LETTER

Human ectoparasite transmission of the plague during the Second Pandemic is only weakly supported by proposed mathematical models

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Dean et al. (1) infer that human ectoparasites were the dominant mode of transmission of plague (*Yersinia pestis*) during the Second Pandemic by comparing models representing distinct transmission routes. The authors are to be commended for providing detailed information on their computational approach (2). However, due to inconsistent modeling choices and reliance on strong assumptions, their analysis does not support their main conclusion.

Comparing discrete mechanistic models to infer biological processes is a powerful approach (3), but only for mutually exclusive competing hypotheses. Given that bubonic plague infection can cause secondary pneumonic infection, the possibility of mixed transmission modes cannot be neglected. In particular, the authors' model provides no evidence that human ectoparasite transmission was more likely to have driven the plague patterns than a highly plausible combination of pneumonic and rat-flea transmission.

The authors' conclusion that either pneumonic or rat-flea transmission alone produces worse fits to plague epidemic curves than human ectoparasite transmission models is also based on problematic assumptions. For example, the authors assume that humans (in the pneumonic model) and rat fleas (in the rat-flea model) become infectious immediately upon infection, whereas previous studies suggest incubation periods of 4 and 9–26 d, respectively (4, 5). They also assume that most of their model parameters are known exactly (point priors), which leads to overstated certainty of conclusions (6). The exact values assumed for some ectoparasite-model parameters are particularly hard to justify, given their statement that ectoparasite-to-human plague transmission has never been directly observed. Overall, the authors fail to make a convincing case that rat-flea and pneumonic transmission models fit worse than the human ectoparasite model across all combinations of biologically plausible parameter values.

The authors make several questionable technical assumptions, which generally lead to underestimates of uncertainty—for example, Poisson rather than negative binomial error (7), deterministic dynamics (8), and use of uniform priors (9, 10). While we do not know for certain that relaxing these assumptions will change the outcome of their analysis, the narrow confidence intervals in figure 1 of ref. 1, as well as the unrealistically precise $\mathcal{R}_0$ estimates reported (most with zero-width confidence intervals), strongly suggest that the models fail to capture the true uncertainty in the data. Such overconfidence leads to overly strong discrimination among competing hypotheses, which in turn would mistakenly suggest that we can distinguish the dominant mode of transmission on the basis of epidemic curves alone.

Modeling studies are invaluable probes of underlying biological processes, but they provide only indirect evidence for the true mechanisms and are strongly sensitive to assumptions. While Dean et al. (1) show that human ectoparasites could plausibly have been a vector for plague transmission, their conclusion that ectoparasites were likely to have been important is not adequately supported.

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