This requires the fundamental assumption that each infectious unit has a non-zero probability of initiating an infection. Although these methods are based on probabilistic arguments, they do not provide any estimate of the variation around the single deterministic values and are therefore of limited value in stochastic risk assessments. The present study has developed the arguments further by fitting stochastic microbial dose-response models to the same experimental data used by Cannon and Garner [7]. This allows us to estimate the relationship between inhaled dose and the probability of infection and disease with an estimate of the uncertainty surrounding these values.

Two models were fitted to experimental data; the exponential and beta-poisson model. Both are widely used in microbial quantitative risk assessments [8, 9] to model the relationship between the dose of a pathogen and the probability of infection using experimental and observational data. The former is an extension of the basic 'hit theory' model in which the pathogen is assumed to follow a poisson distribution in the inoculum and the latter allows for heterogeneity in response between individuals. The methods used here have a number of advantages over simple deterministic calculations; they allow uncertainty in parameter estimates to be represented by probability distributions and extrapolation to estimate the risk from low-dose exposures. However, as with all model-based approaches, the model assumptions need to be considered. Arguably the most important is the fundamental assumption that a single $TCID_{50}$, and by implication a single virus particle, has a non-zero probability of initiating infection. Furthermore, we

also make the assumption that all virus particles have the same independent probability of initiating infection and this probability does not change with dose. To date we do not have the experimental data to test these assumptions although, arguably, they are more plausible than assuming a simple cut-off minimum infectious dose.

Using the exponential model, the maximum likelihood estimate of the probability of infection in cattle and sheep (defined as sero-conversion and/or recovery of virus from oesophageal/pharyngeal fluid) with a single inhaled $TCID_{50}$, was between 3% and 5% – similar to those reported by Cannon and Garner [7]. Although there is considerable overlap of the uncertainty distributions for dose-infection in cattle and sheep, there appears to be a marked difference in the probability of becoming viraemic and developing lesions; cattle have a much lower probability of developing disease (and presumably transmitting infection to other animals) than sheep. Simply using the minimum infectious doses reported in the literature in disease spread and risk assessment models fails to recognise the important difference between cattle and sheep and could result in an underestimate of the risk of infection and disease from low-dose exposure [4].

In this study it was not possible to provide appropriate estimates of the parameters in the beta-poisson model. The difficulty in fitting this model to the data arises because none of the three likelihood surfaces has a single isolated peak, but rather a long ride of (α, β) values which are all almost equally plausible as parameter estimates. This suggests that the beta-poisson model is not an appropriate model of the relationship between dose and response for FMDV and/or there are insufficient data to estimate the parameters. Considering the small number of animals exposed to each dose, the experimental model appeared to describe the dose-infection relationship for cattle and sheep reasonably well. However, the fitted dose-disease curve for cattle appeared to underestimate the probability of infection for low doses and was not, on visual inspection, a good description of the data. This could result from a more complex relationship between the conditional probability of disease given infection for different exposure doses and requires further investigation.

The data were produced by controlled experiments in which animals were subjected to varying doses of virus over a short period of time (5–15 min). The dose-response relationship for longer periods of exposure has not been determined and the cumulative effects of multiple exposures has not been considered in this study. The uncertainty distributions presented in this paper represent the uncertainty around the parameters r, α and β and reflect both the variation in response to estimated doses of FMDV and the sample size. A more complete assessment of the uncertainty would need to consider error in the estimation of exposure dose (e.g. variation in tidal volumes, air flow rates and aerosol sampling) and response (e.g. the sensitivity and specificity of diagnostic tests) [5, 6].

By fitting stochastic models to experimental data we have provided more informative estimates of the relationship between virus dose and FMDV infection in cattle and sheep. Given available data this approach can be extended to include other species and other routes of infection. Provided the assumptions are carefully considered, the outputs can be of considerable value in assessing the risk of infection and disease under different scenarios.

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APPENDIX

Exponential model: $P(D; r) = 1 - e^{-rD}$

Obtaining the maximum likelihood (MLE) estimate of 'r'

Suppose we have observations at j different doses. For $i = 1, 2, \ldots, j$, denote by N_i the number of individuals exposed to dose D_i, and by Y_i the number to become infected/diseased. Then given r, the distribution of Y_i is Binomial with parameters N_i, $1 - e^{-rD_i}$. Hence the likelihood is

$$L(r; Y_1, Y_2, \ldots, Y_j) = \prod_{i=1}^{j} \left\{ \binom{N_i}{Y_i} (1 - e^{-rD_i})^{Y_i} e^{-rD_i(N_i - Y_i)} \right\},$$

and the log-likelihood is

$$l(r; Y_1, Y_2, \ldots, Y_j) = \sum_{i=1}^{j} \left\{ \ln \binom{N_i}{Y_i} + Y_i \ln(1-e^{-rD_i}) - rD_i(N_i - Y_i) \right\}.$$

To find the maximum likelihood estimate of r we therefore need to maximize numerically the function

$$l_1(r) = \sum_{i=1}^{j} Y_i \ln(1-e^{-rD_i}) - r \sum_{i=1}^{j} D_i(N_i - Y_i).$$

Estimating the posterior distribution of 'r'
We took the prior distribution for r to be exponential with mean 1, so that the prior density for r is $f(r) = e^{-r}$ for $r > 0$. Bayes' Theorem then yields that the posterior density of r satisfies

$$f(r \mid Y_1, Y_2, \ldots, Y_j) \propto e^{-r} L(r; Y_1, Y_2, \ldots, Y_j) \propto e^{-r} \prod_{i=1}^{j} \{(1-e^{-rDi})^{Y_i} e^{-rD_i(N_i - Y_i)}\}.$$

In order to compute the posterior distribution, we need to know the constant of proportionality in the above relationship, which we can determine using the condition

$$\int_0^\infty f(r \mid Y_1, Y_2, \ldots, Y_j)\, dr = 1. \tag{A1}$$

In practice, intermediate calculations are carried out using the log of the posterior distribution,

$$\ln(f(r \mid Y_1, Y_2, \ldots, Y_j)) = K - r + \sum_{i=1}^{j} Y_1 \ln(1-e^{-rD_i}) - r \sum_{i=1}^{j} D_i(N_i - Y_i),$$

where the constant K is to be determined. Note also that although the condition (A1) requires a numerical integration to be carried out for r values over the range $[0, \infty]$, in reality the value of the posterior density drops to zero rapidly as r increases. For instance, in the case of dose-infection for cattle, we can see from Figure 1 that it is quite sufficient to evaluate the integral over the range [0, 0.1].

Beta poisson model: $P(D; \alpha, \beta) = 1 - \left(1 + \frac{D}{\beta}\right)^{-\alpha}$
Obtaining the maximum likelihood (MLE) estimates of 'α' *and* 'β'

The likelihood in this case is

$$L(\alpha, \beta; Y_1, Y_2, \ldots, Y_j) = \prod_{i=1}^{j} \left\{ \binom{N_i}{Y_i} \left(1 - \left(1 + \frac{D_i}{\beta}\right)^{-\alpha}\right)^{Y_i} \left(1 + \frac{D_i}{\beta}\right)^{-\alpha(N_i - Y_i)} \right\}.$$

Taking logs, we find that maximizing the likelihood is equivalent to maximizing the function

$$l_1(\alpha, \beta;\ Y_1, Y_2, \ldots, Y_j) = \sum_{i=1}^{j} Yi \ln\left(1 - \left(1 + \frac{D_i}{\beta}\right)^{-\alpha}\right) - \alpha \sum_{i=1}^{j} (N_i - Y_i) \ln\left(1 + \frac{D_i}{\beta}\right),$$

and hence we can compute numerically maximum likelihood estimates of α and β.

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