Supplementary material for:

Mechanistic dose-response modeling of animal challenge data shows that intact skin is a crucial barrier to leptospiral infection

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I. Mixture model fits, inoculation of abraded rat skin

When fit to data from inoculation of abraded rat skin, the mixture model did not return a unique maximum likelihood estimate for parameter set (α, β). Instead, a ridge of local maxima were found along the line defined by the ratio, $\frac{\alpha}{\alpha+\beta} = 0.0218$ (Fig. S1). The likelihood increased continuously as the α or β values in pairs satisfying the above ratio approached infinity.

These patterns show the mixture model fitted to rat data is degenerate, and that its maximum likelihood estimate is asymptotically equivalent to the basic model:

Argument 1:

- The ratio $\frac{\alpha}{\alpha+\beta}$ defines the mean of a Beta distribution.
- 0.0218 is exactly equal to the maximum likelihood estimate of p_c from the basic model fit to data from inoculation of abraded skin in rats.

Thus, the line $\frac{\alpha}{\alpha+\beta} = 0.0218$ defines a ridge of maximum likelihood values at which the mixture model's fitted Beta distribution of p_c values has a mean exactly equal to the fixed, maximum likelihood estimate from the basic model.

Argument 2:

Along the line, $\frac{\alpha}{\alpha+\beta} = 0.0218$, the likelihood of the mixture model appears to continue to increase as the values of α or β increase toward infinity (**Fig. S1)**.

- The variance of a Beta distribution is defined by $\frac{n\alpha\beta(\alpha+\beta+n)}{(\alpha+\beta)^2(\alpha+\beta+1)}$.
- $\lim_{\alpha\to\infty} \frac{n\alpha\beta(\alpha+\beta+n)}{(\alpha+\beta)^2(\alpha+\beta+1)} = 0$ and $\lim_{\beta\to\infty} \frac{n\alpha\beta(\alpha+\beta+n)}{(\alpha+\beta)^2(\alpha+\beta+1)} = 0$

Thus, as α or β approach infinity, the variance of the Beta distribution approaches 0. A distribution with zero variance is a Dirac delta function. Thus, the mixture model likelihood is maximized as its distribution of p_c values asymptotically approaches a Dirac delta function, in which all density is concentrated in a spike at the mean value, $\frac{\alpha}{\alpha+\beta} = 0.0218$.

Conclusion:

When fitted to data from inoculation of abraded rat skin, the maximum likelihood mixture model is asymptotically equivalent to the basic model. In both the maximum likelihood mixture model and the maximum likelihood basic model, p_c *(abraded, rat)* takes the fixed value, 0.0218, and shows no random variation at the host level.

As a result, we were not able to report a unique, maximum likelihood estimate for (α, β) from the mixture model fitted to rat data, or corresponding confidence intervals. However, we were able to approximate the best fit using the pair (1114.675, 50000), which falls on the maximum likelihood ridge, and which contains sufficiently large values to approximate the best fit. **Fig. 3E** shows that the mixture model fit obtained using these values is very close to the basic model's fit.

II. Supplementary figures

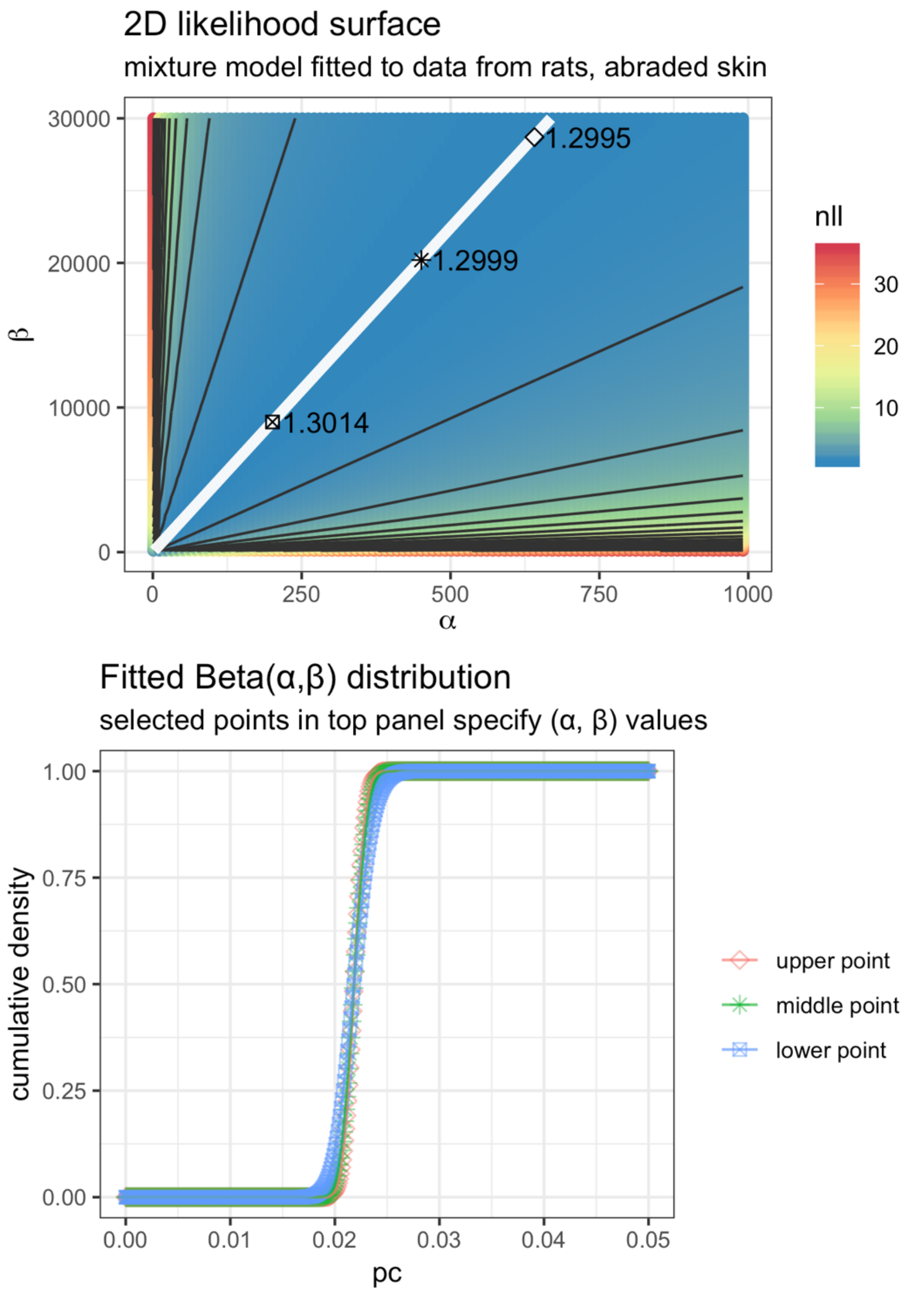

Figure S 1. Two dimensional likelihood profile for the mixture model fitted to rat data, abraded skin (top), and cumulative distribution of the Beta density parametrized by points on the maximum likelihood ridge line (bottom). **Top**: Colors represent negative log likelihood values (lower values correspond to higher likelihood). Dark gray contours are spaced at intervals of one negative log likelihood unit. White line marks the ridge of highest likelihood defined by the line, $\frac{\alpha}{\alpha+\beta} = 0.0218$. Negative log likelihood values are shown at three selected points on the ridge to emphasize that the negative log likelihood decreases slowly as we move upward along the ridge. In other words, the likelihood improves as alpha and beta values increase. **Bottom**: all density in the Beta distributions parametrized by the (α,β) pairs selected from the ridge of maximum likelihood have 100% of probability density at a spike near 0.0218. The spike becomes increasingly steep (variance decreases) as α and β increase.