

REPLY TO PARK ET AL .:

Human ectoparasite transmission of plague during the Second Pandemic is still plausible

Katharine R. Dean^{a,1}, Fabienne Krauer^a, Lars Walløe^b, Ole Christian Lingjærde^c, Barbara Bramanti^{a,d}, Nils C. Stenseth^{a,1}, and Boris V. Schmid^{a,1}

In their letter, Park et al. (1) raise several concerns and question our conclusion (2) that human ectoparasites could have caused plague epidemics during the Second Pandemic.

First, Park et al. (1) state that our study cannot provide evidence that human ectoparasite transmission was more likely than a mixed pneumonic and rat-flea transmission. We have acknowledged this limitation in our discussion, where we wrote that "we did not model mixed transmission routes, and this makes it difficult to fully assess the contribution of pneumonic plague, which commonly occurs during bubonic outbreaks." They assert that this scenario is "highly plausible." We note that while secondary pneumonic infections are common, primary pneumonic transmission through droplets may only occur under particular environmental conditions such as specific temperature or humidity ranges, poor ventilation, and highdensity housing (3, 4). For two of the epidemics we used, Moscow and Stockholm, detailed contemporary descriptions of symptoms are available; they indicate bubonic plague with only a few sporadic cases of pneumonic disease (5, 6).

Second, Park et al. (1) criticize the omission of an incubation period in both humans and vectors in all three models and the values of point priors in the human ectoparasite model. Plague can be transmitted by fleas in various ways, not all of which warrant an incubation period (7). Our assumption of early-phase transmission (EPT) is based on current literature stating that EPT provides a better explanation for rapidly spreading epidemics than biofilm-dependent transmission (8). For pneumonic plague, the incubation period is extremely short and it is unlikely that including it in our model would change the fitted dynamics

substantially. Furthermore, we demonstrated that the models for pneumonic plague and rat-flea transmission fit well to the outbreaks of known transmission mode during the Third Pandemic, which confirms their individual validity. Point priors used in the human ectoparasite model were largely taken from experimental studies (9, 10). Estimation of all of the parameters in all of the models is problematic due to high parameter correlation, which leads to identifiability problems.

Finally, Park et al. (1) raise an important issue that several technical assumptions such as point priors, uniform priors, and deterministic dynamics may have led to an underestimation of the uncertainty, which could have been better captured using a stochastic model. We agree that the uncertainty in our models could have been larger under different assumptions, which may reduce the possibility of distinguishing between the models based on fit alone. In this situation, we can consider the biological reasonableness of the fitted models. For example, to fit the European mortality curves, the rat-flea model requires a large, highly susceptible rat population and a high transmission rate, which is difficult to justify in Nordic countries (11).

We would like to emphasize that we do not provide evidence against rat-borne plague transmission but explore an alternative explanation of human ectoparasites, which has been suggested by many plague researchers for decades. Our results support our conclusion that human ectoparasites are a plausible and likely vector of plague epidemics during the Second Pandemic. However, we are open to alternative scenarios that could similarly explain the epidemiology of plague in preindustrial Europe under biologically reasonable assumptions.

^aCentre for Ecological and Evolutionary Synthesis, Department of Biosciences, University of Oslo, N-0316 Oslo, Norway; ^bDepartment of Physiology, Institute of Basic Medical Sciences, University of Oslo, N-0317 Oslo, Norway; ^cDepartment of Computer Science, University of Oslo, N-0316 Oslo, Norway; and ^dDepartment of Biomedical and Specialty Surgical Sciences, Faculty of Medicine, Pharmacy and Prevention, University of Ferrara, 35-441221 Ferrara, Italy

Author contributions: K.R.D., F.K., L.W., O.C.L., B.B., N.C.S., and B.V.S. wrote the paper.

The authors declare no conflict of interest.

Published under the PNAS license.

¹To whom correspondence may be addressed. Email: k.r.dean@ibv.uio.no, n.c.stenseth@ibv.uio.no, or boris.schmid@gmail.com. Published online August 3, 2018.

- 1 Park SW, Dushoff J, Earn DJD, Poinar H, Bolker BM (2018) Human ectoparasite transmission of the plague during the Second Pandemic is only weakly supported by proposed mathematical models. *Proc Natl Acad Sci USA* 115:E7892–E7893.
- 2 Dean KR, et al. (2018) Human ectoparasites and the spread of plague in Europe during the Second Pandemic. Proc Natl Acad Sci USA 115:1304–1309.
- 3 Kool JL (2005) Risk of person-to-person transmission of pneumonic plague. Clin Infect Dis 40:1166–1172.
- 4 Boisier P, et al. (2002) Epidemiologic features of four successive annual outbreaks of bubonic plague in Mahajanga, Madagascar. Emerg Infect Dis 8:311–316.

5 de Mertens C, trans Pearson R (1799) An Account of the Plague Which Raged at Moscow in 1771 (printed for F. and C. Rivington, London).

- 6 Broberg JV (1879) Om pesten i Stockholm 1710 (P. A. Norstedt & Söner, Stockholm).
- 7 Bland DM, Jarrett CO, Bosio CF, Hinnebusch BJ (2018) Infectious blood source alters early foregut infection and regurgitative transmission of Yersinia pestis by rodent fleas. *PLoS Pathog* 14:e1006859.
- 8 Eisen RJ, Dennis DT, Gage KL (2015) The role of early-phase transmission in the spread of Yersinia pestis. J Med Entomol 52:1183–1192.
- 9 Houhamdi L, Lepidi H, Drancourt M, Raoult D (2006) Experimental model to evaluate the human body louse as a vector of plague. J Infect Dis 194:1589–1596.
 10 Evans FC, Smith FE (1952) The intrinsic rate of natural increase for the human louse, Pediculus humanus L. Am Nat 86:299–310.
- 11 Hufthammer AK, Walløe L (2013) Rats cannot have been intermediate hosts for Yersinia pestis during medieval plague epidemics in Northern Europe. J Archaeol Sci 40:1752–1759.

SANG SANG