An Adaptive Dose Seeking Design: Challenges in Implementation

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H-Flu: *Haemophilus influenzae* Study

- Primary objective to demonstrate feasibility of colonization of humans by nasal inoculation of NTHi 2019 StrR #1.
- Secondary objective to determine HCD50 and HCD90.
- Healthy volunteers (18-40 years old) were inoculated nasally with one of 8 different doses of NTHi 2019 StrR #1.
- Nasal washes and nasopharyngeal swabs were taken and analyzed for recovery of NTHi 2019 StrR #1. The response of "colonization" is of primary interest in the dose response objective. (Takes 2 weeks to evaluate the endpoint).
- Other responses: symptoms and immunoglobulin response.
- Human colonization is common ($>$50% of humans have asymptomatic colonization).
- Only 2 humans previously deliberately colonized with a different strain.

- 25% of otitis media associated with NTHi infection (so 25% of $3.5 billion annual cost of 24.5 billion office visits).
- NTHi frequent cause of acute bronchitis and pneumonia in patients with current lung disease.
- Most *H. influenzae* complications in very young, old, pregnant and immnosuppressed. Native Americans, Alaskans, certain aboriginal populations appear to be at increased risk of invasive *H. influenzae* disease.
- Long term interest is to developing vaccines or treatments to prevent colonization.
- A model for human colonization would provide a mechanism for screening vaccine candidates.

Design Considerations

- Obtain information on HCD50 and HCD90 for subsequent studies.
- Start at a reasonably low dose, but high enough to have a good chance of colonization. Based on human colonization model of a different pathogen *streptococcus pneumoniae* start at 1,000 cfu.
- Escalate slowly, but fast enough to get information with a small number of subjects.
  - Stage 1: 6 subjects with doses determined one at a time (takes 2 weeks to determine response).
  - Stage 2: 9 additional subjects with 3 subjects at each of 3 doses.
  - Trial to be completed in summer, outside of the 'flu season.
  -
    - Binary outcome: subject was colonized or not colonized.
    - Simple logistic regression model for dose respopnse.
    - Goal is to infect, but not to make subjects sick.

  .

H-Flu Design

Stage 1: n=6

- Potential doses ($log_{10}(cfu)$) range from 1.5 to 5.0, with increment of 0.5.
- Starting dose chosen lower than HCD50 of another pathogen.
- The design used was modified from the Up-and-Down Method (Dixon & Mood, 1948; Wu, 1985):
- Using Up-and-Down Method with dose range $[1.5, 5.0]$, there may be more than two subjects with the same dose. Replication increases the probability of no MLE. (Silvapulle, 1981, Agin, 1997).
- The Up-and-Down design was modified (no more than two subjects were inoculated with the same dose and increase the range).

H-Flu Design

Stage 1: First Subject Colonized

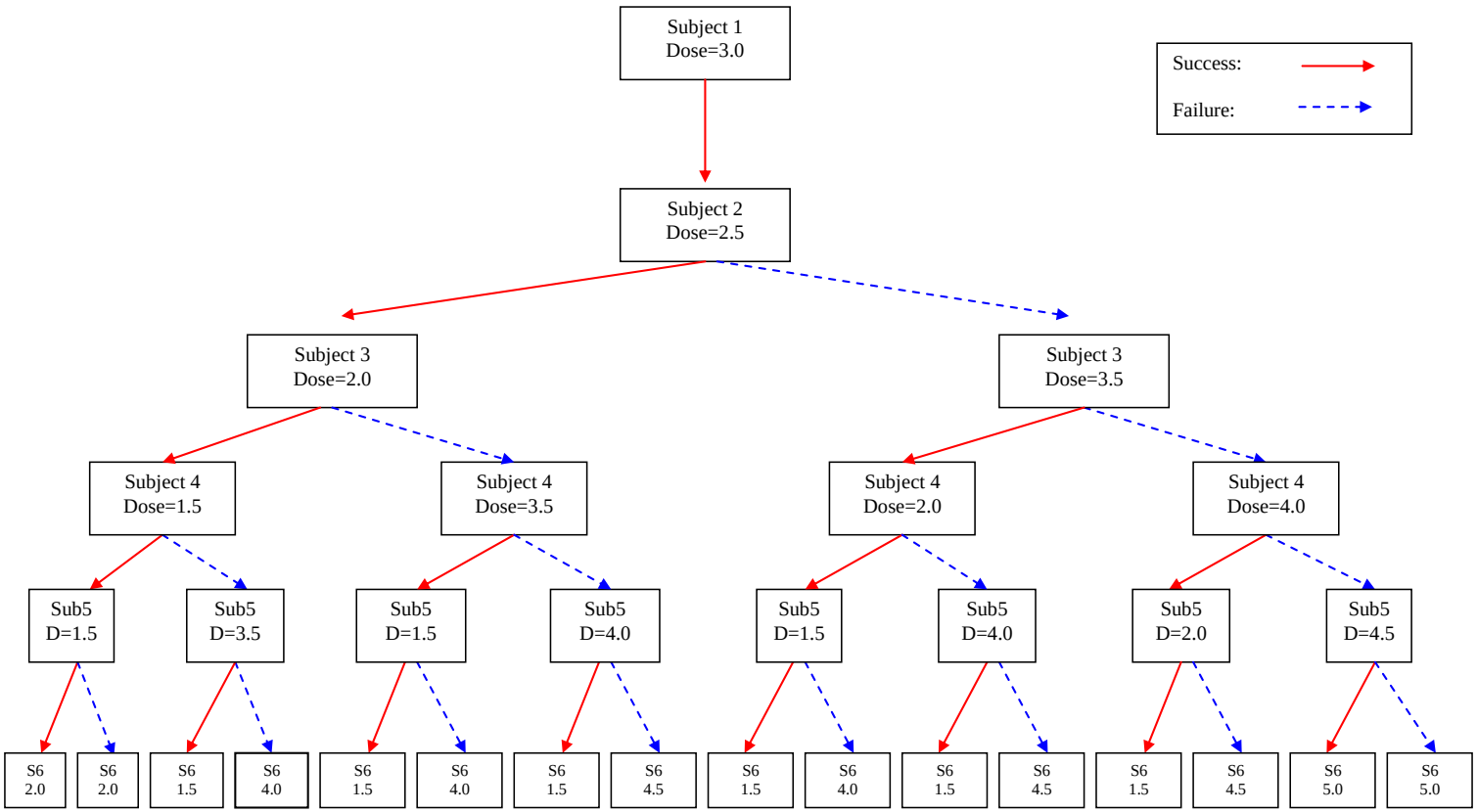


Figure: Diagram for H-Flu Design (Stage 1)

H-Flu Design

Stage 1: First Subject Not Colonized

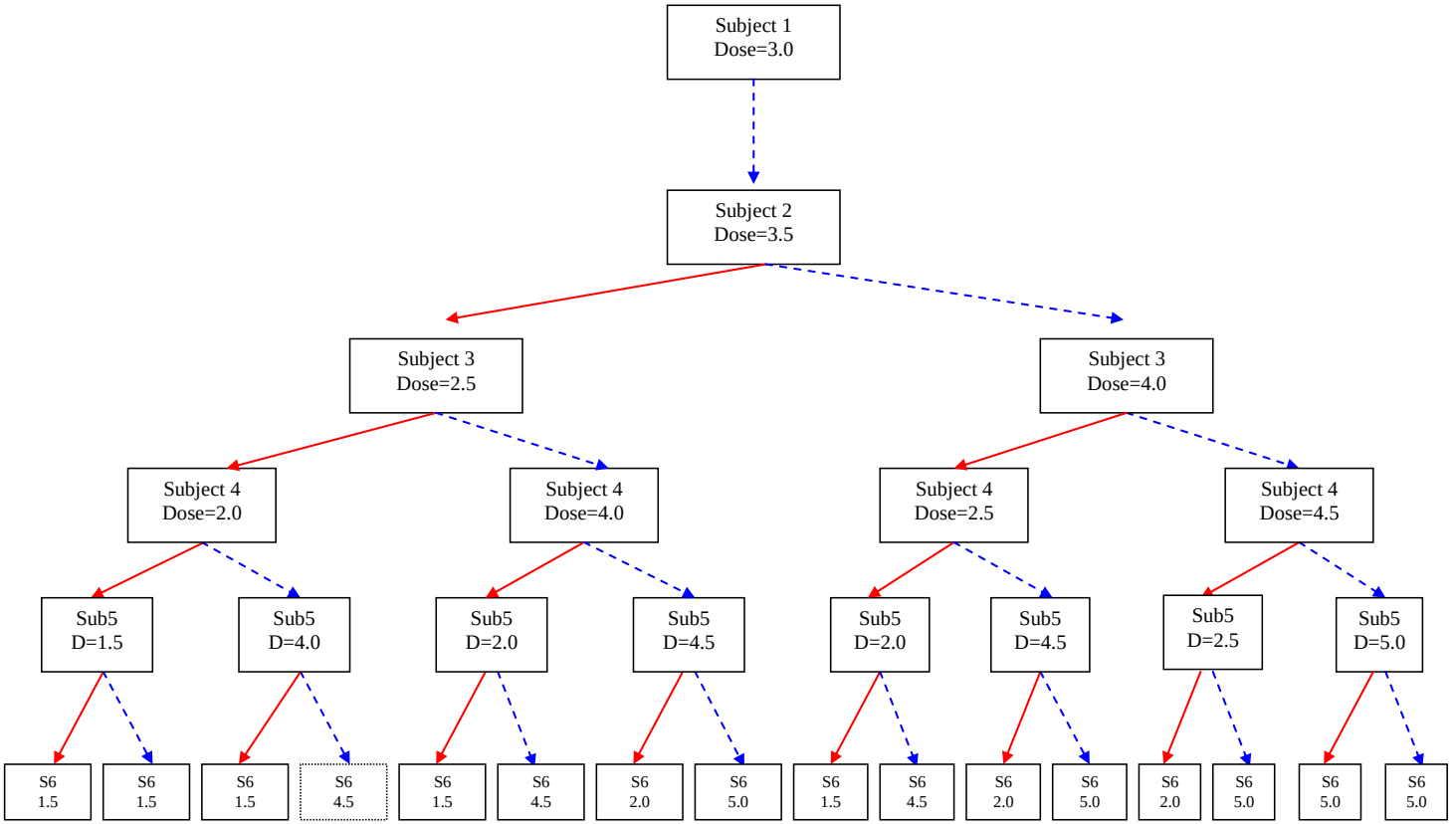


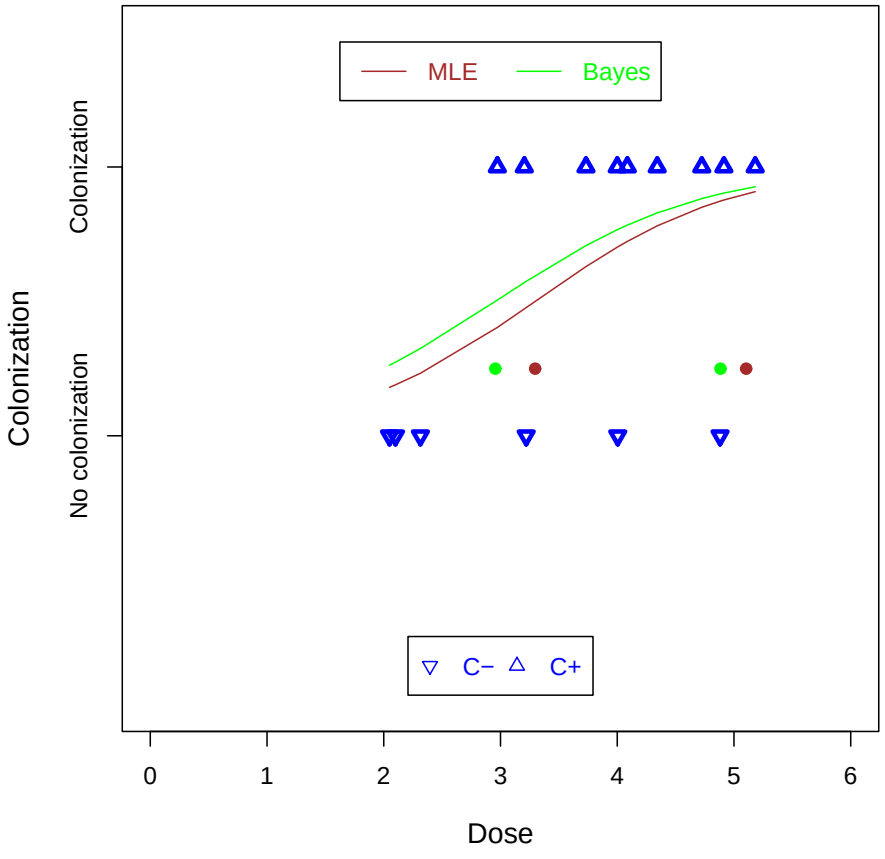
Figure: Diagram for H-Flu Design (Stage 1)

Simulation Study

- Settings for simulation:
  - Nineteen combinations of true $(HCD50, HCD90)$.
  - For each combination of $(HCD50, HCD90)$, simulate 1,000 of (x_i, y_i), $i = 1, \ldots, 6$.
  - Compute MLEs for our design and for up-and-down design.
  - Compute Bayes estimates for both designs.
- Results:
  1. Normal approximation for MLE does not hold (very small sample size).
  2. Probability of MLE not existing is high for our design (> 0.4).
  3. Probability of MLE not existing is even higher for up-and-down design (> 0.8).
  4. Bayes estimates have considerably smaller MSEs when true values in range of prior distribution.

Results

- Trial completed successfully.
- PI found design very intuitive: "this is what I would have done intuitively".
- Some subjects were colonized, some were not, with an apparent dose response.
- For safety and reactogenicity evaluations monitoring each subject before determining the next dose made sense for stage 1.
- DSMB reviewed the data from the first 6 subjects, and design for next 9 subjects.
- Stage 2 went ahead as planned. (3 subjects at each of estimate HCD50, HCD90 and somewhere in between).
- Hospitalization of subjects make it hard to recruit and so the small sample size was pragmatic.

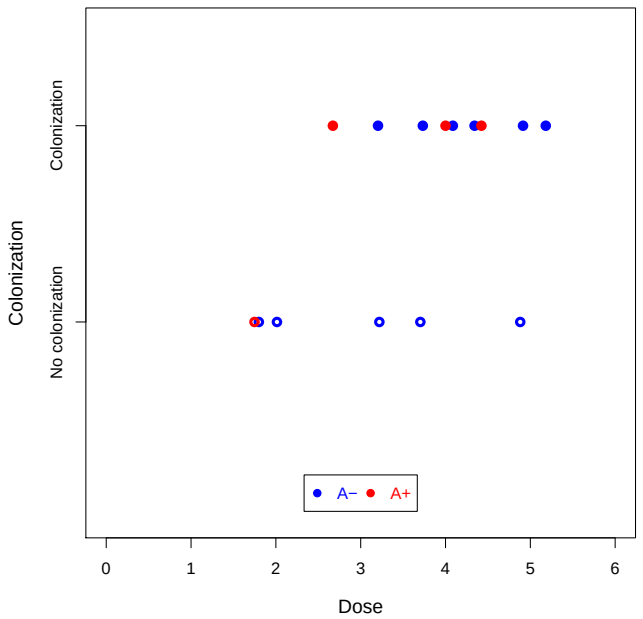


Posterior from this study is prior distribution for subsequent study.

Adverse Event Results

- Adverse event is defined as those who had moderate reactogenicity reaction.
- Summary of the data:

Colonization	Adverse event		Total
	Yes	No	
Yes	3	6	9
No	1	5	6
Total	4	11	15



One Operational Challenge: Error in Doses

There were two sources of error in delivering the dose:

- Dose of biologic product is not easy to determine exactly.
- Pharmacist error in dilution.

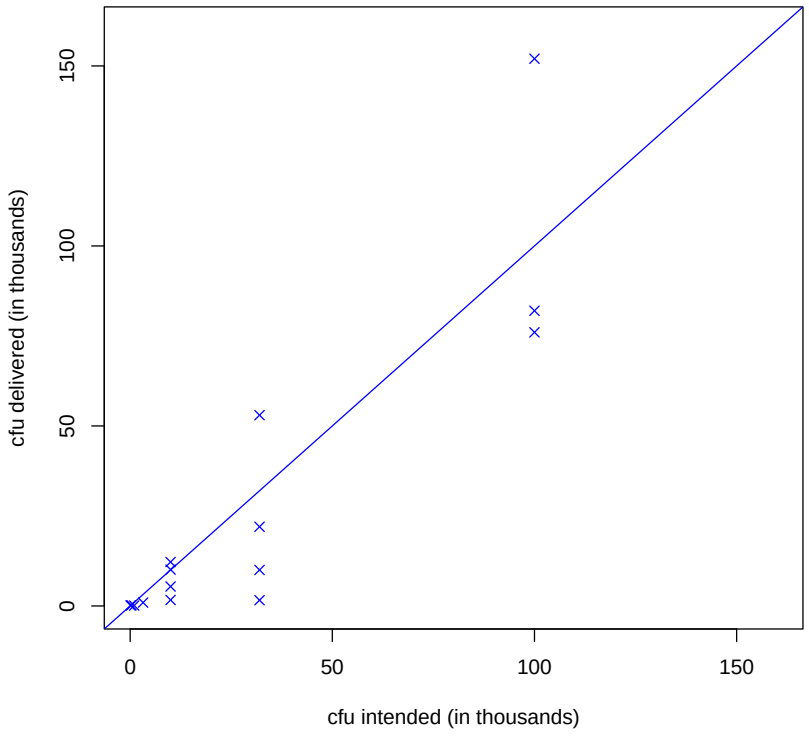


Figure: Intended Dose *versus* Dose Delivered

Other Challenges

- NIH (NIAID/DMID): scientific review and regulatory review
  - Scientific review:
    - initially NIAID officers were "puzzled" about the design.
    - frequent turnover of scientific officers, some very new.
    - officers did not appear to be familiar with sequential dose designs (CRM etc.).
    - concern about release of genetically modified bacteria into community.
- The protocol PI, Dr. Winokur, provided reassurance to NIAID.
- NIAID regulatory review
  - not a GLP product (isolated in 1985, processed in clinical lab).
  - process needed to check for purity and lack of contamination.
- Dr. Winokur developed a process.

- FDA review:
  - *Although the up down statistical model provides a rapid method to achieve the study objectives, this method from a safety perspective, is less conservative than a dose escalation approach. Please describe in the IND submission the number of participants needed for each dose, and the estimated study duration, using a dose escalation approach. Acceptability of the up down model would depend on the response to the requested information.*
  - Concern above was addressed after conference call.

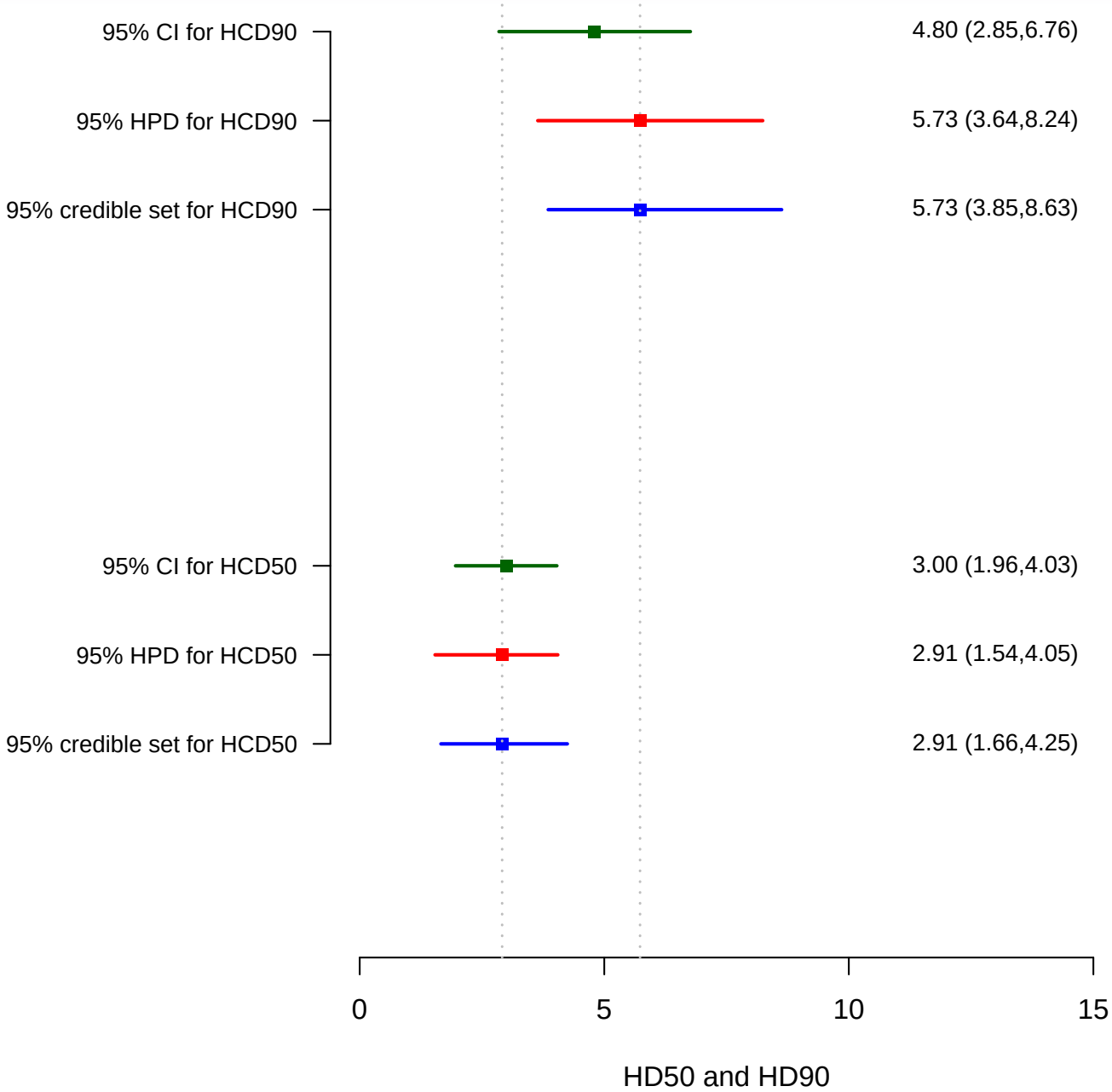
- EMMES provides data management and statistical support for DMID protocols.
  - EMMES had considerable concerns about the design.
  - Concern about sequential algorithm.
  - Concern about analysis and sample size.
- Phone call and discussion where I provided reassurance.

- After the review by NIAID, FDA and Emmes, no additional concerns were raised.
- Next study is now designed, not yet implemented, and is about to be sent for FDA review.
- NIH concern is primarily about the possibility steptomycin resistant NTHi being released into the community.

Adaptive Designs in NIH Studies

- Compared to other concerns, the adaptive nature of the design, although initially controversial, was not an obstacle. The initial concerns about the design were satisfactorily addressed.
- The primary NIH issue was, and is, risk. The subsequent study has so many additional restrictions that it may be undoable (hospitalization for 6 days, enrollment testing and consent of intimate partners, no intimate contact of inoculated subjects with intimate partners).

Thanks!


95% CI for HCD90
95% HPD for HCD90
95% credible set for HCD90
95% CI for HCD50
95% HPD for HCD50
95% credible set for HCD50
4.80 (2.85,6.76)
5.73 (3.64,8.24)
5.73 (3.85,8.63)
3.00 (1.96,4.03)
2.91 (1.54,4.05)
2.91 (1.66,4.25)
0
5
10
15
HD50 and HD90

Bayesian Approach

- Define $\mu = HCD50$, $\delta = HCD90 - HCD50$
- Prior distribution:
  - Assume $HCD50 = \mu \in [1.5, 5],\ \delta \in [0.1, 5.1]$
  - Assume $\frac{\mu - 1.5}{3.5} \sim$ Beta and $\frac{\delta - 0.1}{5} \sim$ Beta, specifically

$$\frac{\mu - 1.5}{3.5} \sim \text{Beta}(1, 1),\ \frac{\delta - 0.1}{5} \sim \text{Beta}(0.25, 1)$$

$$(\mu,\ \delta \textit{ independent})$$

$$\left(\mu = -\frac{\alpha}{\beta},\ \delta = \frac{\log 9}{\beta}\right)$$

- Estimates will always be available, simulation indicates good sampling properties.