Challenges in Dose-Response Assessment

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Road Map

- Dose response modeling
  - –issues
  - –infection
  - –illness
- Sensitive subpopulations
- Use of surrogates
- Future directions

Dose-Response Assessment: General Approach

- Determining the relationship between the dose of a pathogen and the incidence of infection or specific adverse health effects in an exposed population.
- Response probability determined by fitting a mathematical model to dose-response data
- One-hit theory applies
  - –Each organism capable of surviving host defenses to initiate an infection
  - –Non-zero probability no matter how low
  - –Thresholds?

Dose-Response Assessment: Exposure Media Issues

- Key issues are different for different exposure scenarios
  - –Food exposure or person-to-person contact
    - high-dose occasional exposures (buffered?)
    - risks usually in the range of the data
  - –Drinking water exposure
    - low-dose frequent exposures (un-buffered)
    - need extrapolated unit-risk measures

Data Requirements (?)

- Need response data for:
  - –a specific effect from
  - –a specific pathogen administered to
  - –a specific host by
  - –a specific route under
  - –specific conditions
- Need both low- and high-response data (“response anchoring”)

Dose-Response Models: functional forms

Exponential

$Pr = f(d) = 1 - e^{-rd}$

d = dose; r = unit infectivity

beta-Poisson (beta-exponential)

$Pr = f(d) = 1 - {}_1F_1(\alpha, \beta - \alpha, -d)$

${}_1F_1$ = confluent hypergeometric function

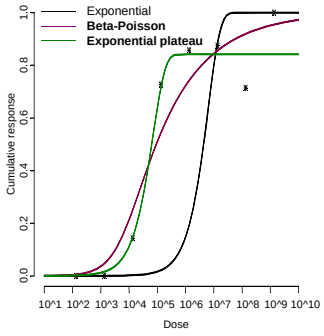
α, β = beta distribution parameters

unit infectivity (r) = $\alpha \div (\alpha + \beta)$

Plateau model

$Pr = (1 - fr) \times f(d)$

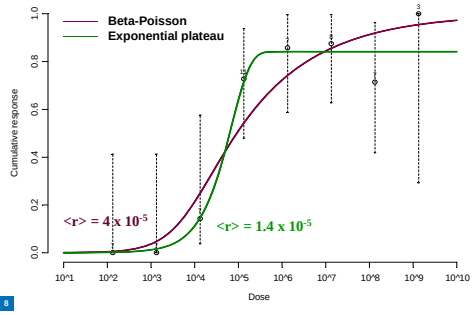
fr = immune fraction



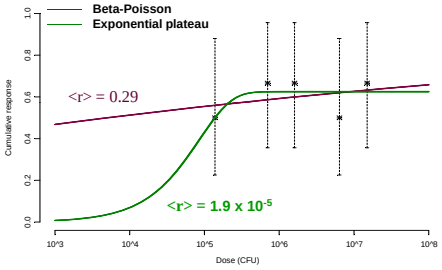
Modeling Infection

- Infection measures (sero-conversion, excretion)
- Fit dose-response models to data directly
- Compare fits statistically
- Select preferred model based on statistics and biological plausibility
- Data issues
  - –Non-monotonicity
  - –Lack of response “anchoring”

Rotavirus
Infection Dose-Response



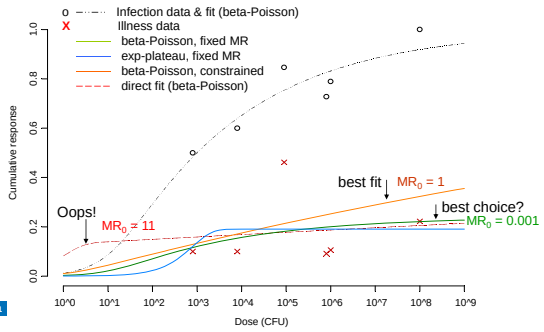
Salmonella derby
Infection Dose-Response



Modeling Illness

- Illness measures (GI symptoms)
- Fit models constrained on infection parameters
  - – $Pr_{ILL} \leq Pr_{INF}$
- Pay attention to the morbidity ratio (MR)
  - –Probability of illness given infection
  - –Fixed or variable
  - –MR_0 = morbidity ratio at unit dose
- Select preferred model based on statistics and biological plausibility

Campylobacter jejuni
Illness Dose-Response



Human Population Variability

- Very little information
- *C. parvum* infectivity in sero-positive and sero-negative adult subjects
  - –Sero-positive subjects much less susceptible
  - –No data on sensitive subpopulations (go figure)
- Poliovirus administered to infants and adults
  - –Infants less susceptible than adults (get out of town!)
  - –Confounded by buffering issues
- *V. cholerae* administered with and without stomach-acid buffering
  - –Unit infectivities might vary by orders of magnitude
  - –Confounded by “response-anchoring” issues

Modeling Sensitive Subpopulations

- Simulation
  - –speculative
- Safety & adjustment factors
  - –very tricky
  - –some applications (*Listeria, Salmonella*)
- Use animal data
  - –data generally lacking
- Use epidemiological data
  - –*Salmonella* outbreak data

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Pathogen Variability:
Use of Surrogates?

- Infectivity of pathogens in any given category varies widely (8 O.M. for bacteria)
- Pathogenicity of closely related species can vary dramatically (4 O.M. for *Salmonella*)
- Infectivity & virulence across strains can vary substantially
  - – *C. parvum* isolates (50-fold variation)
  - – *E. coli* 157 *vs E. coli* 221 (death vs. diarrhea)
- Virulence factors not well defined
- Identifying a pathogen surrogate is a challenge
  - –still an open issue

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Host Surrogates?
Human vs. Animal

- Defense mechanisms can be similar
- Endpoints can differ
- Pathogenic strains can differ
- Susceptibilities can differ
- Population variabilities differ
- Identifying a host surrogate is a challenge
  - –still an open issue

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Surrogates:
Using Animal Data

- Apply directly with adjustment factors
  - –hard to establish uncertainty bounds
- Establish sensitive subpopulation relative risk
  - –extrapolate the relative risk, not the absolute risk
- Establish new animal models
  - –swine, primates
- Estimate variability in pathogen virulence

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Future Directions

- Artificial neural networks
  - –make sense out of the nonsense?
- New animal models
  - –swine, primates ?
- Mechanistic modeling
  - –physiologically based
    - Salmonellosis (Coleman and Marks, 2000)
    - Cryptosporidiosis (Teunis et al., 2002)
    - Anthrax (Diamond et al., 2008)
    - Anthrax (Gutting, 2008)
    - Smallpox (Weir et al., 2008)
  - –utilize animal and *in vitro* data
  - –fundamental knowledge still lacking

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