Dose Response Model for *Burkholderia pseudomallei*

Sushil B. Tamrakar and Dr. Charles N. Haas

Center for Advancing Microbial Risk Assessment (CAMRA), Civil Architectural and Environmental Engineering Department, Drexel University

Burkholderia pseudomallei

- Flagellated gram negative saprophyte.
- Causative agent of Melioidosis.
- Diabetic population are high risk group (6).
- Found in tropical region, e.g. South East Asia, Northern Australia.
- Category B agent (5).

Model used

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

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

Log probit $P(d) = \phi\left[\frac{1}{q_1} \cdot \ln\left(\frac{d}{q_2}\right)\right]$

Data and Methods

- Data from open literature.
- Cochran-Armitage test for trend.
- Dose-response relationships were fit to data using MLE
- Difference in deviances (D)
- Compared to c2 a,1
- Ho: simpler model is best fit

- Low dose extrapolation from best fit model.
- Comparison of responses in different hosts.

Acknowledgement

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Table 1: Data used

Test Animal/mode of Inoculation	Dose (CFU)	Number of Test Animals	Positive Responses	Negative Responses
BALB/c mice: i.n**	405	6	6	0
	135	6	4	2
	45	4	3	1
	15	6	0	6
	5	6	0	6
C57BL/6 mice: i.n.	12150	6	5	1
	4050	6	3	3
	1350	6	1	5
	450	6	1	5
	150	6	0	6
Guinea pigs: i.p. *	4400000	5	4	1
	440000	5	5	0
	44000	5	5	0
	4400	5	4	1
	440	5	3	2
	44	5	1	4
Diabetic rats: i.p.	30000000	10	10	0
	3000000	10	10	0
	300000	10	7	3
	30000	10	7	3
	3000	10	6	4

*i.p.-intraperitoneal **i.n.- intranasal

Table 2: Best Fit Models

Host	No. of Doses	Minimized Deviance (Δ)	Best fit Model	Parameters
BALB/c mice	5	5.25	Exponential	k=0.010448
C57BL/6 mice	5	3.34	Exponential	k=0.0001004
Guinea pigs	6	3.97	Beta-Poisson	α = 0.25060
				N50= 192.264
Diabetic rats	5	4.39	Beta-Poisson	α = 0.2649
				N50= 2273.10

Table 3: Comparative susceptibilities

Dose (CFU)	Responses			
	BALB/c mice	C57BL/6 mice	Guinea Pigs	Diabetic rats
1.0	0.0104	0.0001	0.0186	0.0014
10	0.0992	0.0010	0.1340	0.0143
100	0.6480	0.0099	0.4196	0.1109
1000	1	0.0955	0.6630	0.3930
10000	1	0.6634	0.8110	0.6570

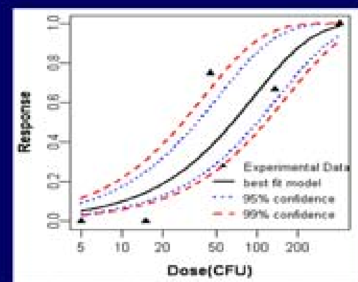

Fig.1 Dose Response Data and Exponential Model Fits for Mortality in BALB/c mice Exposed Intranasally

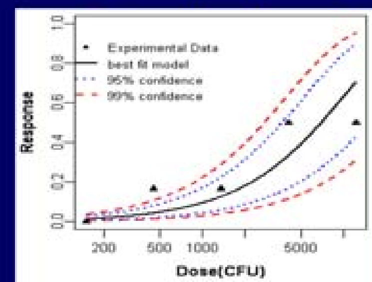

Fig. 2 Dose Response Data and Exponential Model Fits for Mortality in C57BL/6 mice Exposed Intranasally

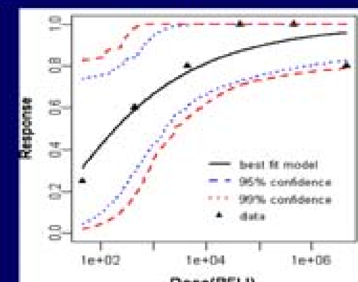

Fig. 3 Dose Response Data and Beta-Poisson Model Fits for Mortality in Guinea pig Exposed Intraperitoneally

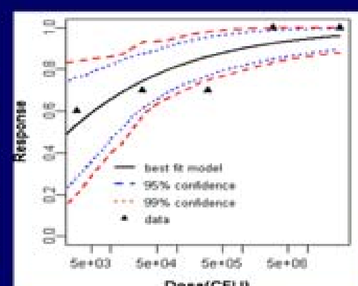

Fig.4 Dose Response Data and Beta-Poisson Model Fits for Mor-

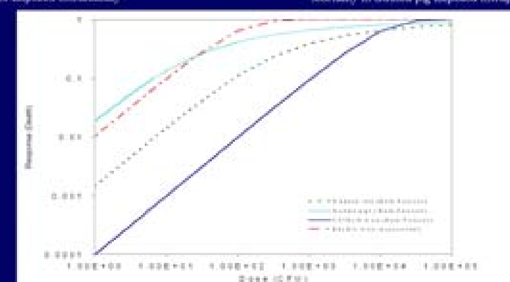
Fig.5 Comparison of Dose Response in Different hosts

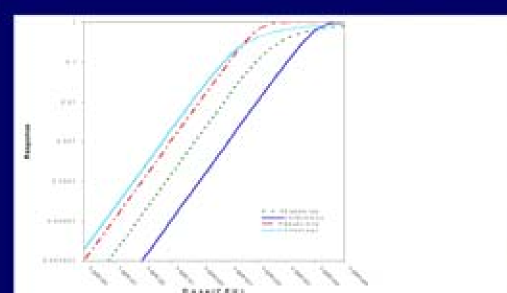
Fig.6 Comparative Low Dose Prediction for BALB/c mice, C57BL/6 mice, Diabetic rats and Guinea pigs

Conclusions

- BALB/c mice are most susceptible among the host animals.
- Diabetic rats are more susceptible (15 times more at a dose of 1 CFU and 11 times at 100 CFU) than C57BL/6 mice (Ref. to Table 3 & Fig. 5).
- Diabetic population is more susceptible than nondiabetic (reason may be the innate immunity of diabetic person is suppressed especially the neutrophil function).
- At low doses, BALB/c mice need 10 times less pathogens (exposed i.n.) than diabetic rats (i.p.) and C57BL/6 mice need 10 times more organ-

References:

1 Barnes, J. L. and N. Ketheesan, 2005. Route of Infection in Melioidosis. Emerging Infectious Diseases, 11:4: 638
2 Brett, P. J. and D. E. Woods, 1996. Structural and immunological characterization of Burkholderia pseudomallei O-polysaccharide-flagellin protein conjugates. Infection and Immunity, 64:7: 2824
3 Liu, B., et al., 2002. Model of Differential Susceptibility to Mucosal Burkholderia pseudomallei Infection. Infection and Immunity 70:2: 504
4 Miller, W. R., et al, 1947. Studies on Certain Biological Characteristics of Malleomyces mallei and Malleomyces pseudomallei II. Virulence and Infectivity for Animals. Journal of Bacteriology 55:1: 127
5 Schell, M. A., et al., 2007. Type VI secretion is a major virulence determinant in Burkholderia mallei. Molecular Microbiology 64:6: 1466
6 Woods, D. E., et al. 1999. Current studies on the pathogenesis of melioidosis. Microbes and Infection 2: 157