Asymptotic Confidence Ellipses of Parameters for the Beta-Poisson Dose-Response Model

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Abstract

The objective of this study is to argue that two classical estimation methods (method of moments and method of maximum likelihood) cannot be applied for a construction of an asymptotic confidence ellipse for the Beta-Poisson dose-response model directly. That is, the first moment for the probability density function of the Beta-Poisson dose-response model exists for $\alpha > 1$, but data known from literature show that a typical values of α is around a few hundredths, while a typical values of β is around a few hundred. And the method of maximum likelihood, we cannot find parameter estimators of the Beta-Poisson dose-response model and also it is not possible to find the asymptotic covariance matrix from the Fisher information matrix, hence it is also not possible to construct an asymptotic confidence ellipse based on the maximum likelihood estimates.

For this purpose we need to use a suitable approximation for the Beta-Poisson dose-response model. After that, we derive maximum likelihood equations for parameters of the approximate Beta-Poisson dose-response model. For this model, we

find the Fisher information matrix and construct a normal approximation that gives elliptical confidence regions of the approximate Beta-Poisson dose-response model. We use the coverage probabilities as the criteria for comparing with the nominal level 0.98 and investigate the accuracy of the confidence ellipses are fulfilled by the Monte-Carlo method. Three sample sizes (n) are 100, 500, 1,000 and four cases of values for parameters of the Beta-Poisson dose-response model ((i) $\alpha = 0.1, \beta = 10$ (ii) $\alpha = 0.08, \ \beta = 100$ (iii) $\alpha = 0.3, \ \beta = 150$ (iv) $\alpha = 0.7, \ \beta = 180$) are studied here. R (2.13.0) software is used for simulation technique with 10,000 iterations. The results of this study are as followed:

The coverage probabilities of confidence ellipses for parameters of the approximate Beta-Poisson dose-response model increase when sample sizes (n) increase and also they are close to the confidence coefficient 0.98.

In addition, at various values of parameters of Beta-Poisson dose-response model, the coverage probabilities are similar when n is fixed.

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Keywords: Quantitative microbiological risk assessment (QMRA), Method of moments, Method of maximum likelihood, Fisher information, Delta method.

1. Introduction

Risk analysis is a complex process consisting of risk assessment, risk management, and risk communication. Over the past decade it has been developed as a structured model for improving production control system in many branches of World economy. For example, it can be applied for our food control systems with the objectives of producing safer food, reducing the numbers of food-borne illnesses and facilitating domestic and international trade in food. It also should be mentioned that risk assessment helps us to organize all available data for better understanding the interaction between human illnesses, microorganisms, and foods. Importantly, we are able to estimate the risk that specific microorganisms in food can do to human health [1].

Microbiological risk assessment can be considered as a tool that can be used in the management of the risks posed by food-borne pathogens and in the elaboration of standards for food in international trade.

As it is mentioned in Haas et al. [2] "Quantitative microbiological risk assessment (QMRA), is recognized as a resource-intensive task requiring a multidisciplinary approach. Yet, food-borne illness is among the most widespread public health problems creating social and economic burdens as well as human suffering,

making it a concern that all countries need to address. In a QMRA framework, the dose-response assessment phase is the quantitative yardstick for risk estimation, as this phase estimates a risk of response (infection, illness or death) with respect to a known dose of a pathogen. The basis of the dose-response phase is the dose-response models, which are mathematical functions that take as an argument a measure of dose (which can be any non-negative number) and yields the probability of the particular adverse effect, which is bounded by zero (no effect) and one (complete conversion to adverse state). There are an infinite number of such possible functions. Even restricting the universe to those functions that are monotonic (as dose increases, response probability is nondecreasing) and bounded by zero and one (at dose = 0, no response; as dose $\rightarrow \infty$, complete response), there remain an infinite number of possible functions. In particular, the last set of conditions is identical to those required of cumulative distribution functions, so any cumulative distribution function with support over $(0, \infty)$ can be a candidate dose-response function".

To be plausible, a model should consider the particulate nature of organisms, which has a high variability at low dose. It should also be based on the concept of infection from one or more "survivors" of the initial dose. Therefore dose response models for QMRA need to be physiologically plausible and be derived from what is known of the general infection process. There are two models which are derived based on these needs for the QMRA dose response relationship, the Exponential and Beta-Poisson models, specifically, the Beta-Poisson dose-response model (model with two parameters) which is enlarged from the Exponential dose-response model (model with only one parameter).

Furumoto & Mickey [3] described the Beta-Poisson as a random model of an infection growing on a tobacco plant by a Mosaic virus. The infection can be described in the following way. A leaf of tobacco plant is attacked by viruses. The number of viruses is random and has a Poisson distribution with the intensity parameter x, denoted by $Pois(x)$. The plant is infected if at least one virus penetrates its cell. Each cell has some (different for different types of cells) resistance, and hence the infection happens with probability θ, which is also considered to be a random variable. If we assume that θ has a Beta distribution with parameters α and β, then the probability of the infection as a function of the intensity of virus flow x has a probability distribution of the Beta-Poison dose-response model with the shape parameter α and scale parameter β.

Beta-Poisson dose response model has been considered in experimental data of various infection cases; for example, Medema et al. [4] presented an assessment of

the Beta-Poisson dose-response model of *Campylobacter jejuni (C.jejuni)*, Teunis & Havelaar [5] found that the Beta-Poisson dose-response model is not a single-hit model. Single-hit models have played a prominent role in dose-response assessment for pathogenic microorganisms. In particular the Beta-Poisson model, are used for extrapolation of experimental dose-response data to low doses, as are often present in drinking water or food products., Latimer et al. [6] described the development of a weighted composite dose–response model for human Salmonellosis and Moon et al. [7] presented comparison of microbial dose–response models fitted to human data.

Nevertheless, all authors mentioned above have studied only point and interval estimators of the parameters of Beta-Poisson dose-response model, but they have not yet studied confidence regions of those parameters that have been studied in various cases; such as, Takada [8] studied confidence sets for the mean of a multivariate normal distribution with an unknown covariance matrix of the form $\sigma^2 I$, Dilba et al. [9] dealt with the problem of simultaneously estimating multiple ratios, Menendez et al [10] presented confidence sets for the parameters of a logistic regression model based on preliminary minimum Φ-divergence estimators, Azad [11] invented a new method to test the significance levels of common periodicities (if any) among sub-divisional rainfall time series using the confidence ellipse technique and Chaudhuri [12] studied a simple least squares method for fitting of ellipses and circles (depending on border points) of a two-tone image and their 3-D extensions.

In this paper we focus on the Beta-Poisson dose-response model. This includes investigating some limitations of parameters estimation for the Beta-Poisson dose-response model and its approximation. Moreover, we find the Fisher information matrix for construction of a normal approximation that gives elliptical confidence regions for parameters. The article is organized as follows. In Section 2 we reveal framework for mechanistic dose-response relationships. In Section 3 we present methodology. The results are shown in Section 4 and simulation study is presented in Section 5. In Section 6 we show an example and concluding remarks are offered in Section 7.

2. Framework for Mechanistic Dose-Response Relationships

Haas et al. [2] described framework for mechanistic dose-response relationships as follows:

The probability of investigating precisely *j* organisms from an exposure in which the mean dose (the product of volume and density) is x (i.e., the first of the sequential processes) is written as $P_1(j|x)$, the probability of *k* organisms $(\leq j)$ surviving to initiate

an infectious process (the second step) is written as $P_2(k|j)$. If these two processes are regarded as independent, the overall probability of k organisms surviving to initiate infectious foci is given by (the law of independent events)

$$P(k) = \sum_{j=1}^{\infty} P_2(k|j) P_1(j|x)$$

The function P_1 incorporates the individual-to-individual variation in actual numbers of organisms ingested or otherwise exposed, and the function P_2 expresses the factors of the organisms-host interaction in vivo that allow some organisms to survive to initiate infectious foci.

Infection occurs when at least some critical numbers of organisms survive to initiate infection. If this minimum number is denoted as k_{min} , the probability of infection (the fraction of subjects who are exposed to an average dose x who become infected) may be written as

$$P_i(x) = \sum_{k=k_{min}}^{\infty} \sum_{j=k}^{\infty} P_2(k|j) P_1(j|x)$$

The two conceptual alternatives have been termed the *hypothesis of independent action*, in which in principle k_{min} equals 1, and the *hypothesis of cooperative interaction*, in which k_{min} is some number greater than 1.

The simplest dose-response model that can be formulated assumes that the distribution of organisms between doses is random (i.e., Poisson), that each organism has an independent and identical survival probability, θ. From the Poisson assumption, we have

$$P_1(j|x) = \frac{\exp(-x)\, x^j}{j!}$$

The assumption with respect to survival means that the Binomial distribution can be used as

$$P_2(k|j) = \frac{j!}{k!\,(j-k)!}\, \theta^k (1-\theta)^{j-k}$$

Hence,

$$P_i(x) = \sum_{k=k_{min}}^{\infty} \sum_{j=k}^{\infty} \left[\frac{j!}{k!\,(j-k)!}\, \theta^k (1-\theta)^{j-k} \right] \left[\frac{\exp(-x)\, x^j}{j!} \right]$$

$$= 1 - \left[\sum_{k=0}^{k_{min}-1} \frac{\exp(-x\theta)\,(-x\theta)^k}{k!} \right]$$

with the assumption of $k_{min} = 1$, this yields

$$P_I(x) = 1 - \exp(-x\theta) \tag{1}$$

The Beta-Poisson dose-response model is enlarged from the Exponential dose-response model. The Exponential dose-response model assumes constancy of the pathogen-host survival probability (θ). For some agents and populations of human hosts, there may be variation in this success rate. Such variation may be due to diversity in human responses, diversity of pathogen competence, or both. This variation can be captured by allowing θ to be governed by a probability distribution. This phenomenon of host variability was perhaps first invoked by Moran [13].

The mixing distribution $f(\theta)$ should have (its only) support over the interval (0,1), corresponding to the allowable range of variability of θ itself. Use of the above equation is identical to applying the mixture operation directly to equation (1) if the Poisson distribution for dose-to-dose variation is assumed, thus yielding

$$P_I(x) = \int_0^1 [1 - \exp(-x\theta)]f(\theta)\,d\theta$$

$$= 1 - \int_0^1 \exp(-x\theta)\,f(\theta)\,d\theta$$

A logical distribution, which offers a great deal of flexibility, is the Beta distribution. Incorporating this into above equation, yields

$$P_I(x) = 1 - \int_0^1 [\exp(-x\theta)]\left[\frac{1}{B(\alpha,\beta)}\theta^{\alpha-1}(1-\theta)^{\beta-1}\right]d\theta \tag{2}$$

Notice that, equation (2) describes the cumulative distribution function of the Beta-Poisson dose-response model.

The cumulative distribution function of a continuous random variable X under the Beta-Poisson dose-response model (*BP*-dose-response model) with parameters α and β, denoted by $BP(\alpha,\beta)$ is

$$F(x; \alpha, \beta) = 1 - \frac{1}{B(\alpha, \beta)} \int_0^1 \exp\{-\theta x\}\, \theta^{\alpha-1}(1-\theta)^{\beta-1} d\theta, \qquad (3)$$

where $x > 0$, $\alpha > 0$, $\beta > 0$ and α and β are the slope and scale parameter, respectively. The probability density function of the Beta-Poisson dose-response model is

$$f(x; \alpha, \beta) = \frac{1}{B(\alpha, \beta)} \int_0^1 \exp\{-\theta x\}\, \theta^{\alpha}(1-\theta)^{\beta-1} d\theta. \qquad (4)$$

3. Methodology

Firstly, we argue that two classical estimation methods (method of moments and method of maximum likelihood) do not work to construct an asymptotic confidence ellipse for the Beta-Poisson dose-response model directly and for this purpose we need to find a suitable approximation for the Beta-Poisson dose-response model. Next, we derive maximum likelihood equations for parameters of the approximate Beta-Poisson dose-response model. Moreover, we find the Fisher information matrix and construct a normal approximation that gives elliptical confidence regions of approximating the Beta-Poisson dose-response model.

Three sample sizes (n) are 100, 500, 1,000 and four cases of values for parameters of the Beta-Poisson dose-response model ((i) $\alpha = 0.1, \beta = 10$ (ii) $\alpha = 0.08,\ \beta = 100$ (iii) $\alpha = 0.3,\ \beta = 150$ (iv) $\alpha = 0.7,\ \beta = 180$) are studied here. R (2.13.0) software is used for simulation technique with 10,000 iterations. For each case we compare coverage probability of confidence ellipse with the nominal level 0.98 and investigate the accuracy of the confidence ellipses by the Monte-Carlo method.

4. Results

In this section, we describe results of this study as follows:

4.1 Beta-Poisson Dose-Response Model

4.1.1 The problem of parameters estimation by Method of Moments to Construct an Asymptotic Confidence Ellipse

If $E(X^k)$ is finite, where k is a positive integer, then $E(X^k)$ is called the k-th moments of X (or the distribution of X). Given X has a probability distribution of the $BP(\alpha, \beta)$. Then the k-th moments of X is

$$E(X^k) = \mu_k = k! \frac{(\alpha + \beta - 1)(\alpha + \beta - 2) \cdots (\alpha + \beta - k)}{(\alpha - 1)(\alpha - 2) \cdots (\alpha - k)}, \quad \alpha > k.$$

Note that $E(X^k)$ exists only if $\alpha > k$ and the method of moments estimators (MME) $\hat{\alpha}^{(MME)}$ and $\hat{\beta}^{(MME)}$ of parameters α and β are as follows:

$$\hat{\alpha}^{(MME)} = 2 \frac{S^2 - \bar{X}}{S^2 - \bar{X}^2}$$

$$\hat{\beta}^{(MME)} = (\bar{X} - 1) \frac{S^2 + \bar{X}^2 - 2\bar{X}}{S^2 - \bar{X}^2}$$

where $\bar{X} = \frac{1}{n} \sum_{i=1}^{n} X_i$, $S^2 = \frac{1}{n} \sum_{i=1}^{n} (X_i - \bar{X})^2$.

Theoretically by using the Delta method for normal approximation it is possible to find the asymptotic covariance matrix of two parameter estimates by method of moments $\hat{\alpha}^{(MME)}$ and $\hat{\beta}^{(MME)}$ and after constructing an asymptotic confidence ellipse. However, the calculations are extremely cumbersome, and are not recommended for practical applications. Moreover, these lengthy calculations would be useless for statistical analysis of epidemiological data, because data known from literature show that a typical values of α is around a few hundredths, while a typical values of β is around a few hundred. Even the first moment for the probability density function of the Beta-Poisson dose-response model exists for $\alpha > 1$.

4.1.2 The problem of parameters estimation by Method of Maximum Likelihood to Construct an Asymptotic Confidence Ellipse

To construct an asymptotic confidence ellipse we need to find the asymptotic covariance matrix of these two maximum likelihood estimates $\hat{\alpha}^{(MLE)}$ and $\hat{\beta}^{(MLE)}$ from the Fisher information matrix and using the Delta method for normal approximation.

However, we cannot find maximum likelihood estimators and also it is not possible to calculate the Fisher information matrix in closed form for the probability density function of the Beta-Poisson dose-response model (4), hence it is also not possible to construct an asymptotic confidence ellipse based on the maximum likelihood estimates.

4.2 The Approximate Distribution Function of the Beta-Poisson Dose-Response Model

From the distribution function (3) we make a substitution $t = \beta\theta$ and obtain the integral

$$J = \frac{1}{B(\alpha,\beta)} \int_0^\beta \exp\left\{-\frac{tx}{\beta}\right\} \left(\frac{t}{\beta}\right)^{\alpha-1} \left(1-\frac{t}{\beta}\right)^{\beta-1} d\left(\frac{t}{\beta}\right)$$

$$= \frac{1}{B(\alpha,\beta)\beta^\alpha} \int_0^\beta \exp\left\{-\frac{tx}{\beta}\right\} t^{\alpha-1} \left(1-\frac{t}{\beta}\right)^{\beta-1} dt.$$

If $\beta \longrightarrow \infty$ and $\alpha \longrightarrow 0$ such that $\alpha\beta = $ constant then

$$\left(1-\frac{t}{\beta}\right)^{\beta-1} \sim \exp\{-t\}$$

then the integral J possesses an equivalent form

$$J \sim \frac{1}{B(\alpha,\beta)\beta^\alpha} \int_0^\infty \exp\left\{-\frac{tx}{\beta}-t\right\} t^{\alpha-1} dt$$

$$= \frac{1}{B(\alpha,\beta)\beta^\alpha \left(\frac{x}{\beta}+1\right)^\alpha} \int_0^\infty \exp\left\{-t\left(\frac{x}{\beta}+1\right)\right\} \left\{t\left(\frac{x}{\beta}+1\right)\right\}^{\alpha-1} d\left\{t\left(\frac{x}{\beta}+1\right)\right\}$$

with the help of the Gamma function

$$\Gamma(\alpha) = \int_0^\infty x^{\alpha-1} \exp\{-x\}\, dx$$

In our case $x = t\left(\frac{x}{\beta}+1\right)$. Applying these formulae we obtain

$$J = \frac{\Gamma(\alpha)}{B(\alpha,\beta)\beta^\alpha \left(\frac{x}{\beta}+1\right)^\alpha}$$

$$= \frac{\Gamma(\alpha+\beta)\Gamma(\alpha)}{\Gamma(\alpha)\Gamma(\beta)\beta^\alpha \left(\frac{x}{\beta}+1\right)^\alpha}$$

$$= \frac{\Gamma(\alpha+\beta)}{\Gamma(\beta)\beta^\alpha} \left(1+\frac{x}{\beta}\right)^{-\alpha}.$$

The approximation error is the order $1/\Gamma(\beta)$.

Because under our assumptions on α and β, the expression

$$\frac{\Gamma(\alpha+\beta)}{\Gamma(\beta)\beta^\alpha} \longrightarrow 1.$$

We obtain the cumulative distribution function of a continuous random variable X under the approximate Beta-Poisson dose-response model (*ABP*-dose-response model) with parameters α and β, denoted by $ABP(\alpha,\beta)$ is

$$F(x; \alpha, \beta) \sim \tilde{F}(x; \alpha, \beta) = 1 - \left(1 + \frac{x}{\beta}\right)^{-\alpha}. \tag{5}$$

The density function of this model is

$$f(x; \alpha, \beta) = \frac{\alpha}{\beta\left(1 + \frac{x}{\beta}\right)^{\alpha+1}}. \tag{6}$$

As $x \to 0$ or $x \to \infty$ this function is equivalent to the density function of a Beta-Poisson dose-response model and this function is proposed in Furumoto & Mickey [3].

4.2.1 The problem of parameters estimation by Method of Moments to Construct an Asymptotic Confidence Ellipse for the Approximate Beta-Poisson Dose-Response Model

The Beta function is defined as follows:

$$B(\alpha, \beta) = \int_0^1 t^{\alpha-1}(1-t)^{\beta-1}dt, \qquad \alpha > 0, \beta > 0.$$

In this integral, if we make a substitution $u = \frac{t}{1-t}$, we can have the following equivalent form of the Beta function

$$B(\alpha, \beta) = \int_0^\infty \frac{u^{\alpha-1}}{(1+u)^{\alpha+\beta}}du.$$

Now we calculate k-th moments for the probability density function of the approximate Beta-Poisson dose-response model

$$E(X^k) = \mu_k = \int_0^\infty x^k f(x; \alpha, \beta)dx$$

$$= \int_0^\infty x^k \frac{\alpha}{\beta\left(1 + \frac{x}{\beta}\right)^{\alpha+1}}dx.$$

Making the substitution $u = \frac{x}{\beta}$, then $du = \frac{dx}{\beta}$. Hence

$$E(X^k) = \mu_k = \int_0^\infty (\beta u)^k \frac{\alpha}{\beta(1+u)^{\alpha+1}}\beta du$$

$$= \alpha\beta^k \int_0^\infty \frac{u^{(k+1)-1}}{(1+u)^{(k+1)+(\alpha-k)}}du$$

$$= \alpha\beta^k B(k+1, \alpha-k).$$

Note that the Beta function $B(\alpha, \beta)$ is defined for $\alpha > 0$ and $\beta > 0$, we obtain that the last integral exists if $k+1 > 0$ and $\alpha - k > 0$, that is $\alpha > k$.

For the probability density function of the $ABP(\alpha, \beta)$, the k-th moments exist only if $\alpha > k$. Hence we cannot apply method of moments to construct an asymptotic confidence ellipse, because data known from literature show that a typical values of α is around a few hundredths, while a typical values of β is around a few hundred.

4.2.2 The Equations for Finding Maximum Likelihood Estimators for the Approximate Beta-Poisson Dose-Response Model

The likelihood function of $ABP(\alpha, \beta)$ is

$$L(\alpha, \beta; x) = \alpha^n (\beta)^{-n} \prod_{i=1}^{n} \left(1 + \frac{x_i}{\beta}\right)^{-(\alpha+1)}.$$

We obtain the system of maximum likelihood equations by evaluating derivatives with respect to α and β.

$$\frac{\partial}{\partial \alpha} \ln L(\alpha, \beta; x) = \frac{n}{\alpha} - \sum_{i=1}^{n} \ln\left(1 + \frac{x_i}{\beta}\right),$$

$$\frac{\partial}{\partial \beta} \ln L(\alpha, \beta; x) = -\frac{n}{\beta} + (\alpha+1) \sum_{i=1}^{n} \frac{x_i}{\beta^2 \left(1 + \frac{x_i}{\beta}\right)}.$$

Hence the Maximum likelihood estimators (MLE) $\hat{\alpha}^{(MLE)}$ and $\hat{\beta}^{(MLE)}$ of α and β can be obtained by simultaneously solving $\frac{\partial}{\partial \alpha} \ln L(\alpha, \beta; x) = 0$ and $\frac{\partial}{\partial \beta} \ln L(\alpha, \beta; x) = 0$, i.e.,

$$\alpha = \frac{n}{\sum_{i=1}^{n} \ln\left(1 + \frac{x_i}{\beta}\right)}$$

$$\alpha = \frac{n}{\sum_{i=1}^{n} \frac{x_i}{\beta + x_i}} - 1.$$

4.2.3 The Fisher Information of Parameters for the Approximate Beta-Poisson Dose-Response Model

From the approximate distribution function of the Beta-Poisson dose-response model (4), we obtain the second derivatives of log function $ABP(\alpha, \beta)$ as

$$\frac{\partial^2}{\partial \alpha^2} \ln f(x; \alpha, \beta) = -\frac{1}{\alpha^2}$$

$$\frac{\partial^2}{\partial \beta^2} \ln f(x; \alpha, \beta) = \frac{1}{\beta^2} - \frac{(\alpha+1)x(2\beta + x)}{\beta^4 \left(1 + \frac{x}{\beta}\right)^2}$$

$$\frac{\partial^2}{\partial \alpha \partial \beta} \ln f(x; \alpha, \beta) = \frac{x}{\beta^2 \left(1 + \frac{x}{\beta}\right)}$$

and expected values of the second derivatives with respect to α, β and $\alpha\beta$ as follows:

$$E\left[\frac{\partial^2}{\partial \alpha^2} \ln f(x; \alpha, \beta)\right] = E\left[-\frac{1}{\alpha^2}\right] = -\frac{1}{\alpha^2}$$

$$E\left[\frac{\partial^2}{\partial \beta^2} \ln f(x; \alpha, \beta)\right] = -\frac{\alpha}{\beta^2(\alpha+2)}$$

$$E\left[\frac{\partial^2}{\partial \alpha \partial \beta} \ln f(x; \alpha, \beta)\right] = \frac{1}{\beta(\alpha+1)} = E\left[\frac{\partial^2}{\partial \beta \partial \alpha} \ln f(x; \alpha, \beta)\right].$$

Now we can present the Fisher information matrix about α, β obtained from a single observation X.

$$I(\theta) = I(\alpha, \beta) = \begin{pmatrix} \dfrac{1}{\alpha^2} & -\dfrac{1}{\beta(\alpha+1)} \\ -\dfrac{1}{\beta(\alpha+1)} & \dfrac{\alpha}{\beta^2(\alpha+2)} \end{pmatrix},$$

the Fisher information matrix for a sample size n:

$$I_n(\theta) = nI(\theta)$$

where θ is a two-dimensional parameters vector, $\theta' = (\alpha, \beta)$.

The Fisher's information matrix about α, β obtained from $X_1, X_2, ..., X_n$ is

$$I_n(\theta) = n \begin{pmatrix} \dfrac{1}{\alpha^2} & -\dfrac{1}{\beta(\alpha+1)} \\ -\dfrac{1}{\beta(\alpha+1)} & \dfrac{\alpha}{\beta^2(\alpha+2)} \end{pmatrix}.$$

Because properties of maximum likelihood estimators (MLE) are under certain regularity conditions on $f(x; \theta)$, The MLE $\hat{\theta}^{(MLE)}$ of θ based on a sample sizes n from

$f(x;\theta)$ is asymptotic normal distribution. The vector of estimates $\hat{\theta}_n^{(MLE)'} = \left(\hat{\alpha}_n^{(MLE)} \quad \hat{\beta}_n^{(MLE)}\right)$ has a two-dimensional normal distribution with the mean equal to the vector of true values of the parameters, that is $\theta' = (\alpha \quad \beta)$ and the covariance matrix equals the inverse to the Fisher information matrix, denoted by $\Lambda = I_n^{-1}(\theta)$. That is, as $n \to \infty$,

$$\hat{\theta}_n^{(MLE)} = N_2\left(\theta, I_n^{-1}(\theta)\right)$$

and the inverse of the Fisher information matrix is computed as

$$\Lambda = I_n^{-1}(\theta) = \frac{\alpha\beta^2(\alpha+1)^2(\alpha+2)}{n^2} \begin{pmatrix} \frac{n\alpha}{\beta^2(\alpha+2)} & \frac{n}{\beta(\alpha+1)} \\ \frac{n}{\beta(\alpha+1)} & \frac{n}{\alpha^2} \end{pmatrix}$$

$$= \frac{1}{n} \begin{pmatrix} \alpha^2(\alpha+1)^2 & \beta\alpha(\alpha+1)(\alpha+2) \\ \beta\alpha(\alpha+1)(\alpha+2) & \beta^2(\alpha+1)^2\frac{(\alpha+2)}{\alpha} \end{pmatrix}.$$

4.2.4 Asymptotic Normal Distribution

From the Delta method theorem, consider the sequence of random variables $\left\{\hat{\theta}_n^{(MLE)}\right\}$ such that

$$\sqrt{n}\left(\hat{\theta}_n^{(MLE)} - \theta\right) \xrightarrow{d} X$$

are distributed as the bivariate normal distribution, denoted by $N_2\left(0, I^{-1}(\theta)\right)$

$$\sqrt{n}\left(\hat{\theta}_n^{(MLE)} - \theta\right) \xrightarrow{d} X \sim N_2\left(0, I^{-1}(\theta)\right).$$

Asymptotic normal distribution as $n \to \infty$, we get

$$\frac{\sqrt{n}\left(\hat{\theta}_n^{(MLE)} - \theta\right)}{\sqrt{I^{-1}(\theta)}} \xrightarrow{d} Z \sim N_2(0, I_2)$$

$$\frac{\left(\hat{\theta}_n^{(MLE)} - \theta\right)}{\sqrt{I_n^{-1}(\theta)}} \xrightarrow{d} Z \sim N_2(0, I_2)$$

which is equivalent to

$$\frac{\left(\hat{\theta}_n^{(MLE)} - \theta\right)}{\sqrt{\Lambda}} \xrightarrow{d} Z \sim N_2(0, I_2)$$

$$\left(\Lambda^{\frac{1}{2}}\right)^{-1}\left(\widehat{\theta}_n^{(MLE)} - \theta\right) \xrightarrow{d} Z \sim N_2(0, I_2) \tag{7}$$

where $I_2 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$.

If Z_1 and Z_2 are independent $N(0,1)$ random variables, Then $Z' = (Z_1, Z_2)$ has the bivariate normal distribution $N_2(0, I_2)$. From equation (7)

$$\left(\widehat{\theta}_n^{(MLE)} - \theta\right)'\left(\Lambda^{-\frac{1}{2}}\right)\left(\Lambda^{-\frac{1}{2}}\right)\left(\widehat{\theta}_n^{(MLE)} - \theta\right) = \left(\widehat{\theta}_n^{(MLE)} - \theta\right)'\Lambda^{-1}\left(\widehat{\theta}_n^{(MLE)} - \theta\right)$$

$$= Z'Z = Z_1^2 + Z_2^2 = \sum_{i=1}^{2} Z_i^2$$

is distributed as χ^2_2, where χ^2_2 denotes the chi-square distribution with 2 degrees of freedom.

4.2.5 Confidence Regions of Parameters for the Approximate Beta-Poisson Dose-Response Model

The $N_2\left(\theta, I_n^{-1}(\theta)\right)$ distribution assigns probability $1-\alpha$ to the ellipse $\left\{\widehat{\theta}_n^{(MLE)}:\left(\widehat{\theta}_n^{(MLE)} - \theta\right)'\Lambda^{-1}\left(\widehat{\theta}_n^{(MLE)} - \theta\right) \leq \chi^2_2(\alpha)\right\}$, where $\chi^2_2(\alpha)$ denotes the upper (100α)th percentile of the χ^2_2 distribution.

The $100(1-\alpha)\%$ confidence region for parameters $\theta' = (\alpha, \beta)$ of a two-dimensional normal distribution is the ellipse determined by all θ such that

$$\left(\widehat{\theta}_n^{(MLE)} - \theta\right)'\Lambda^{-1}\left(\widehat{\theta}_n^{(MLE)} - \theta\right) \leq \chi^2_2(\alpha)$$

which is equivalent

$$\left(\widehat{\theta}_n^{(MLE)} - \theta\right)'I_n(\theta)\left(\widehat{\theta}_n^{(MLE)} - \theta\right) \leq \chi^2_2(\alpha)$$

where

$$\left(\widehat{\theta}_n^{(MLE)} - \theta\right)'I_n(\theta)\left(\widehat{\theta}_n^{(MLE)} - \theta\right)$$

$$= \left(\widehat{\alpha}_n^{(MLE)} - \alpha \quad \widehat{\beta}_n^{(MLE)} - \beta\right) n \begin{pmatrix} \dfrac{1}{\alpha^2} & -\dfrac{1}{\beta(\alpha+1)} \\ -\dfrac{1}{\beta(\alpha+1)} & \dfrac{\alpha}{\beta^2(\alpha+2)} \end{pmatrix} \begin{pmatrix} \widehat{\alpha}_n^{(MLE)} - \alpha \\ \widehat{\beta}_n^{(MLE)} - \beta \end{pmatrix}.$$

So, the $100(1-\alpha)\%$ confidence region for $\boldsymbol{\theta}$ consists of all value (α,β) satisfying

$$\frac{n}{\alpha^2}\left(\hat{\alpha}_n{}^{(MLE)} - \alpha\right)^2 - \frac{2n}{\beta(\alpha+1)}\left(\hat{\alpha}_n{}^{(MLE)} - \alpha\right)\left(\hat{\beta}_n{}^{(MLE)} - \beta\right)$$

$$+ \frac{n\alpha}{\beta^2(\alpha+2)}\left(\hat{\beta}_n{}^{(MLE)} - \beta\right)^2 \leq \chi^2{}_2(\alpha).$$

5. Simulation Study

In this section, a simulation study is carried out to construct asymptotic confidence ellipses for parameters of the approximate Beta-Poisson dose-response model and compare the coverage probabilities for confidence ellipses of parameters for approximation of the Beta-Poisson dose-response model with the confidence coefficient 0.98.

The results of this study are classified according to the values of parameters for the Beta-Poisson dose-response model and sample sizes.

In an effort to find maximum likelihood estimates we will study by numerical method. For calculate the simulated errors of maximum likelihood estimates and construct sets of parameters we need a sample from the probability density function of the Beta-Poisson dose-response model. First we generate a sample θ from the Beta distribution with parameters α and β and we use this θ to generate a sample x from the Exponential distribution with parameter θ. For the Exponential distribution we use the density function

$$f_E(x;\theta) = \theta \exp\{-\theta x\}.$$

A sample, $x_1, x_2 \ldots, x_n$, is thus obtained from $\theta_1, \theta_2, \ldots, \theta_n$. This $x_1, x_2 \ldots, x_n$ will have the probability density function from the Beta-Poisson dose-response model with parameters α and β.

After we obtain 10,000 replications of each sample, we compute the Monte-Carlo estimations of errors of the estimates: average of differences between the true value of the parameters and the true values of simulation and the percentages of absolute relative errors. If we obtained 10,000 replications of estimators of $\boldsymbol{\theta}$ where $\theta' = (\alpha,\beta)$, that is, $\hat{\theta}_1{}^{(MLE)}, \hat{\theta}_2{}^{(MLE)}, \ldots, \hat{\theta}_{10,000}{}^{(MLE)}$, we will estimate the errors as

$$\text{Errors of } \hat{\theta}_n{}^{(MLE)} = \frac{1}{10,000}\sum_{i=1}^{10,000}\left(\theta - \hat{\theta}_i{}^{(MLE)}\right)$$

and the percentages of absolute relative errors as

$$\frac{\left|Errors\ of\ \widehat{\theta}_n^{(MLE)}\right|}{\theta} \times 100.$$

Now, we present confidence ellipses of parameters as shown in Figures 1 – 12 and present maximum likelihood estimates of α and β, the percentages of absolute relative errors and coverage probabilities of confidence ellipses for parameters of the approximate Beta-Poisson dose-response model at 98% confidence level as follows Tables 1 – 3.

1) Case $n = 100$,

Figure 1: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.1, \beta = 10$.
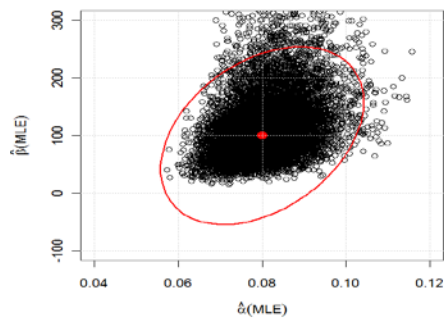
Figure 2: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.08, \beta = 100$.
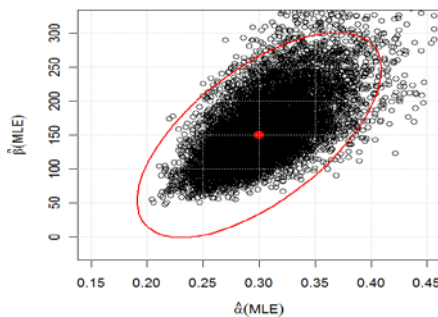
Figure 3: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.3, \beta = 150$.
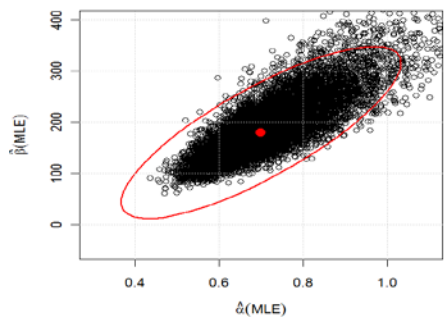

Figure 4: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.7, \beta = 180$.
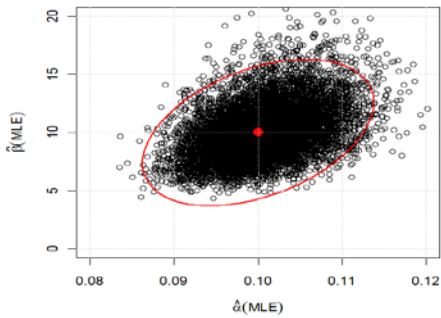
Table 1. Maximum likelihood estimates of α and β, these errors and coverage probabilities of confidence ellipses for parameters of the approximate Beta-Poisson dose-response model when $n = 100$ at 98% confidence level.

α	β	Maximum likelihood estimates		The percentages of absolute relative errors		Coverage probabilities
		$\hat{\alpha}_n^{(MLE)}$	$\hat{\beta}_n^{(MLE)}$	$\hat{\alpha}_n^{(MLE)}$	$\hat{\beta}_n^{(MLE)}$	
0.1	10	0.10159	10.85432	1.59000	8.54320	0.9549
0.08	100	0.08097	109.39572	1.21250	9.39572	0.9491
0.3	150	0.30588	161.38292	1.96000	7.58861	0.9648
0.7	180	0.71743	194.31646	2.49000	7.95359	0.9604

2) **Case $n = 500$,**
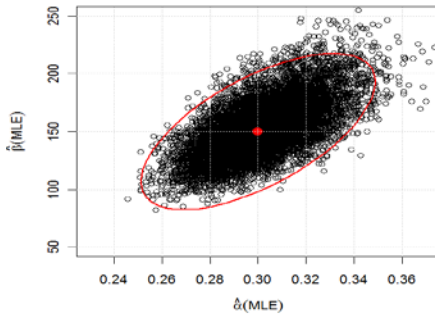

Figure 5: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.1, \beta = 10$.
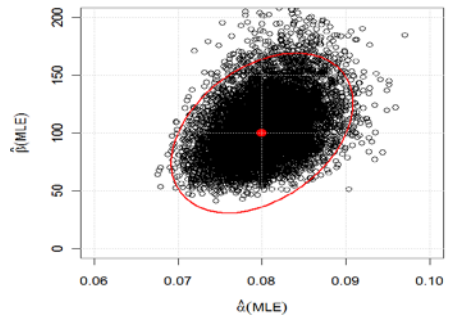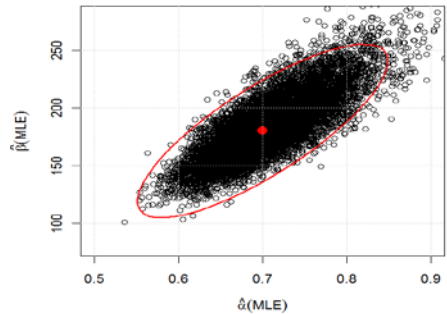

Figure 6: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.08, \beta = 100$.

Figure 7: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.3, \beta = 150$.
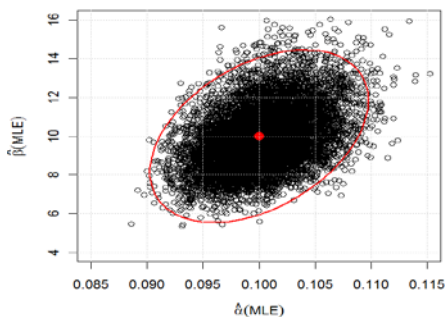

Figure 8: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.7, \beta = 180$.

Table 2. Maximum likelihood estimates of α and β, these errors and coverage probabilities of confidence ellipses for parameters of the approximate Beta-Poisson dose-response model when $n = 500$ at 98% confidence level.

α	β	Maximum likelihood estimates		The percentages of absolute relative errors		Coverage probabilities
		$\hat{\alpha}_n^{(MLE)}$	$\hat{\beta}_n^{(MLE)}$	$\hat{\alpha}_n^{(MLE)}$	$\hat{\beta}_n^{(MLE)}$	
0.1	10	0.10059	10.13029	0.59000	1.30290	0.9684
0.08	100	0.08022	102.77953	0.27500	2.77953	0.9639
0.3	150	0.30165	152.77005	0.55000	1.84670	0.9704
0.7	180	0.70505	183.40679	0.72143	1.89266	0.9687

3) Case when $n = 1,000$,

Figure 9: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.1, \beta = 10$.
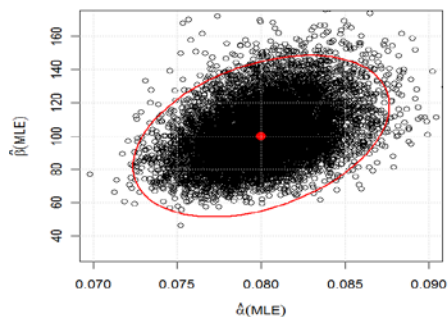
Figure 10: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.08, \beta = 100$.
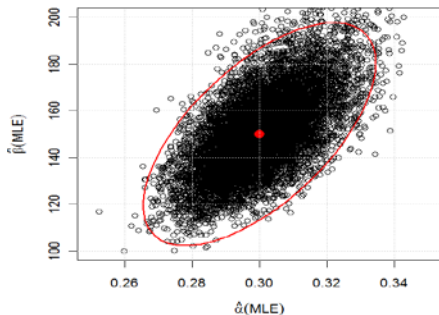

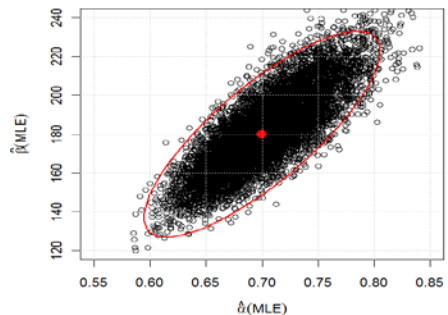
Figure 11: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.3, \beta = 150$.

Figure 12: A 98% confidence ellipse for α and β based on maximum likelihood estimates when $\alpha = 0.7, \beta = 180$.

Table 3. Maximum likelihood estimates of α and β, these errors and coverage probabilities of confidence ellipses for parameters of the approximate Beta-Poisson dose-response model when $n = 1{,}000$ at 98% confidence level.

| α	β	Maximum likelihood estimates		The percentages of absolute relative errors		Coverage probabilities
		$\hat{\alpha}_n^{(MLE)}$	$\hat{\beta}_n^{(MLE)}$	$\hat{\alpha}_n^{(MLE)}$	$\hat{\beta}_n^{(MLE)}$	
0.1	10	0.10034	9.94527	0.34000	0.54730	0.9771
0.08	100	0.08015	101.05571	0.18750	1.05571	0.9729
0.3	150	0.30079	151.33427	0.26333	0.88951	0.9779
0.7	180	0.70253	181.66574	0.36143	0.92541	0.9773

6. An Example

We consider the 33 outbreak reports collected from the published literature and from unpublished data received by Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) [14] following Table 4, 23 contained sufficient information on the number of people exposed, the number of people that become ill, and the number of organisms in the implicated food to enable calculation of a dose-response relationship. Of the 23 outbreaks, 3 were excluded because the immune status of the persons exposed could not be determined. The remaining 20 outbreaks comprise the database used to calculate a dose-response relationship.

Of the 20 outbreaks in the database, 11 occurred in Japan and 9 occurred in North America. Several *Salmonella (S.)* serotypes were associated with the outbreaks, including *S.* Enteridies (12 outbreaks), *S.* Typhimurium (3 outbreaks), and in single outbreaks, *S.* Heidelberg, *S.* Cubana, *S.* Infantis, *S.* Newport and *S.* Oranienburg. Several vehicles were implicated, including food (meat, eggs, dairy products and others), water, and a medical dye capsule (carmine dye).

The maximum likelihood technique was used as the basis for generating the best fitting curve to the data. The fit was optimized using an iterative technique that minimized the deviance statistic, based upon a Binomial assumption. The parameters of the Beta-Poisson dose-response relationship are $\alpha = 0.1324$ and $\beta = 51.45$.

Using our study, we obtain the maximum likelihood estimates $\alpha = 0.1635$ and $\beta = 50.42$ and we compare the outbreaks data with the Beta-Poisson dose-response model as follows Figure 13. If we use the Beta-Poisson as the mathematical form for the

relationship, and this was fitted to the outbreaks data. The model tends to close to estimate the probability of illness as observed in the outbreaks data.
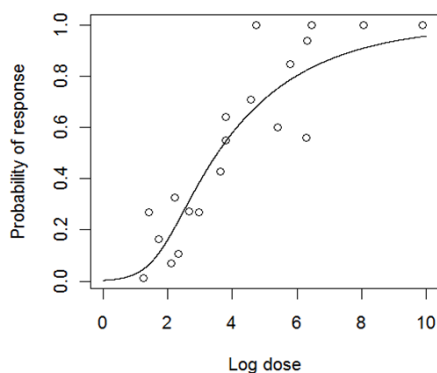
Figure 13: Comparison of the Beta-Poisson dose-response model and reported outbreaks data.

We construct confidence ellipse of parameters for the Beta-Poisson dose-response model is shown in Figure 14.
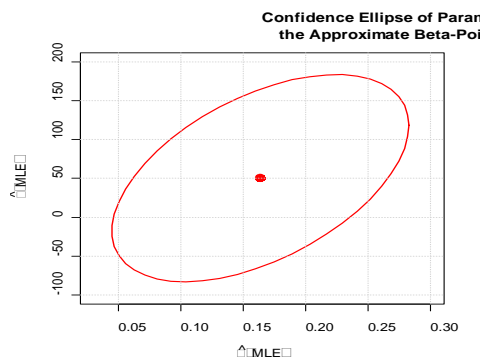
Figure 14: A 98% confidence ellipse for α and β based on outbreaks data.

7. Conclusions

In this article, we have investigated some limitations of parameters estimation for the Beta-Poisson dose-response model and its approximation.

For the Beta-Poisson dose-response model, theoretically by using the Delta method for normal approximation it is possible to find the asymptotic covariance matrix of two parameter estimates by method of moments and after constructing an asymptotic confidence ellipse. However, the calculations are extremely cumbersome, and are not recommended for practical applications. Moreover, these lengthy calculations would be

useless for statistical analysis of epidemiological data, because data known from literature show that a typical values of α is around a few hundredths, while a typical values of β is around a few hundred. Even the first moment for the probability density function of the Beta-Poisson dose-response model exists for $\alpha > 1.$ For the method of maximum likelihood, we cannot find parameter estimators of the Beta-Poisson dose-response model and also it is not possible to find the asymptotic covariance matrix for maximum likelihood estimates of the Beta-Poisson dose-response model from the Fisher information matrix in closed form for the probability density function of the Beta-Poisson dose-response model, hence it is also not possible to construct an asymptotic confidence ellipse based on the maximum likelihood estimates.

For the approximate Beta-Poisson dose-response model, the first moment for the probability density function with parameters α and β exists only if $\alpha > 1$. Hence we cannot apply method of moments to construct an asymptotic confidence ellipse, because data known from literature show that a typical values of α is around a few hundredths, while a typical values of β is around a few hundred. Nevertheless, we can derive the parameter estimators of the approximate Beta-Poisson dose-response model by the method of maximum likelihood. After that, we calculate the Fisher information matrix in closed form for the probability density function of the approximate Beta-Poisson dose-response model. In addition, we find the covariance matrix which equals the inverse to the Fisher information matrix to construct a normal approximation that gives elliptical confidence regions with center $\boldsymbol{\theta}' = (\alpha, \beta)$ for all 12 cases.

In simulation study, we construct asymptotic confidence ellipses for parameters of the approximate Beta-Poisson dose-response model and compared the coverage probabilities for confidence ellipses of both parameters for approximating a Beta-Poisson dose-response model with the nominal level 0.98. The coverage probabilities of confidence ellipses for parameters of an approximation of the Beta-Poisson dose-response model increase when sample sizes (n) increase and also they are close to the confidence coefficient 0.98. In addition, at various values of parameters of the Beta-Poisson dose-response model, the coverage probabilities are similar when n is fixed.

Acknowledgement

Appendix

Table 4   Summary of outbreaks data [14]

Case no.	Serovar	Food	Pop.[1]	Dose[2] Log CFU	Attack Rate[2](%)
1	*S.* Typhimurium	Water	N	2.31	10.63%
	S. Typhimurium	Water	S	2.31	18.91%
2	*S.* Heidelberg	Cheddar cheese	N	2.22	32.76%
3	*S.* Cubana	Carmine dye	S	4.57	70.93%
4	*S.* Infantis	Ham	N	6.46	100.00%
5	*S.* Typhimurium	Imitation ice cream	N	3.79	55.00%
7	*S.* Newport	Hamburger	N	1.23	1.07%
11	*S.* Enteritidis	Hollandaise sauce	N	4.74	100.00%
12	*S.* Enteritidis	Ice cream	N	2.09	6.80%
13	*S.* Typhimurium	Ice cream	N	8.70	100%
	S. Typhimurium	Ice cream	S	8.00	100%
18	*S.* Enteritidis	Roasted beef	N	5.41	60.00%
19	*S.* Enteritidis	Grated yam with soup	N	6.31	93.93%
20	*S.* Enteritidis	Beef and bean sprouts	N	2.97	26.86%
22	*S.* Enteritidis	Scallop with egg yolk	N	6.30	56.01%
23	*S.* Enteritidis	Cake	N	5.80	84.62%
24	*S.* Enteritidis	Peanut sauce	N	1.72	16.41%

Table 4   (Continue)

Case no.	Serovar	Food	Pop.[1]	Dose[2] Log CFU	Attack Rate[2](%)
25	*S.* Enteritidis	Chicken and egg	N	3.63	18.75%
	S. Enteritidis	Chicken and egg	S	3.63	42.74%
30	*S.* Enteritidis	Cooked egg	N	3.80	64.18%
31	*S.* Enteritidis	Cake	N	2.65	27.33%
32	*S.* Enteritidis	Egg salad	S	1.40	26.92%
33	*S.* Oranienburg	Grated yam with soup	N	9.90	100%

Notes: (1) Pop. = population exposed, where N = Normal population and

S = Susceptible population.

(2) Expected value based on defined uncertainty ranges and distributions.

Susceptibility in this analysis was therefore limited to outbreaks data for individuals less than 5 years old being classified as "susceptible", with other outbreaks data representing a "normal" population [15].

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