

A Bayesian Statistical Modeling Approach for *Bacillus anthracis* Dose Response Data

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Background

- Little human dose data is available for Category A Bioterrorism Agents
- Anthrax has been extensively studied using non-human animals as surrogate species
- Attempts have been made to validate with the only existing human data from the Sverdlovsk outbreak (Meselson, 1994)
- Uncertainty associated with extrapolation to unobserved species has not been quantified



Objectives

1. Use Bayesian statistical approach to fit dose response parameters for *Bacillus anthracis* and compare to a classical, or frequentist, likelihood-based approach
2. Conduct a meta-analysis using hierarchical methods for three different species- rhesus monkeys, guinea pigs, and rabbits (Druett et al., 1953; Pitt et al., 2001; Altboum et al., 2002)
3. Estimate susceptibility and associated uncertainty of unobserved species based on species with observed susceptibilities

Organism / Strain Used	Host Species	Dose (Inhaled Spores)	Number of Test Subjects	Response	Positive Response	Negative Response
<i>Bacillus Anthracis</i> Vollum Strain	Guinea Pig (Altboum, 2002)	20000000	7	Death	7	0
		2000000	8	Death	7	1
		200000	12	Death	10	2
		20000	12	Death	6	6
		2000	8	Death	0	8
		200	4	Death	0	4
<i>Bacillus Anthracis</i> ATCC_6605 Strain	Guinea Pig (Altboum, 2002)	3000000	10	Death	10	0
		300000	10	Death	8	2
		30000	10	Death	3	7
		3000	10	Death	0	10
		300	6	Death	1	5
		30	6	Death	0	6
<i>Bacillus Anthracis</i> Ames Strain	New Zealand White Rabbit (Pitt, 2001)	14600000	10	Death	10	0
		9240000	8	Death	8	0
		19110000	5	Death	5	0
<i>Bacillus Anthracis</i> Vollum Strain	Rhesus Monkeys (Druett, H.A., et. al., 1953)	70320	8	Death	1	7
		77040	8	Death	4	4
		108720	8	Death	5	3
		137520	8	Death	6	2
		155520	8	Death	5	3
		160800	8	Death	3	5
		240000	8	Death	8	0
		300000	8	Death	7	1
		398400	8	Death	8	0



Methods

Maximum Likelihood Estimation (MLE) Approach

- The exponential dose response model was fit to the three sets of host-species/organism-strain groups using the MLE to determine the best fit parameter, r .
- Confidence intervals were calculated from a bootstrap re-sampling technique.

Bayesian Hierarchical Model

- Markov Chain Monte Carlo (MCMC) techniques were used to sample an array of parameter estimates for r from the four sets of host-species/organism-strain groups using both an informed and an uniformed prior estimate of the distribution
- Mean, median and credible intervals were calculated for each group using this data



Methods

Exponential Dose Response Model

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

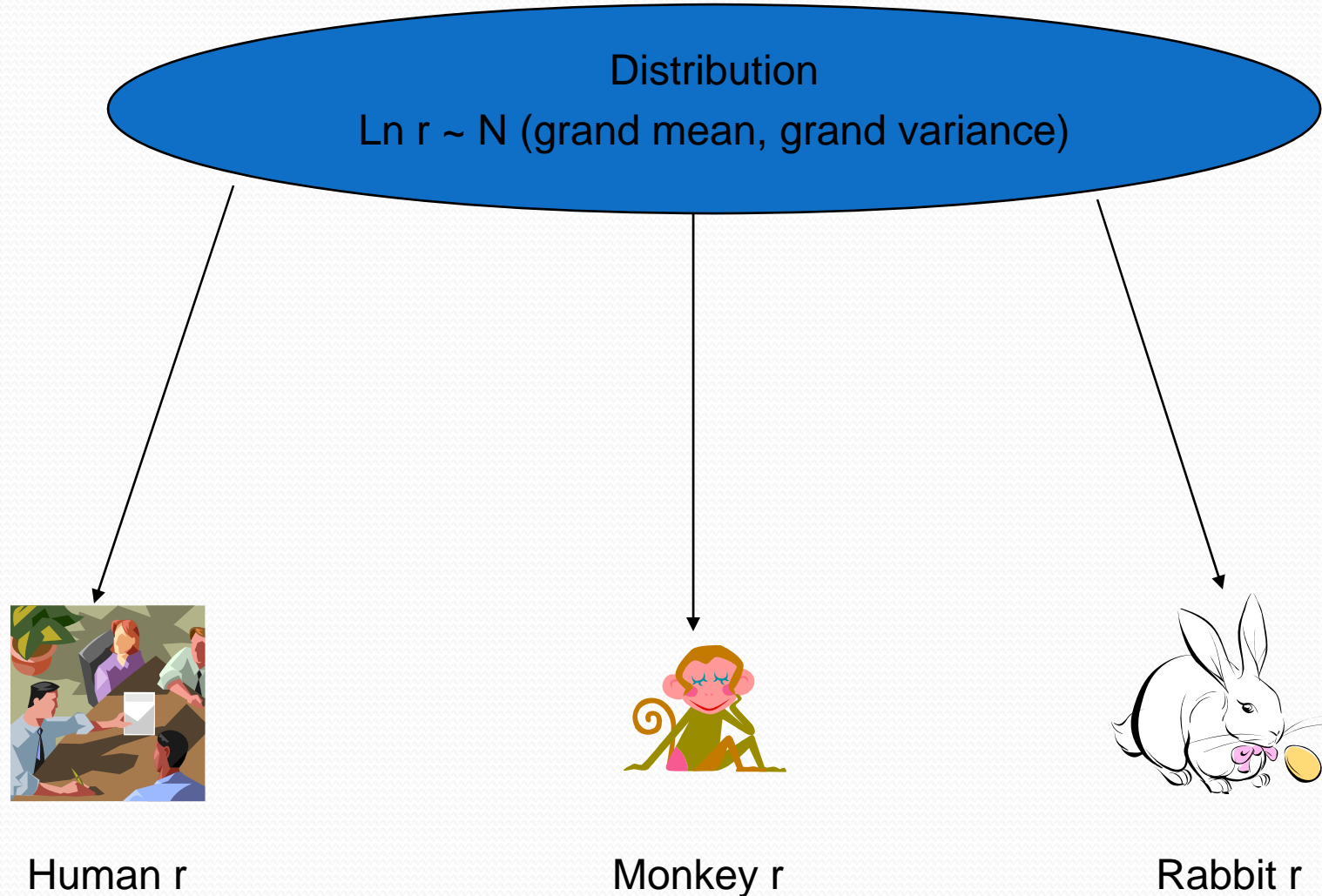
Where:

$P(d)$ = Probability of death

r = pathogen-host survival probability

d = dose of organisms to host

Bayesian Hierarchical Modeling



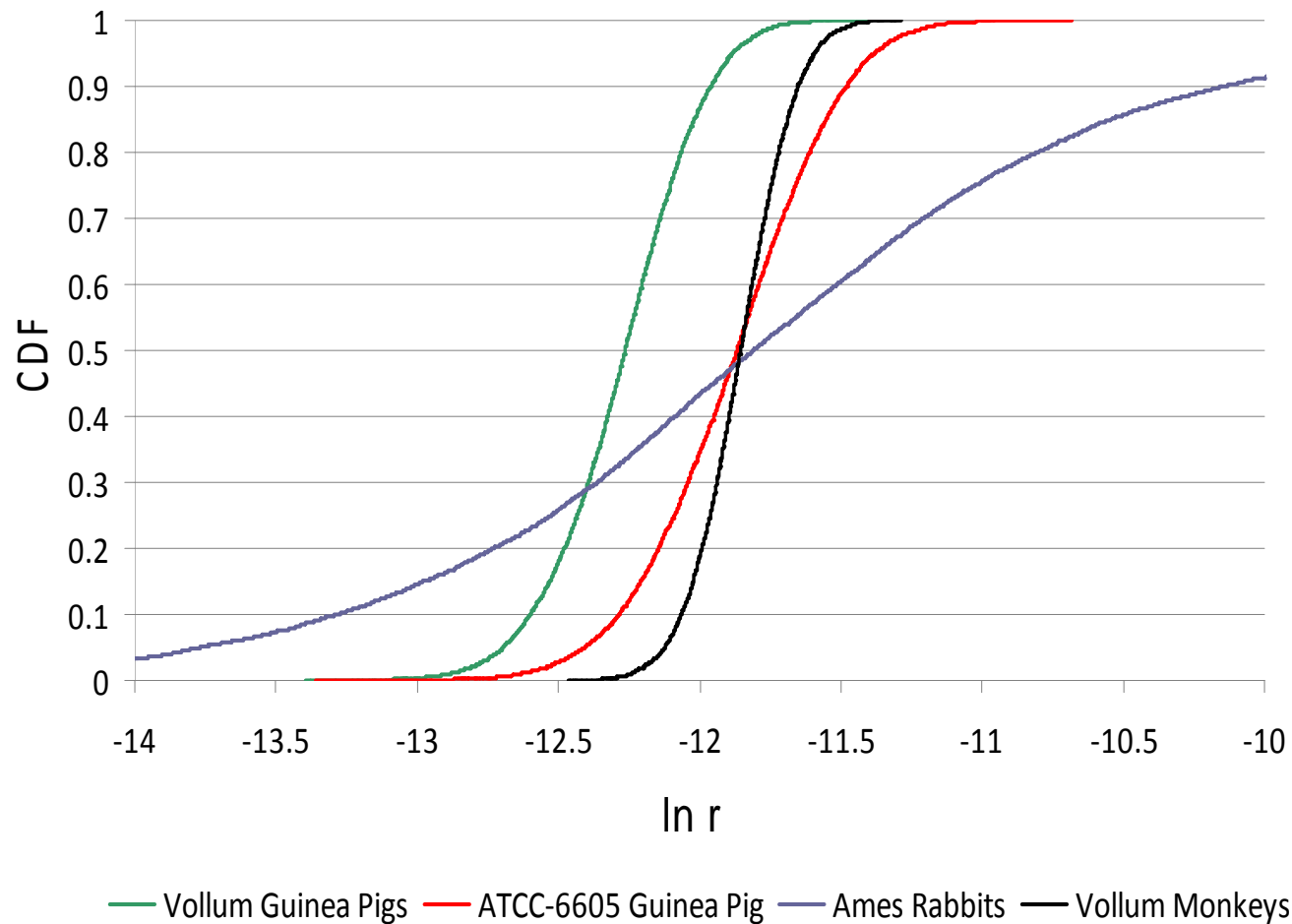
Prior Assumptions

$$\ln r \sim n(\mu_{\ln r}, \sigma^2)$$

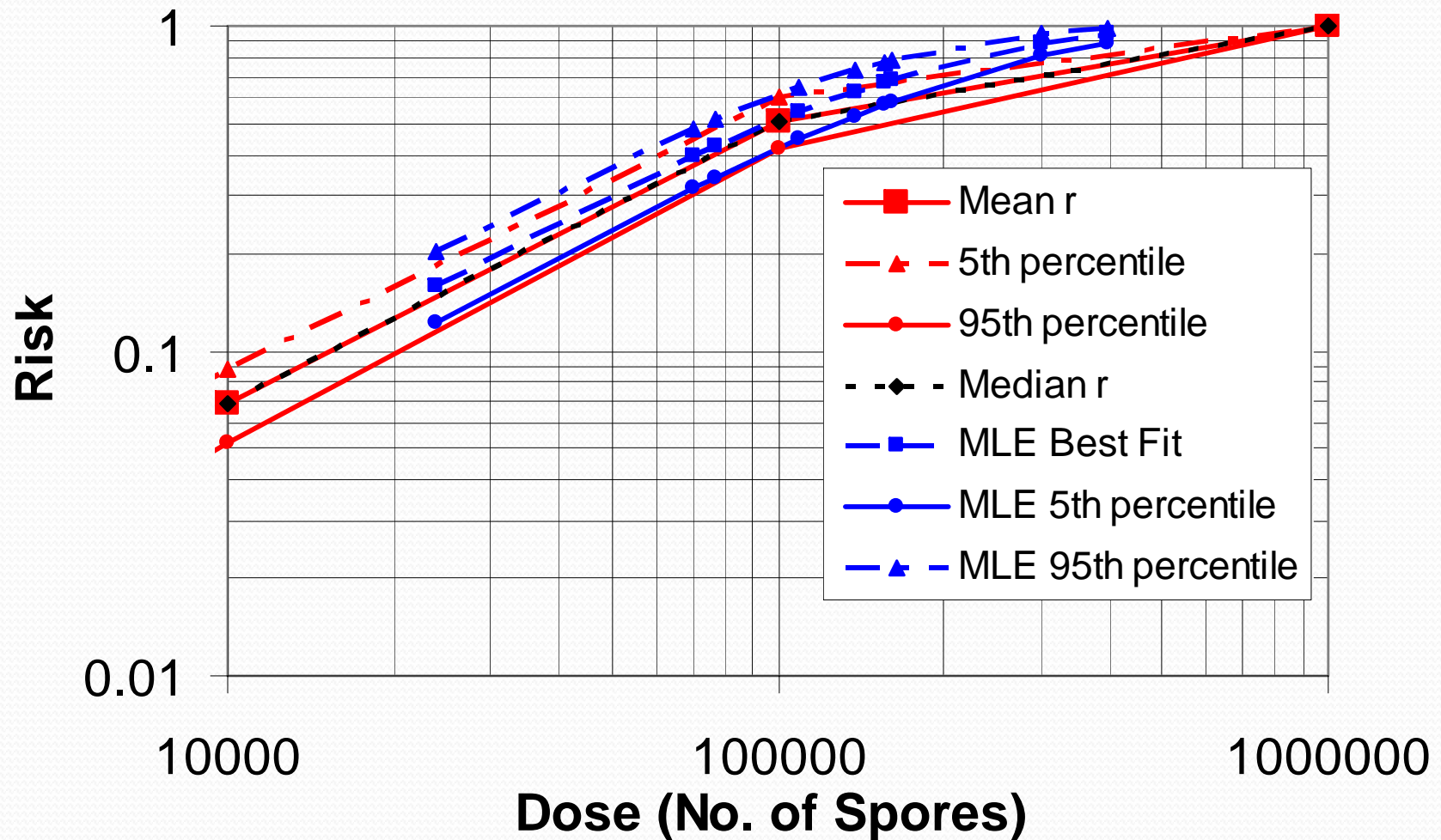
$$\ln \mu_{\ln r} \sim n(-11.9, 2^2)$$

$$-2 \ln \sigma^2 \sim n(-0.67, 0.84^2)$$

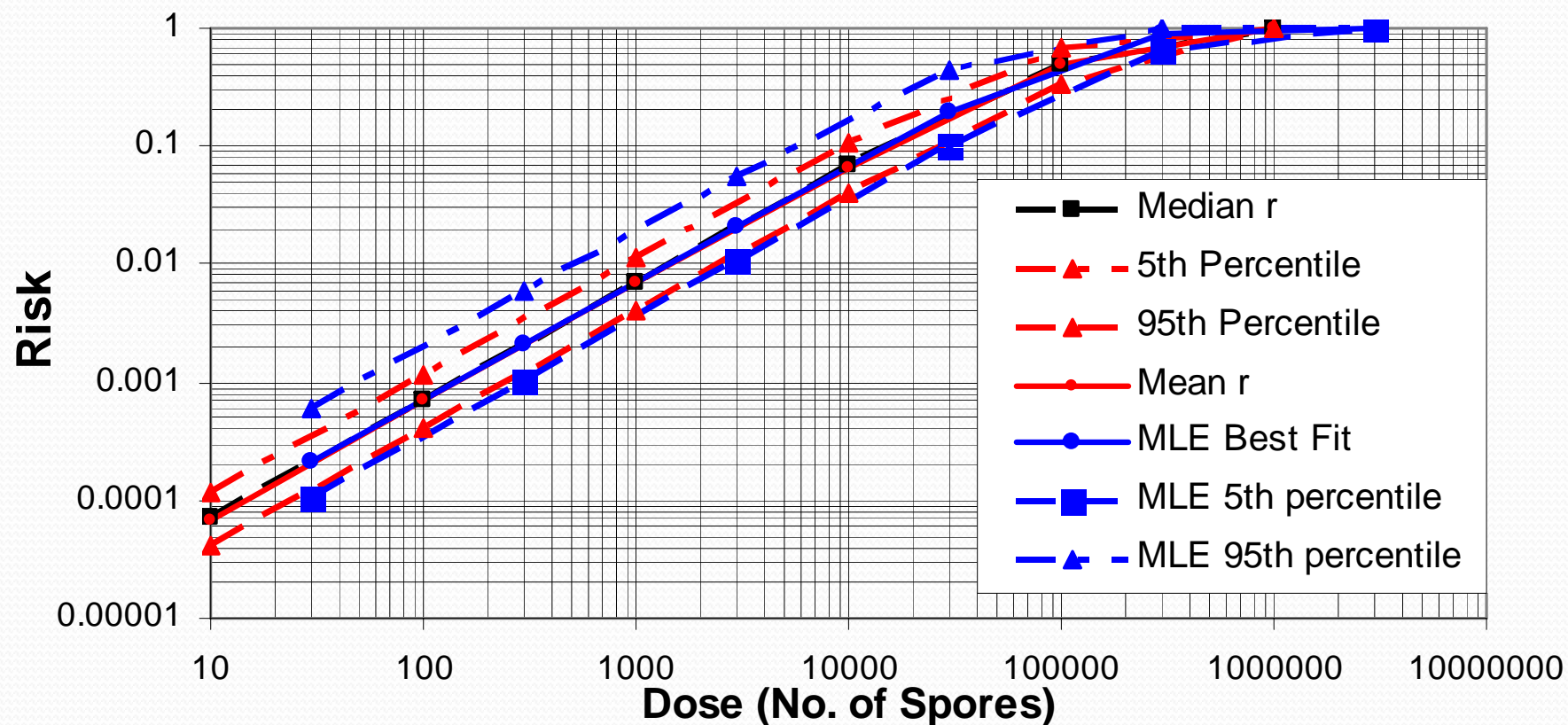
Results of Hierarchical Approach



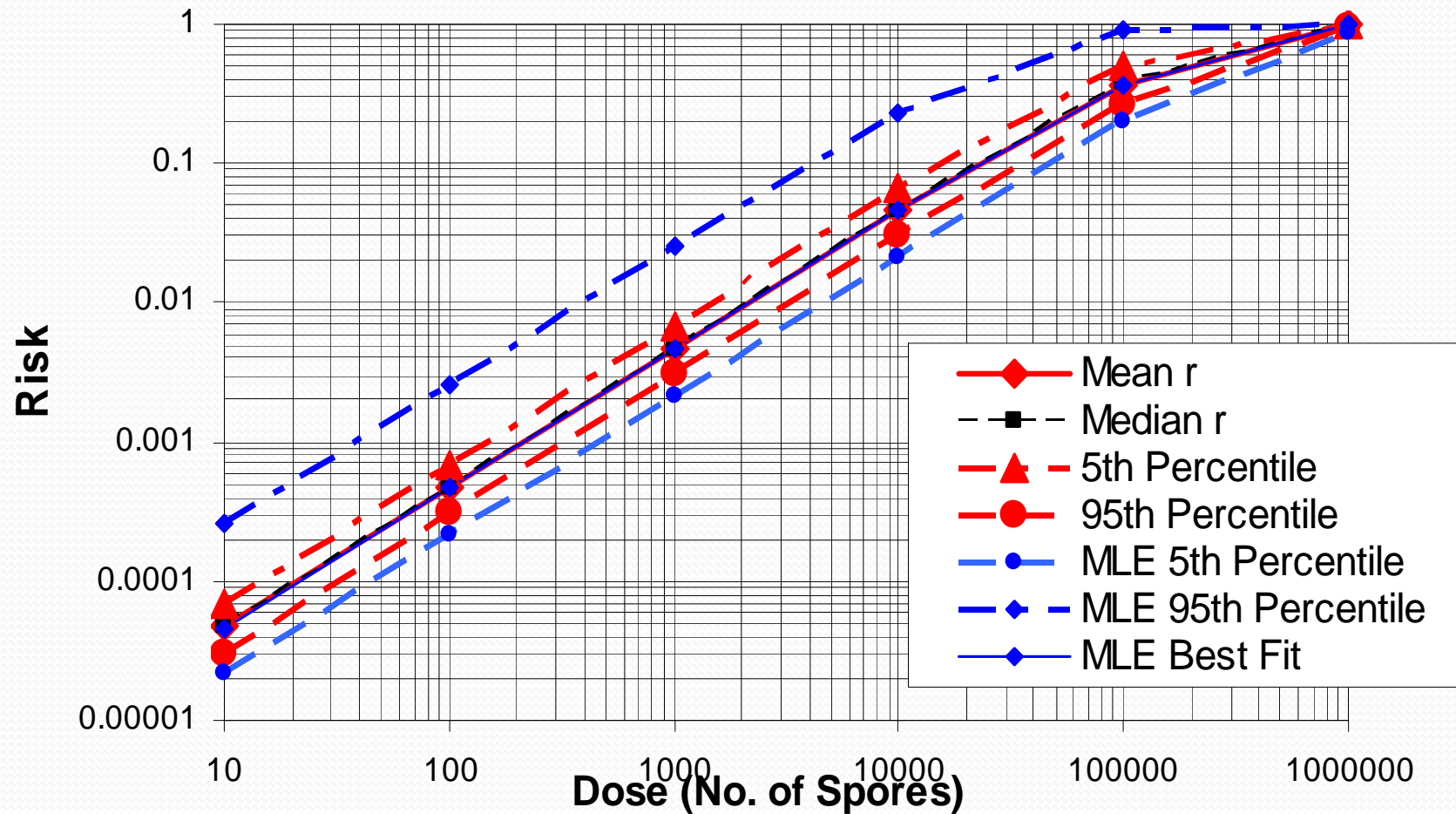
Vollum Monkeys



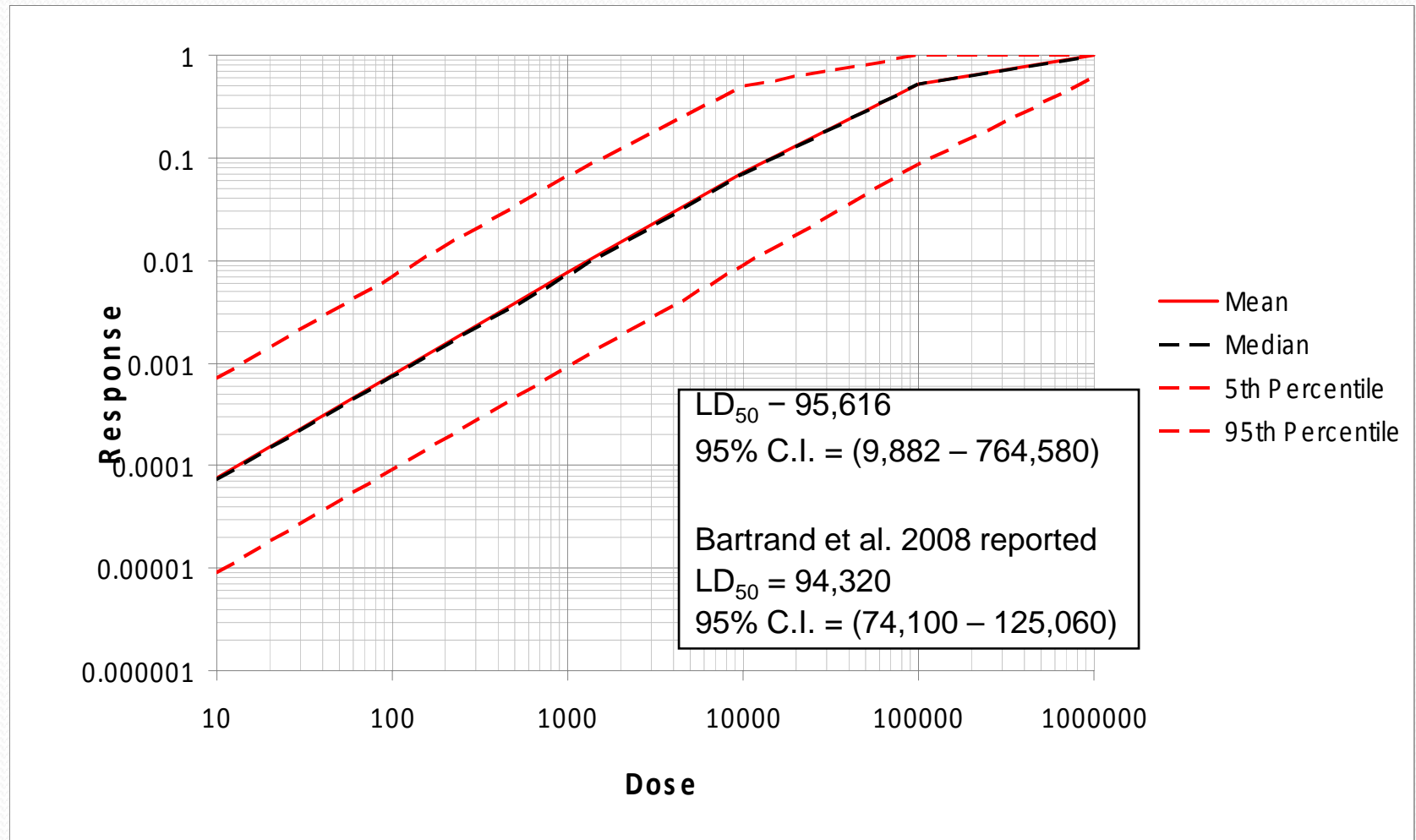
ATCC-6605 Guinea Pig



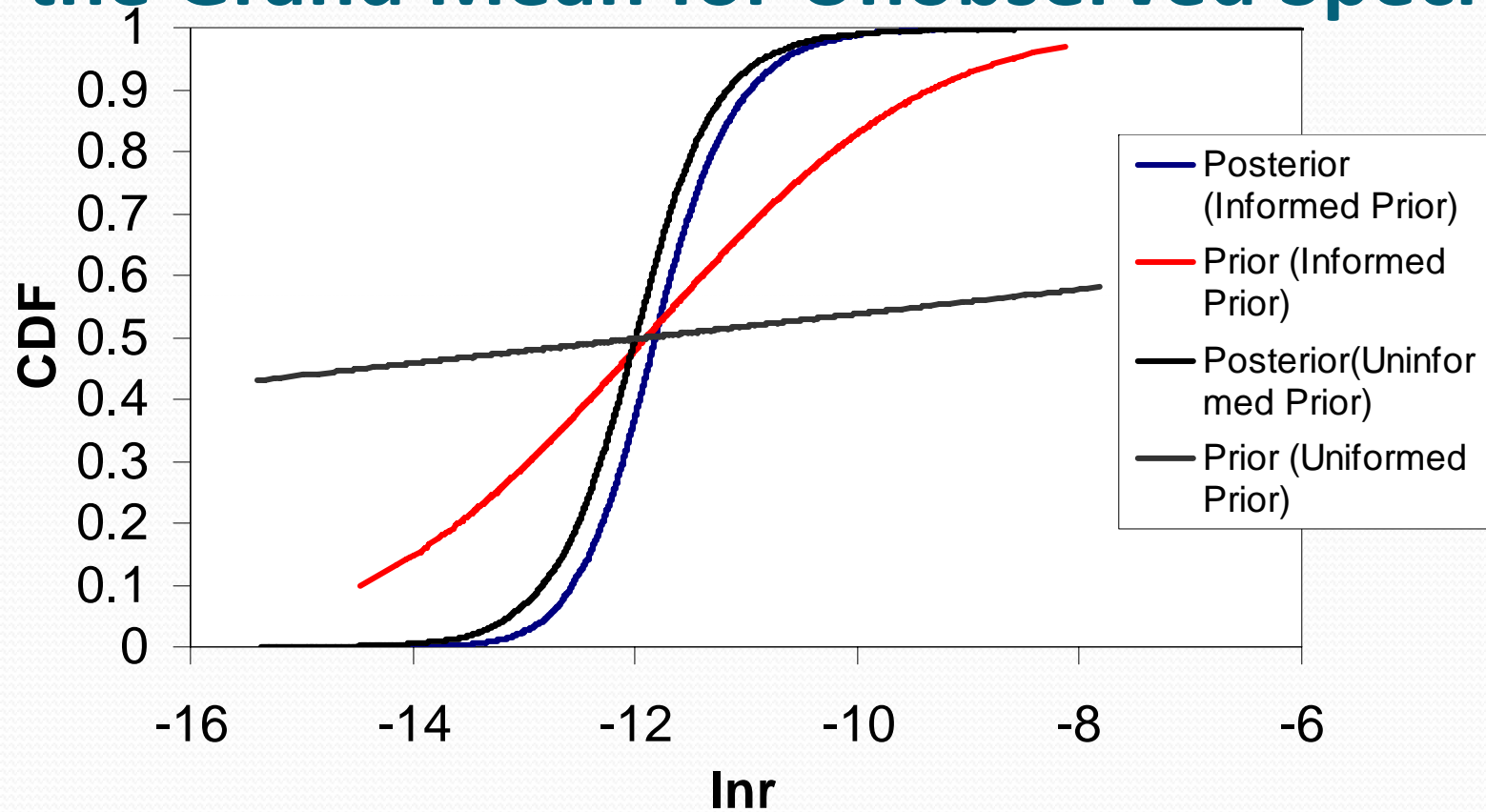
Vollum Guinea Pig



Prediction for Unobserved Species



Prior vs. Posterior Distributions of the Grand Mean for Unobserved Species



Distribution	Informed	Uninformed
Prior	$\ln \mu_{\ln r} \sim n(-11.9, 2^2)$ $-2 \ln \sigma^2 \sim n(-0.67, 0.84^2)$	$\ln \mu_{\ln r} \sim n(-11.9, 20^2)$ $-2 \ln \sigma^2 \sim n(-0.67, 0.84^2)$
Posterior	$\ln \mu_{\ln r} \sim n(-11.78, 0.67^2)$	$\ln \mu_{\ln r} \sim n(-11.99, 0.72^2)$



Model Validation

- Internal
 - Generally consistent with MLE
 - Deviations from MLE are consistent with the influence of data from other experiments
- External
 - Will require cross-validation
 - More data



Conclusions

- Variance is reduced as more information from data is gained
- Bayesian hierarchical model yields more narrow credible percentiles of risk when looking individual species
- Bayesian hierarchical model yields wider credible percentiles of risk when looking at overall pooled data



Future Work

- Extrapolation to unobserved data sets, including humans may be possible
- Characterizing the degree of relatedness of different dose-response experiments
 - Host/Species
 - Organism/Strain



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