Dose response relationships for *Listeria monocytogenes* in ready-to-eat foods

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Factors affecting Dose-response

Infectious Disease Triangle
Factors affecting Dose-response

**Food**
- Protection against physiological barriers
- Induction of stress response
- Effects on transport through GI tract

**Host**
- Age
  - Immune status / underlying conditions
  - Medications
  - Pregnancy

**Pathogen**
- Survival properties of pathogen
- Virulence /pathogenic mechanisms
- Strain variability
- Antibiotic resistance
End-point of Dose-response model

Major steps in infectious disease process

End-points in available DR-models for *L. monocytogenes*
- infection, illness (morbidity), death (mortality)
- no conditional models (infection given exposure, illness given infection, etc.)
Sources of data

Human volunteer feeding studies
- best direct measure of response
- healthy individuals, high doses, low dose extrapolation
- not available for *L. monocytogenes*

Surrogate animals
- many of the limitations as human data
- need conversion factor
- same mechanisms? (ex. mouse and guinea pig)
Sources of data

Epidemiological data
- may be used to evaluate dose-response models
- outbreak data - information often missing
- surveillance/health statistics - depends on the system
- cost effective, include whole population and range of strains

Expert elicitation
- if lack of data, e.g. input on parameter values
- subjective, dependent on methodology
Dose-response: concepts

WHO/FAO guidelines

- Single-hit, non-threshold models
- Linear in the low-dose region
- Biological basis, biologically interpretable parameters
- Density dependence? (e.g. quorum sensing)
Dose-response: models

Exponential
- non-threshold model, linear in low-dose region
- host/pathogen interaction constant, described by $r$
- $r$ is the probability of a single bacterium to cause illness (infection, mortality)
- $P = 1 - e^{-r \cdot dose}$

Beta-Poisson
- non-threshold model, linear low-dose
- host/pathogen interaction variable; $r$ follows a beta distribution, described by $\alpha$ and $\beta$
- If $\beta >> \alpha$ and 1 then
- $P = 1 - [1 + \frac{dose}{\beta}]^{-\alpha}$
Dose-response: models

Weibull-Gamma

- single hit, linear low-dose
- host/pathogen interaction variable, follows a beta distribution, described by $\alpha$ and $\beta$
- Includes a third parameter, $b$, determining shape
- $P = 1 - [1 + (\text{dose})^b / \beta] - \alpha$
Models based on epidemiological data and expert elicitation

Farber et al. 1996, Bemrah et al. 1998
- Dose-infection model
- Weibull-Gamma model
- General and high risk populations, respectively
- $ID_{10}$ and $ID_{90}$ estimated based on literature data

- Dose-illness
- Exponential model
- Conservative assumptions, susceptible population
- Estimation of $r$ by pairing exposure and illness data
Models based surrogate animals

Notermans et al., 1998
- dose-infection, dose-mortality
- exponential model
- based on data for mice and oral or intravenous exposure

Haas et al, 1999
- dose-infection
- beta-poisson better fit than exponential model
- based on data for mice and oral exposure
Models...combination surrogate animal and epidemiological data

FDA/FSIS 2001

- dose-mortality (X 5 gives dose-illness model)
- weighted combination of models based on goodness of fit
- based on mice data and oral exposure, but anchored to human epidemiological data
- models includes variability in virulence
- general population, elderly, and perinates/neonates
Models prior to WHO/FAO risk assessment

criteria for selection
- WHO/FAO guidelines
- purpose
- resources available
WHO/FAO dose-response model

Approach

- Buchanan et al.: Pairing exposure and statistics on number of illnesses using the exponential model
- Exposure data and epi-data from US Listeria risk assessment
- Uncertainty in input data addressed: # of cases, susceptible population, # cases in population, maximum dose in serving

Assumptions

- Exponential model appropriate for dose-response relation
- $r$ is a constant $\rightarrow$ model reflects mean on population basis
- Strain and host variability reflected in the mean characteristics
- Same consumption in susceptible and non-susceptible
No of cases = \[1-(e^{-r \cdot \text{dose}})\] * No of servings

<table>
<thead>
<tr>
<th>Log Dose</th>
<th>Meals consumed in each dose category</th>
<th># Meals consumed by population</th>
<th>Predicted Number of Listeriosis Cases per Dose Level</th>
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</thead>
<tbody>
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<td>5.93E+10</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>3.66E+11</strong></td>
<td><strong>6.41E+10</strong></td>
<td><strong>559</strong></td>
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</table>
WHO/FAO dose-response model

Uncertainty

- the estimation of $r$ is highly dependent on the accuracy of input data; uncertainty in the data and changes in terms of the distribution of pathogen virulence or host susceptibilities

Assumption of maximum dose in a serving had the largest effect on the estimation of $r$, compared to the no. of cases, the fraction of susceptible consumer, and the no. of cases in the population of interest
WHO/FAO dose response model

Uncertainty in exposure

- Illustration of the effect of uncertainty in exposure: Chen et al. (2003) used same approach, exponential model but new data to estimate exposure and illness. $r$ estimated to $1.8 \times 10^{-10}$

- Including potential for growth (purchase-consumption) $r$ estimated to $8 \times 10^{-12}$
### Presumed Maximum log\(^{10}\) Dose vs Log Dose

<table>
<thead>
<tr>
<th>Presumed Maximum log(^{10}) Dose</th>
<th>Log Dose</th>
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<td>&lt;1</td>
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</tbody>
</table>

Assuming all cases due to highest dose only or to all dose levels had minor effect
Illustration of model uncertainty

- use beta-poisson model (Haas) based on infection in mice
- anchor to the number of cases assuming Probability of illness is constant at any dose given infection
- maximum dose in serving 9.5 log cfu

Difference in slope $\rightarrow$

% cases due to serving with dose $>4.5$ log cfu

WHO/FAO: $>99.3\%$
BP: $75\%$
Comparison with other models

(FDA models approximated to exponential)
Small r-values corresponds to unrealistic large ID$_{50}$

- a substantial variation in the “susceptible” population
- and/or in the virulence of strains
Summary of knowledge gaps

- Absence of human feeding trial data
- Incomplete epidemiological information
- Uncertain extrapolations animals to humans
- Lack of mechanistic models
- Understanding of strain variation
- Understanding of food matrix effects