

Tularemia Dose Response Analysis for Oral Exposure of Multiple Strains

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Francisella tularensis

- Microorganism:
Francisella tularensis (*F. tularensis*): gram negative, enveloped coccobacillus, non motile, thin, non spore forming.
- No toxin secreted
- Typically 3 – 5 day incubation period, up to 21 days maximum.
- Non-communicable in humans

Routes of Exposure

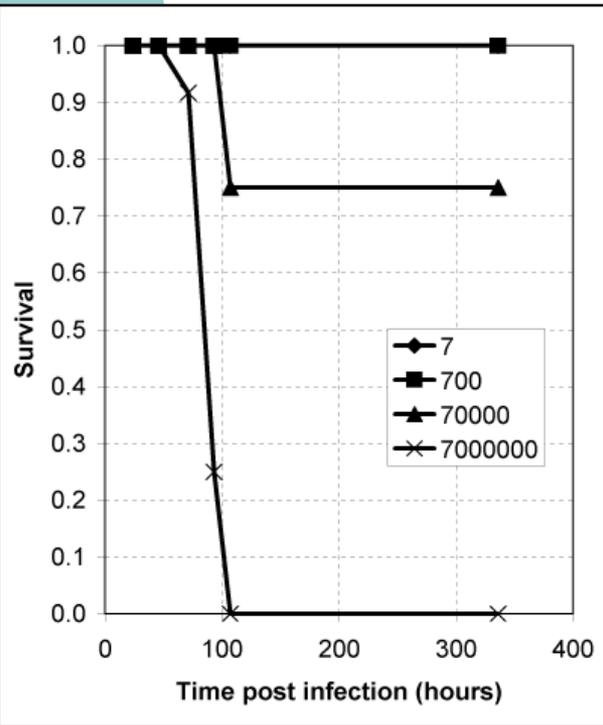
- Arthropod bites (tick, deerfly, etc.)
- Direct contact with infected animals, infected animal tissues or fluids (typically rodents)
- Ingestion of contaminated water or food
- Inhalation of infective aerosols



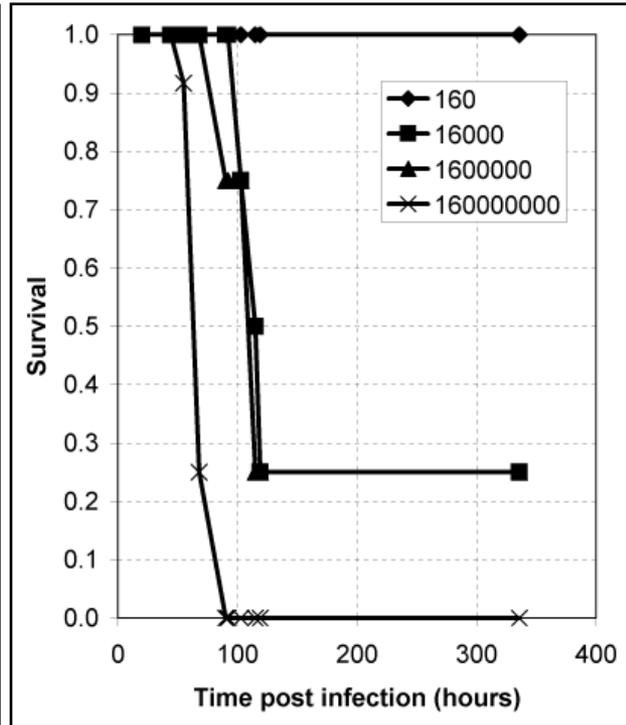
Analyses for Different Strains of *F. tularensis*

- Two sets of animal trial experiments
 - First set
 - Establish minimum and maximum doses among three different strains
 - Second set
 - Expand on the doses
 - Which strain(s) were expected to be most useful based on previous animal trials and initial dose response analysis
- Comparison of inhalation and oral exposure
 - CAMRA QMRA Summer Institute students

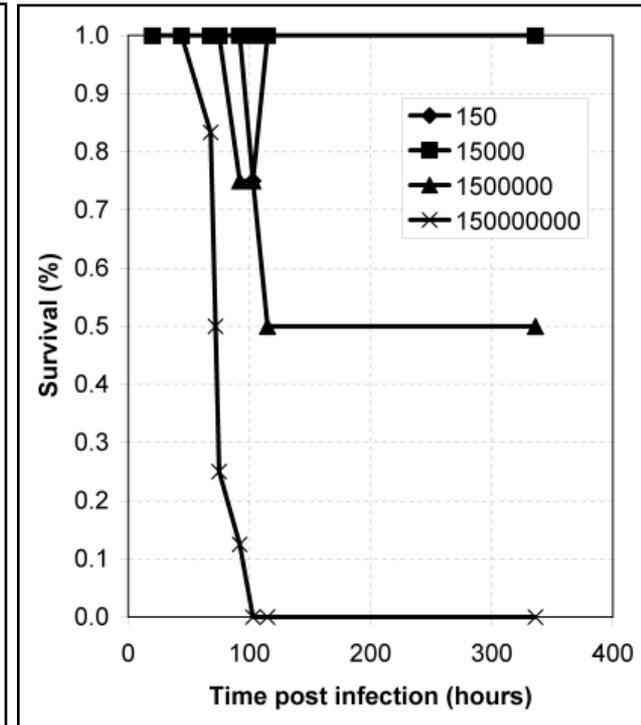
Dose Response for Oral Exposure; First Set of Animal Trial Experiments



Schu S4 Strain



MA00-2987 Strain

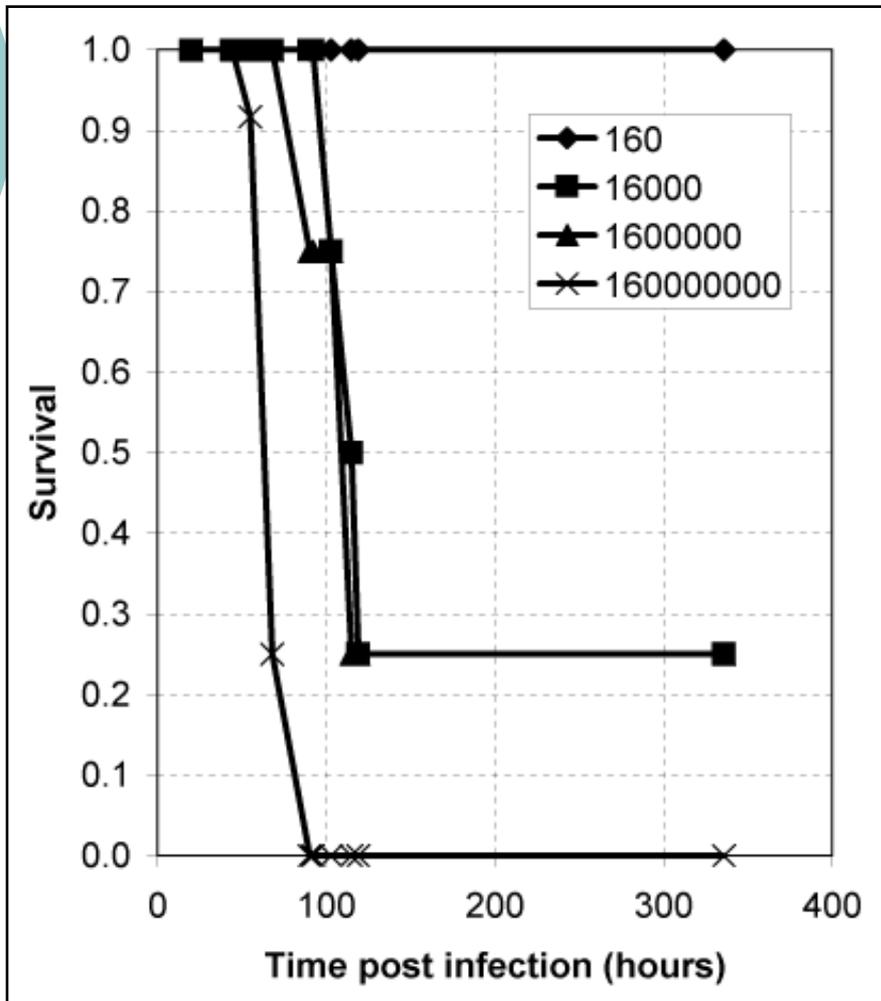


WY96-3418 Strain

Dose Response for Oral Exposure; First Set of Animal Trial Experiments

- Schu-S4 (Schu-strain), MA00-2987 (M-strain) and WY96-3418 (W-strain)
 - Comparison of dose response models
 - Pooling analysis
 - Determination
 - Which strain(s) should be tested again?
 - Which strain(s) show highest response?

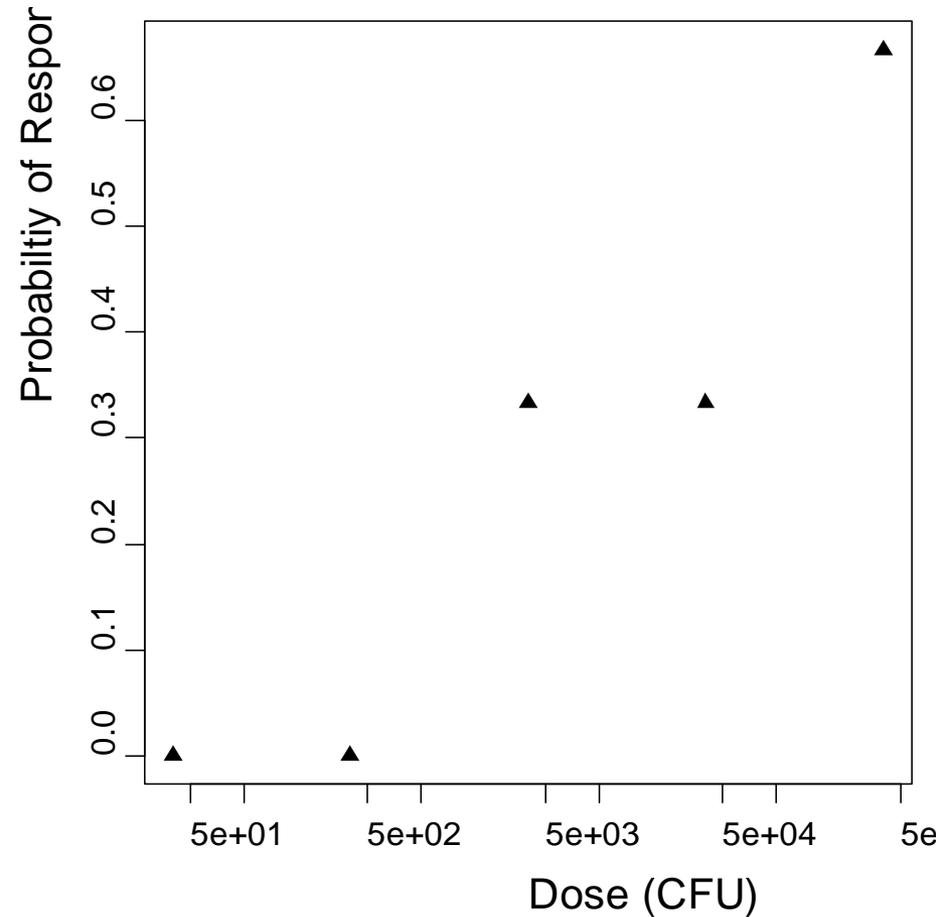
Dose Response for Oral Exposure; First Set of Animal Trial Experiments



Results

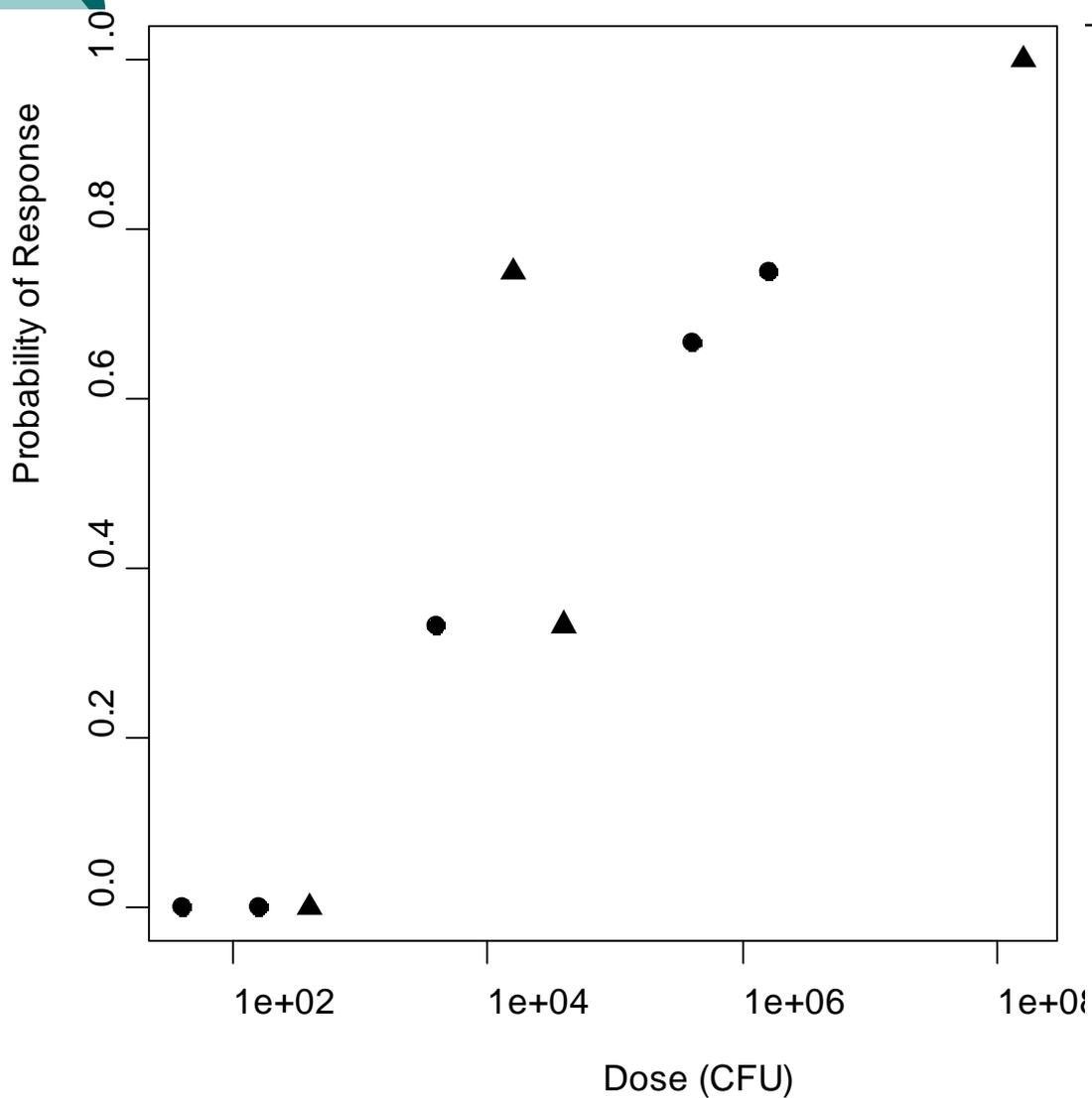
- M-strain is best candidate for Trial 2.
 - Small amount of discrete intermediate responses
 - May have a larger time dependency than others.
- Trial 2 should consist
 - Higher breakdown of doses
 - Collect data for time post inoculation

Dose Response for Oral Exposure; Second Set of Animal Trial Experiments



Dose Response for Oral Exposure; Second Set of Animal Trial Experiments

Results and Future Steps



Comparison of Oral to Inhalation Exposure

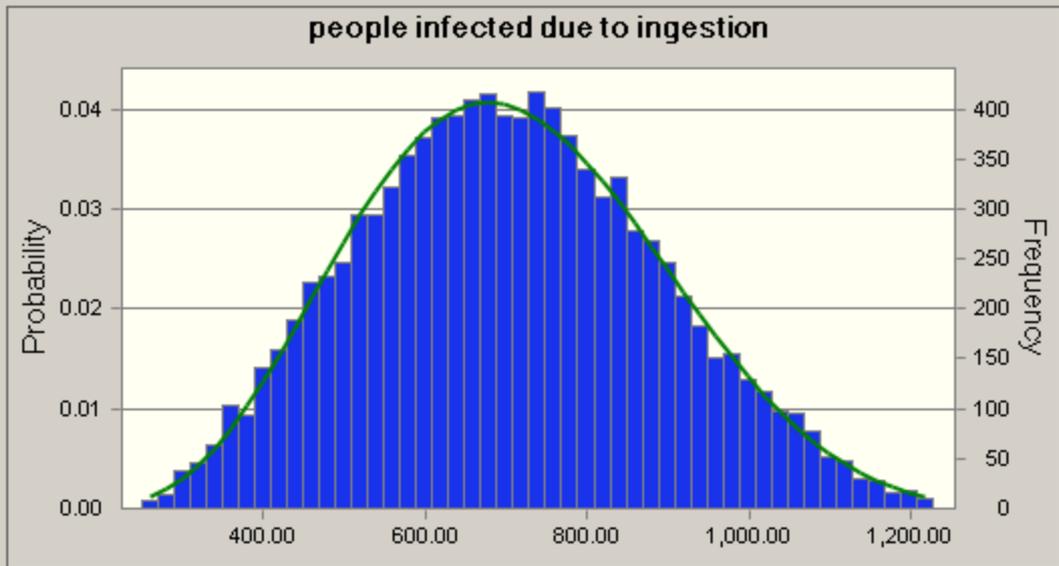
- Student Projects
 - QMRA Summer Institute at Michigan State University, August 2008
- Scenario
 - Tularemia infected rabbit falls into water reservoir
- Analysis performed
 - What is riskier: oral or inhalation exposure.
 - Enumerate the risks
 - Sensitivities of parameters used
 - Feces excreted by rabbit to ingestion or inhalation

Comparison of Oral to Inhalation Exposure

- Strategy
 - Consider system completely mixed
 - Estimate excrement rate for rabbits
 - Tularemia only from excrement
 - Risk modeled using Monte Carlo
 - Modeling two exposure routes
 - Ingestion and inhalation
 - Ingestion from using (drinking) contaminated water
 - Inhalation from showering in contaminated water
 - Dermal contact ignored (information from prior events)
 - No growth/Decay
 - Only sink is use of water
 - Use dose response model for moderate potency strain
 - Response defined as infection
 - Inhalation rate and dose as well as ingestion dose determined using Monte Carlo analysis

Comparison of Oral to Inhalation Exposure

10,000 Trials Frequency View 9,971 Displayed

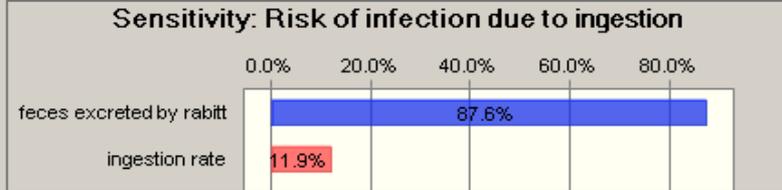


-Infinity

Certainty: 100.00 %

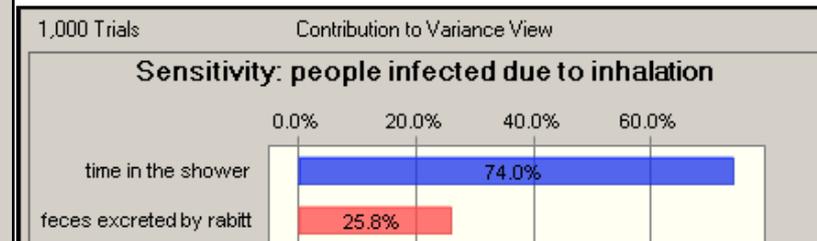
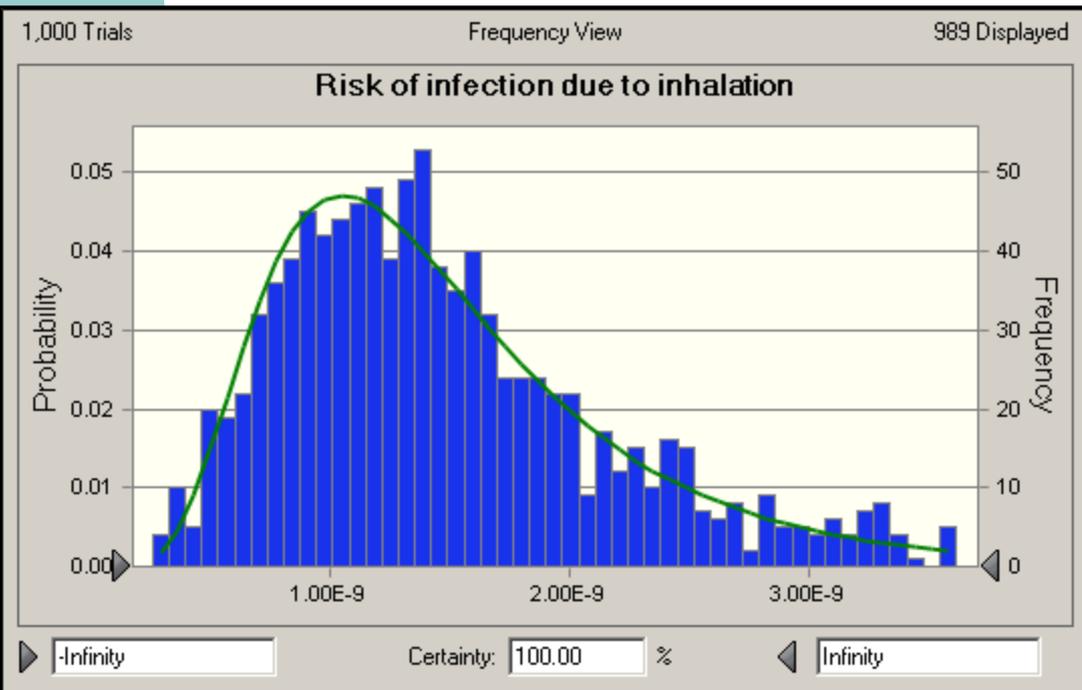
Infinity

1,000 Trials Contribution to Variance View



Mean risk = $1.8(10^{-3})$

Comparison of Oral to Inhalation Exposure



Mean risk = $1.0(10^{-9})$

Summary

- Tularemia
 - Potential to be highly infectious and lethal
 - Will be able to develop
 - Time post inoculation for new animal model data
 - Which can be compared to current time post inoculation work
 - Developed a case study analysis
- Comparing two exposure routes
 - Oral exposure much higher (1.8 million times greater) risk to a contaminated water supply
- For intentional water distribution contamination oral exposure is clearly the riskier exposure route
 - Therefore, according to this analysis boil orders may be best response option post detection.

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