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Future Advancements: Recommendations from the IRAC-JIFSAN *Listeria monocytogenes* Dose- Response Workshop

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Overview

- Workshop held in March 2011 to discuss updating the 2003 FDA/ FSIS Lm DR models
- Suggestions to update the 2003 model
- Future strategies for DR modeling for Lm - development of mechanistic models for microbial risk assessment

- Key need – to reduce uncertainty in current models

Purpose of March 2011 Workshop

- **To identify key factors and data to be considered when the Lm Dose Response models are updated**
- **Presentations followed by general discussion in break out groups**

1. **What new knowledge about *Lm* and listeriosis could be applied to update the 2003 FDA/FSIS/CDC and/or 2004 FAO/WHO dose-response models?**
2. **What approach or modeling methodology could be used to update these dose-response models now?**
3. **What additional data could help to improve the *Lm* dose-response function in the future?**

Does the current approach remain appropriate given new knowledge in the last 10 years? What would be an appropriate alternative approach?

- **Short term, intermediate and long term solution**
  - **Short term:**
    - **Use data collected since 2003 to update risk assessment**
    - **Compare predicted cases to new CDC estimates**
  - **Medium term:**
    - **Start collecting new data in animal models more closely reflective of humans**
    - **Better modeling of data on susceptible populations**
  - **Long term:**
    - **Develop a new mechanistic model**

Short term

- Use data collected since 2003 and use it to update risk assessment – reduce uncertainties
- Compare predicted cases to new CDC estimates
- Re-visit risk ranking – may get new ranking
- Confusion over risk per serving vs risk per annum
  - risk associated with raw vs pasteurized milk
- New data are available:
  - Lm strain variability in virulence
  - Exposure data - levels of Lm in foods
  - Dose response data – studies in monkeys
  - Outbreak data - cantaloupe

Medium term

- Start collecting new data relevant to pathogen, host and environment
- More data on virulence of strains
- More data on susceptible populations
  - May be more relevant to have one DR curve for highly susceptible populations and one for normal healthy population
- Data in animal models more closely reflective of humans
  - Improve extrapolation and reduce uncertainty
- More data on food matrix effect

New data to collect

- Pathogen data
- More data on virulence of strains
  - prevalence and numbers / distribution in food supply and clinical samples
  - Strain ID and inlA sequence

New data to collect

- Host data
- Pregnancy Status
  - Test spontaneous miscarriage tissue for *Lm*
- Age – not just > 60; segregate those >80
- Better data on immune status
  - E.g., transplant patient, chemotherapy
- Examine genetic variation controlling host susceptibility
  - Includes major histocompatibility complex, cellular and humoral immunity, E-cadherin expression
- Stress
- Obesity

New data to collect

- **Host data**
  - Try to determine the exposed population to calculate attack rate
    - Collect data on individuals who were exposed but did not get sick
  - Need better diagnostics including immune status, including possible involvement of anti-Lm IgA?
  - Effect of multiple doses
  - Use of antibiotics – reduces listeriosis in HIV patients

New data to collect - considerations

- Data in animal models
- Rat/ mouse models currently used: realistic? credible?
  - Need to be scaled using human data
- E-cadherin in rats/mice not the same as human
- Guinea pig e-cadherin is the same as human
- Guinea pig and non-human primate models may overestimate risk
- Transgenic (humanized) mice may be more useful
- Gerbils may prove better than rats/ mice
- Cell culture or organ culture data can be used
- Human placenta may be a useful model

New data to collect - considerations

- Data in animal models
- How well do the animal data predict what will happen in humans?
- May need scaling factors if not close
- Endpoint of interest in animal model should be same as that of interest in humans
  - Currently use death
- Susceptibility of animal model
  - Pregnant animal?
  - Immune compromised animal?
  - Old animal?

New data to collect

- **Food data**
  - Collect data during outbreak investigations:
  - Ability to grow in the food vehicle. Consider the actual recipe and typical handling
  - Sampling plan and detection/enumeration method
  - Enumeration, but consider the potential for non-random distribution in the food during sampling – need to test many samples if possible
  - Need to determine whether enough colonies were picked from positive samples, to capture the range of different strains that may be present.

Factors to consider in DR modeling

- Extrapolation from high to low doses of pathogen
- Extrapolation across species
- Extrapolation from normal healthy individuals to susceptible individuals
- Extrapolation from one type of food environment to another

What approaches should be used for extrapolation to low dose?

- Use whole range of data available
  - Consider data from outside USA
- Model constraints – assume one organism causes disease?
  - Threshold vs non threshold models
- Variation in virulence among Lm strains
- Impact of multiple doses
- Need to consider uncertainties associated with data

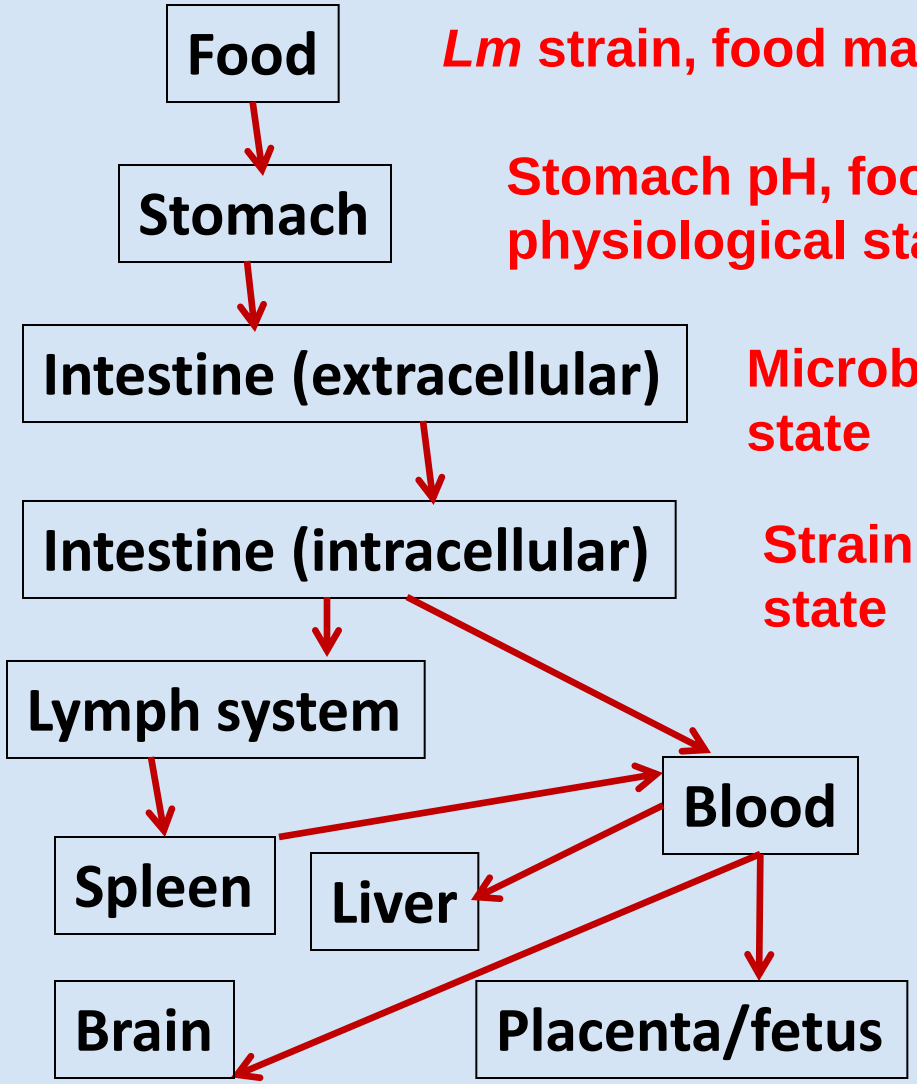
What approaches should be used for extrapolation from animals to humans?

- Biologically based extrapolation – experimental data
- Human relevance
- Scaling factors: May or may not be necessary, use with caution
  - Depend on strain, susceptible population and food
  - Additional data can inform and may reduce need for scaling factors
- Need to consider uncertainties associated with data
- Need to consider susceptibility - look at this as a continuous variable?

Longer term

- Develop mechanistic model for Lm
- Need to integrate disease triangle data
  - Pathogen, host, environment (food)
- Pathogen factors:
  - Strain variability
- Host factors:
  - Not appropriate to use levels in food at consumption as “dose” – host factors should be considered
  - Need to focus more on susceptible populations
- Food matrix effects:
  - Fat levels

PATHOGEN, HOST, ENVIRONMENT (FOOD) FACTORS IMPORTANT AT A GIVEN STAGE



***Lm* strain, food matrix, *Lm* physiological state**

Stomach pH, food matrix, effect of pH on *Lm* physiological state

Microbiome, immunity, *Lm* physiological state

Strain (inlA status), *Lm* physiological state

Strain, blood glucose levels, immunity

Strain (InlB status), stage of pregnancy

Data for mechanistic model

- **Pathogen data:**
  - **Need multiple strains with varying virulence**
  - **Growth and concentration of Lm in the GI lumen (small intestine)**
  - **Role of microbiota in attachment and entry to enterocytes**
  - **Role of gene expression (listeriolysin and other important pathogen proteins) when in foods and after consumption**

Data for mechanistic model

- **Host data**
  - **Immunocompromised hosts—how to define, is there a gradation/ continuum?**
  - **Measures/markers of compromised immunity that can be applied during outbreak investigations**
  - **Role of T cell (cell mediated) and antibody (humoral) immunity**
  - **More data on incubation time for Lm infections**
  - **Lm in clinical samples – are certain strains more frequently associated with diarrhea, meningitis, miscarriage**

Data for mechanistic model

- **Food data**
  - **How does environment impact pathogen**
  - **Characteristics of foods associated with outbreaks/ sporadic illness – food composition, pH, a_w, etc.**
  - **Updated data for foods most likely to be associated with illness**
  - **Enumeration of pathogens in food samples (not just presence/ absence) including in an outbreak or recall**
  - **Levels of *Lm* in the home/ storage time at home**

What factors should be considered in model validation?

- Model validation is difficult due to lack of controlled human data sets – use new CDC data
- What is the purpose of the model? Given the data limitations, is the model "good enough"
- Can you use epi data for both developing and validating model?
- Need separate sets of data, e.g. from another country
- Which mathematical model should you pick? This can impact the result.
- Need some biological plausibility to choosing a model

Other issues to consider

- Success will depend on improved communication among risk assessors and risk managers
- Clearly defined risk management questions are needed to avoid lengthy, ambiguous risk assessments
- Food safety policy should be informed by risk assessments
- Should you use the “worst case” scenario – most virulent strain, most susceptible animal model?
- Low levels of exposure may protect host – confer immunity
  - U shaped DR curve?

How should we quantify uncertainty about Lm DR models?

- Uncertainty ≠ variability
- Need to reduce uncertainty in current models by using more and better data
  - Need better data on susceptible populations
- Need to determine the number of variables that would be sufficient (fit for purpose)
- Focus on data gaps relevant to addressing public health issues of dose threshold and food safety objective
- Multiple tools are available – decision trees, Monte Carlo simulation

Controlling risk

- New information should be provided to industry, (processors, retailers, food service) health care providers, consumers to help them reduce risks associated with Lm in foods
- Extension service should educate small processors/ foodservice
- Education campaigns
  - Target at-risk populations and their caregivers
- Inform policy decisions. Update current standards?
  - Regulation to ensure compliance with standards