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Effect of Host Species on the Dose Response of Inhaled *Bacillus anthracis* Spores

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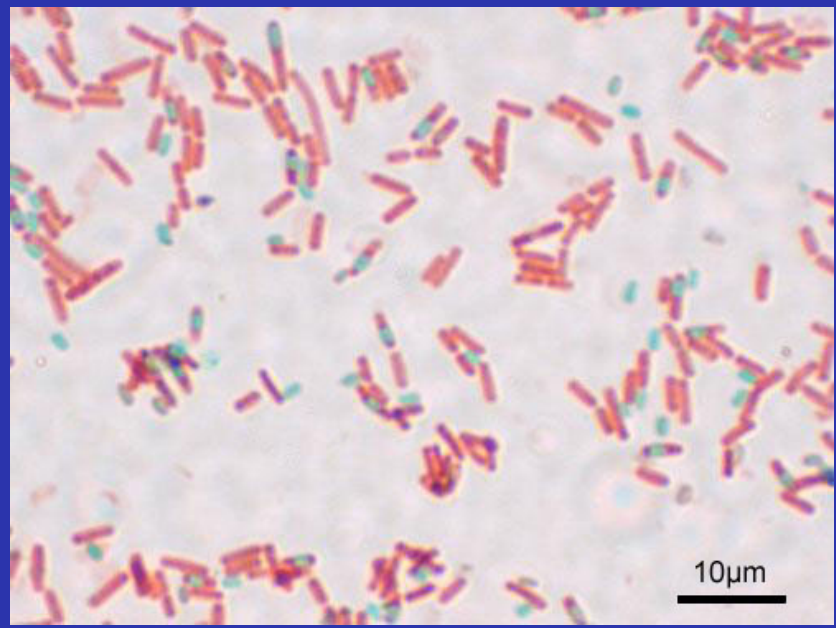
Introduction: *Bacillus anthracis*

Bacillus anthracis:

- Gram positive
- Spore forming
- Non-motile rod
- Causative agent of Anthrax



Spores:

- Tough
- Dormant
- Non-reproductive
- Protection
  - Environmental Stress

Introduction: *Bacillus anthracis*

- Vectors of infection
  - Spores released into water (naturally or otherwise)
  - Spores released into air
  - Cutaneous exposure
    - Biting flies
    - Direct contact with hides
    - Direct contact with hair
    - Direct contact with soil
- Reservoirs
  - Animals
    - Livestock
    - Wild life
  - Spores may remain in soil for many years

Introduction: Inhalation Anthrax

- Infection path
  - Spores inhaled
  - Spore size sufficient to reach alveoli
  - Incubation typically 48 hours (or up to 7 days)
- Symptomology
  - Initially non-descript
    - Resembles common URI
  - As infection progresses
    - Acute respiratory distress symptoms
    - Mediastinal widening
    - Fever and shock
      - 3 to 5 days
    - Death follows shortly after

Introduction: Previous Attacks

- *B. anthracis* spores made to be lethal
  - Small particle size
    - Ease of transport to alveoli
  - Non-polar
    - Maintains small particle size
    - Prolongs aerosolization
- Realized need for action
  - The 2001 attacks
    - Not as lethal as could have been [Brown, 2001]
    - Signs of progress made
      - Treatment and control
    - Understand the risks
      - To the workers
      - Those to decontaminate
      - Secondary exposures

Introduction: Dose Response Modeling

- Extensive literature search
  - Inhalation
  - Death as end point
  - Aerosol size
    - Preferably reported as sufficient to reach alveoli in humans (max~10μm)
- Data sorted to examine interactions
  - Guinea pigs exposed to ATCC-6605 strain
    - [Altboum, 2002]
  - Guinea pigs exposed to Vollum or Ames strain
    - [Altboum, 2002]
  - Pooled guinea pig data
  - Pooled guinea pig and rabbit data
  - Rhesus monkeys exposed to M36 strain
    - [Druett et al., 1953]
  - Pooled guinea pig, rabbit and rhesus monkey data.

Method of Analysis

- R source code written
  - MLE used
    - BFGS algorithm
      - Beta Poisson
      - Exponential
    - Nelder-Mead algorithm
      - Log-Probit
- Risk estimated using R
  - Bootstrap resampling

$$P(d) = 1 - e^{-kd}$$

$$P(d) = 1 - \left[1 + \left(\frac{d}{N_{50}}\right) \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

$$P(d) = \phi\left(\frac{1}{q2} \cdot \ln\frac{d}{q1}\right)$$

Method of Analysis: Extent of Parameterization of Model

- MLE output for each model
  - Minimized deviances
  - Optimized parameters
- Difference in deviances (Δ)
  - Compared to $\chi^2_{\alpha,1}$
  - H_o: simpler model is best fit
- Equal number of parameters
  - χ^2 is an upper tailed test
    - Therefore determine p-value
    - Largest p-value is best fit

Best Fitting Models

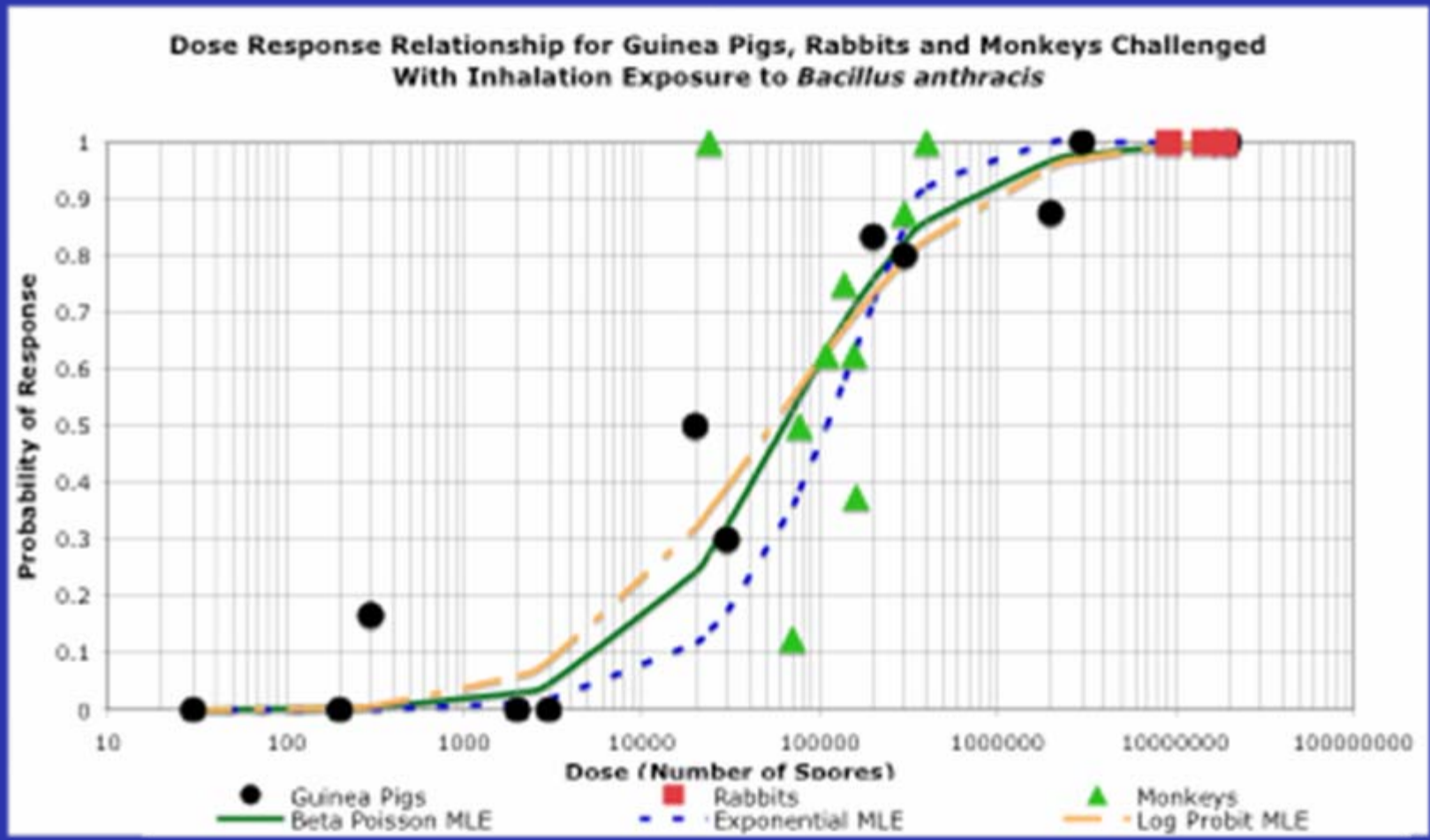
Parameters	Model	Model Parameter	Parameter Value
Guinea Pigs / ATCC-6605 Strain	Exponential	k	7.110 (10^{-6})
Guinea Pigs / Vollum Strain	Beta Poisson	α	0.549
		N_{50}	28,472
Pooled Guinea Pig Data	Beta Poisson	α	0.648
		N_{50}	39,036
Pooled Guinea Pig and Rabbit Data	Beta Poisson	α	0.642
		N_{50}	39,036
Rhesus Monkeys Exposed to Vollum Strain	Exponential	k	7.164 (10^{-6})
Pooled Guinea Pig Rabbit and Monkey Data	Beta Poisson	α	0.974
		N_{50}	62,817

Can This Data be Pooled?

- Different host species
- Different strains
- Difference in deviances
  - Summed deviances
    - Higher parameterized models
  - Deviance of pooled data
- Difference in deviances
  - Comparing this value to $\chi^2_{critical}$ at α and k-1 d.o.f.
  - H_0: data comes from the same distribution (can be pooled)

Pooling to be Compared	Σ Best Fits	Σ Higher Parameterized Model	Δ	$\chi^2_{crit, n-k}$
Guinea Pigs / Multiple Strains	11.134	20.016	8.882	18.307
Pooled Guinea Pig, Rabbit and Monkey Data	22.403	43.907	21.504	33.924

Since the Data can be Pooled



Conclusions

- Overall dose response
  - Beta Poisson best fit for pooled data
    - $\alpha = 0.974$ $N_{50} = 62{,}817$ spores
- Interspecies correction was unnecessary for host species
  - Perhaps extrapolation to humans will not require interspecies correction
- No correction needed for strain

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