Incorporating Time Post Inoculation into a Dose Response Model of *Y. pestis* in Mice

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Objective

Improve the dose response model for *Y. pestis* infection using survival data

Y pestis-Causative agent of plague

Gram negative

Nonmotile

Non-spore-forming coccobacillus

Main hosts: rodents

Primary transmission route for bubonic plague: fleas

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Literature source

Dose response data

Host: Balb/c mice

Y pestis strain: CO92

Exposure route: Intraperitoneal inoculation

End point: death

Methodology

1. Determination of the best model

Determine deviances and estimate best fit parameters for exponential, beta Poisson and log-probit models using maximum likelihood estimation

Difference in deviances (Δ)

Compared to $\chi^2_{\alpha,1}$

H_o: simpler model is best fit

2. Incorporating the time factor into the best model

Functional form of trend of best fit model parameter with TPI determined via trend analysis

Survival data for all dose groups and TPI used to fit time-dependent dose-response model

$$\hat{\pi}_{i,j} = \frac{F(d_i,t_j) - F(d_i,t_{j-1})}{F(d_i,t_{j-1})}$$

$$Y = -2\ln LR = -2\sum_{j=1}^{m_{\text{times}}}\sum_{i=1}^{m_{\text{doses}}}\left[p_{i,j}\ln\left(\frac{\hat{\pi}_{i,j}}{\overset{\circ}{\pi}_{i,j}}\right) + (n_{i,j}-p_{i,j})\ln\left(\frac{1-\hat{\pi}_{i,j}}{1-\overset{\circ}{\pi}_{i,j}}\right)\right]$$

Conclusions

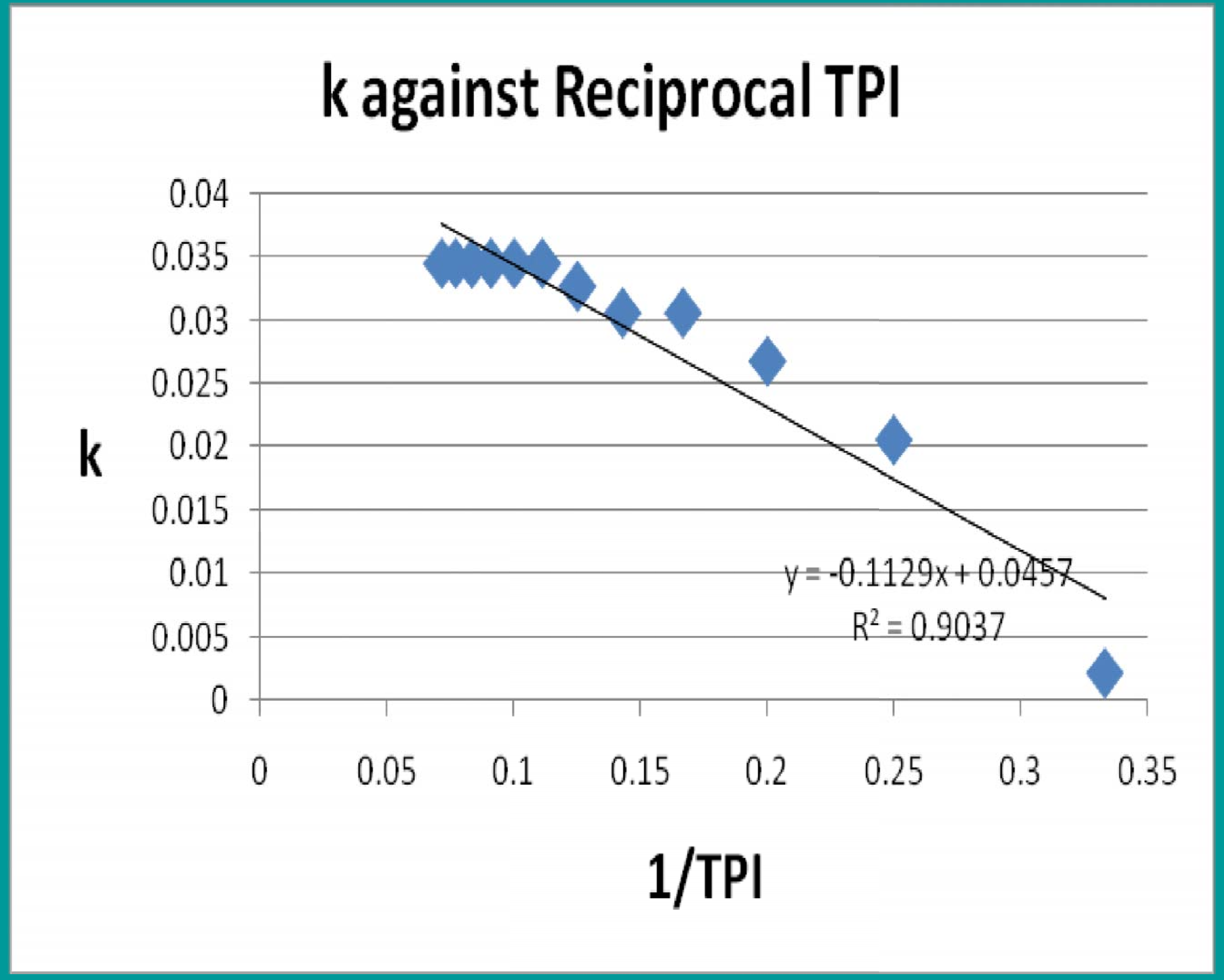
Exponential model with time dependency provides the best fit for pooled data. This is the first study that includes the factor of time post inoculation into the dose response model for *Y. pestis* infection.

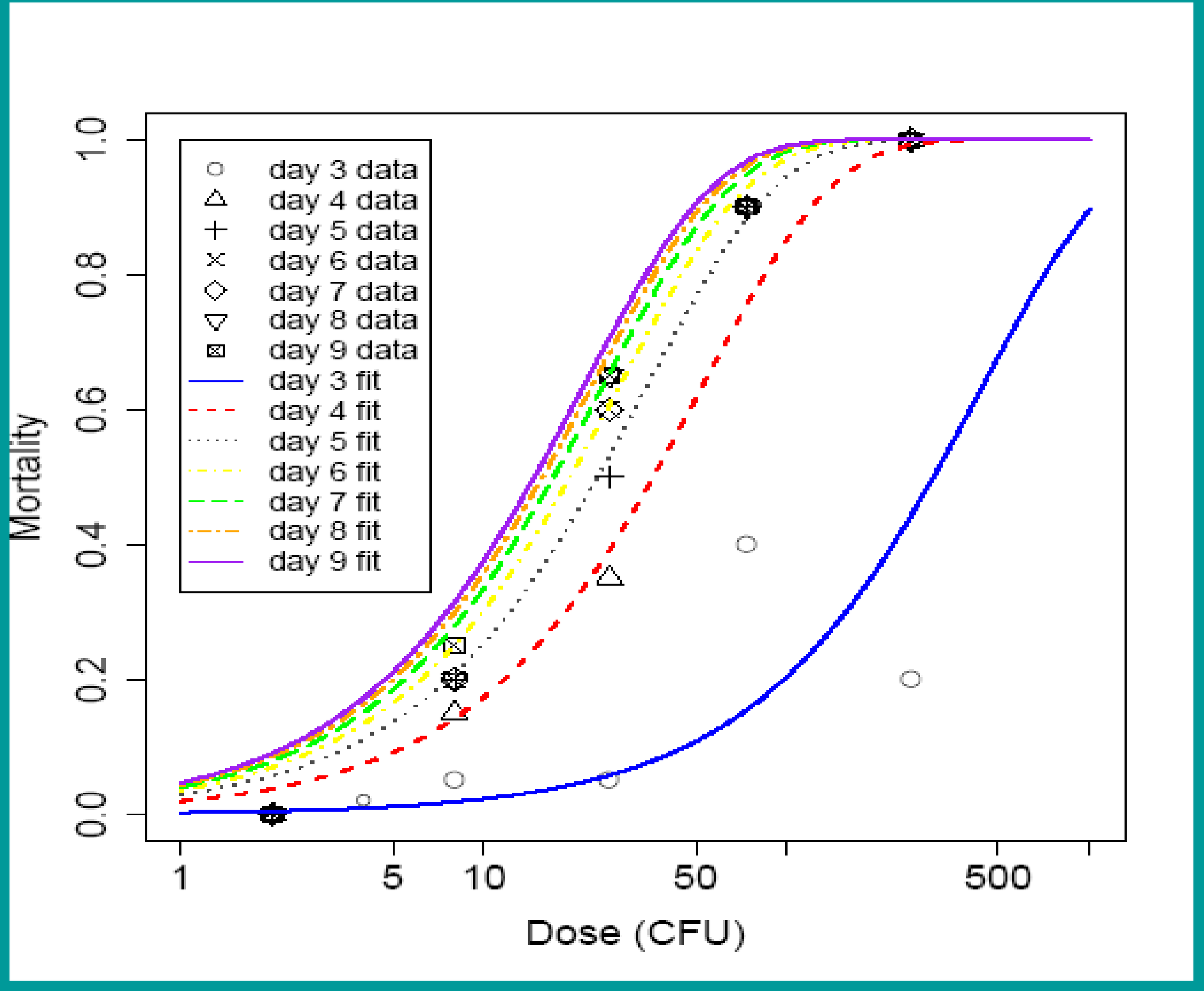
$$P(d) = 1 - e^{-kd} \quad \rightarrow \quad P(d) = 1 - e^{-(-k_0/TPI + k_1)d}$$

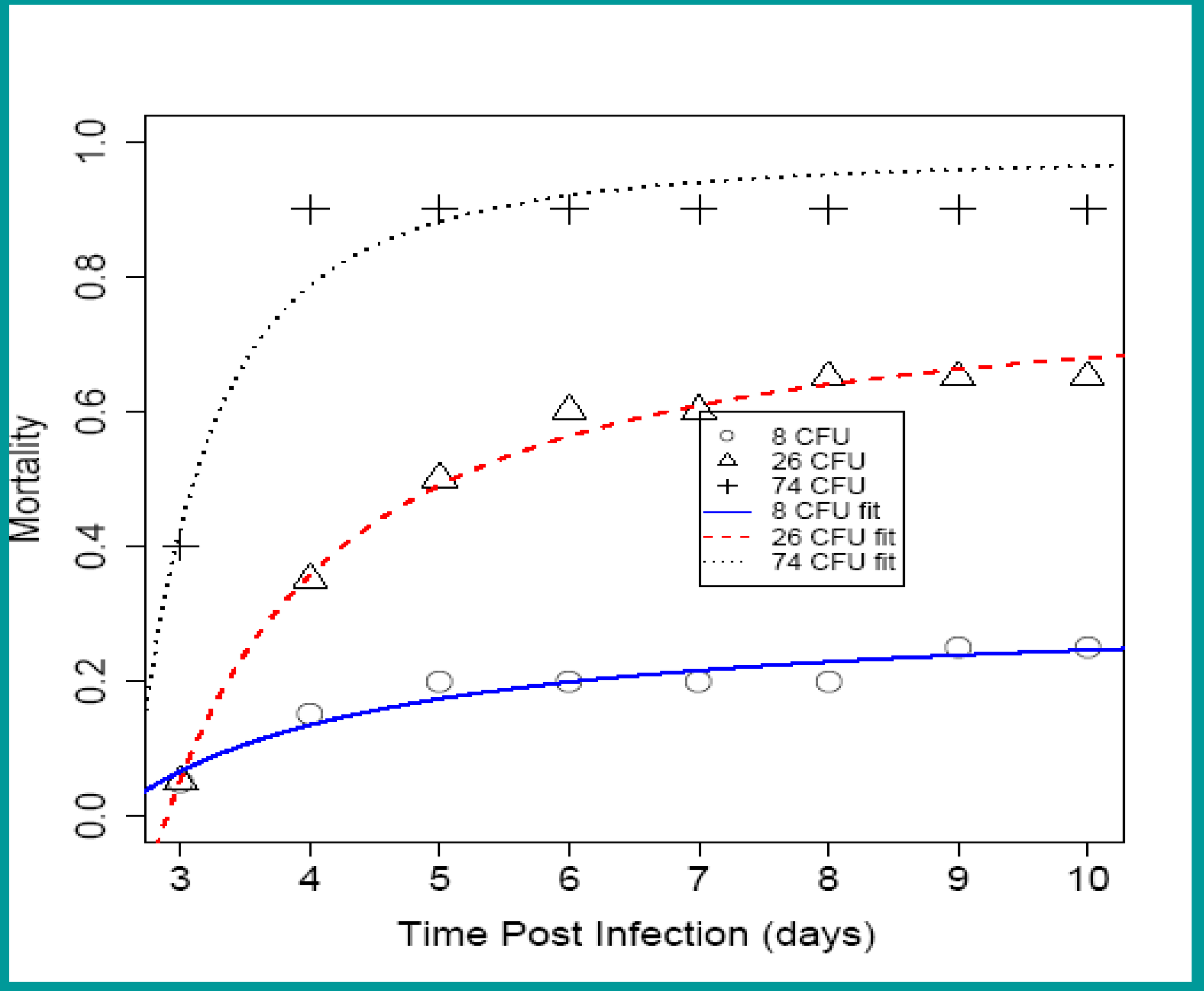
$$P(d) = 1 - \left[1 + \left(\frac{d}{N_{50}}\right)\cdot\left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

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

	GROUP	No. of doses (m)	Model	Parameters	Minimized Deviance (Y)	$\chi^2_{0.95,m-n_{par}}$	Fit?
Exponential with inverse dependency	Pooled 14 days' data	70	Exponential	k_0 = -0.202 k_1 = 0.0696	30.381	89.25	Yes







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