

Reply to Alfani: Reconstructing past plague ecology to understand human history

Nils Chr. Stenseth^{a,b,c,1}, Barbara Bramanti^{b,d}, Ulf Büntgen^{e,f,g,h}, Henry G. Fellⁱ, Samuel Cohn^j, Florent Sebbane^k, Philip Slavin^l, Chutian Zhang^m, Ruifu Yang^{n,1}, and Lei Xu^{o,p,1}

Alfani (1) provides important reflections on our recent work, which argues against long-term wildlife-based plague reservoirs in historical Europe (2). Without natural reservoirs in Europe during the past 2,000 y, the plague bacterium (*Yersinia pestis*) must have repeatedly spilled over from local medium-term reservoirs (3) or was introduced repeatedly from outside Europe by rodents (e.g., rats) and their ectoparasites (e.g., fleas) by infected people or contaminated goods (Fig. 1). While recognized for the Third Pandemic in Europe (4), the hypothesis of several reintroductions of *Y. pestis* into Europe remains under debate for late-antique and medieval outbreaks. Two hypotheses of plague continuity in Europe have been proposed (5): local persistence in reservoirs and external reimportation.

Questioning the importance of rodents and their ectoparasites during past Pandemics in Europe, our study (2) thus contrasts the main factors and processes of plague transmission known from the Third Pandemic in other continents, where wildlife plague reservoirs have been and continue to be essential. Our study also points to the possible importance of human ectoparasites in the interhuman transmission of bacteria (6).

Asking whether long-term wildlife-based plague reservoirs have ever existed in Europe is an important question in the ongoing debate on the processes underlying the spatiotemporal dynamics of human plague over at least the past 2,000 y. To make progress here, a truly interdisciplinary approach is required. In line with Alfani (1), we prioritize two research questions: i) Why plague disappeared from Europe between and after three pandemics, and ii) what role did European rodent and human ectoparasites play in generating the observed patterns of human plague outbreaks across Europe over the past two millennia.

- (i) The end of the Third Pandemic in Europe could theoretically be attributed to a lack of long-term (4, 7) and burnout of medium-term plague reservoirs around 300 y earlier (8). However, it could also have resulted from a combination of natural and societal factors, including improved hygiene standards, together with effective control measures (4, 7). Recently, virulence attenuation of the plague bacterium (5) and the selection of a more robust innate immunity against *Y. pestis* (9) have been suggested as factors contributing to the end of the First and Second Pandemics in Europe (7).
- (ii) The evidence is accumulating for the importance of human-to-human transmission mediated by ectoparasites during plague outbreaks in Europe (6). Though the human flea (*Pulex irritans*) seems not suitable (10), there are other ectoparasites, such as lice, which may have played a critical role. In addition to the examples

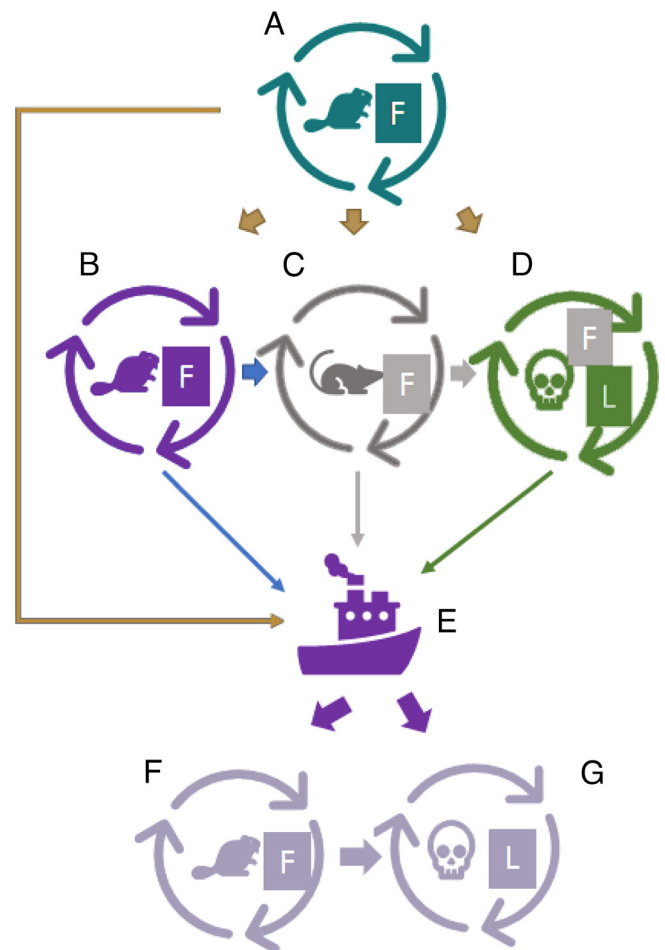


Fig. 1. Simplified schema of plague introduction in new places without long-term reservoirs (*F* and *G* in the figure). *Y. pestis* can cycle between enzootic rodents (*A*), epizootic wild rodents (*B*), epizootic peri-domestic rodents (*C*), or humans and their associated ectoparasites (*D*) [e.g., fleas (*F*) or lice (*L*)]. At any of these stages, *Y. pestis* can be transported to another place (without long-term reservoir) by means of contaminated goods, rodents, people, and/or ectoparasites (*E*). If no reservoir is settled in the new place, plague may circulate among medium-term reservoir (*F*) and/or humans and their ectoparasites (*G*).

raised by Alfani, the 1900 plague outbreak in Glasgow was likely caused by human-to-human transmission (11). However, much research still needs to be carried out on the role of ectoparasites and human plague, for which case studies should be prioritized.

The authors declare no competing interest.

Copyright © 2023 the Author(s). Published by PNAS. This article is distributed under Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND).

¹To whom correspondence may be addressed. Email: n.c.stenseth@ibv.uio.no, ruifyang@gmail.com, or xu_lei@tsinghua.edu.cn.

Published March 6, 2023.

Further reconstructions of the ecology of plague and life cycle of *Y. pestis* in wild and domestic mammals and human populations are needed to understand the course of human history in time and space. The expected insights will also help us be prepared for future pandemics.

ACKNOWLEDGMENTS. As the letter by Alfani only touches upon a subset of the issues covered in our original article, only a subset of the authors of the original paper wrote this response letter. All authors of the original paper have, however, been instrumental in developing our perspectives on the possible existence of persistent natural plague reservoirs in Europe through time.

Author affiliations: ^aCenter for Pandemics and One Health Research, Sustainable Health Unit (SUSTAINIT), Faculty of Medicine, University of Oslo, Oslo 0316, Norway; ^bCentre for Ecological and Evolutionary Synthesis, Department of Biosciences, University of

Oslo, Oslo 0316, Norway; ^cDepartment of Earth System Science, Ministry of Education Key Laboratory for Earth System Modeling, Tsinghua University, Beijing 100084, China; ^dDepartment of Environmental and Prevention Sciences, University of Ferrara, Ferrara 44121, Italy; ^eDepartment of Geography, University of Cambridge, Cambridge CB2 3EN, UK; ^fGlobal Change Research Institute (CzechGlobe), Czech Academy of Sciences, Brno 603 00, Czech Republic; ^gDepartment of Geography, Faculty of Science, Masaryk University, Brno 611 37, Czech Republic; ^hSwiss Federal Research Institute for Forest, Snow and Landscape, Birmensdorf 8903, Switzerland; ⁱSchool of Geography, University of Nottingham, University Park, Nottingham NG7 2RD, UK; ^jDepartment of History, University of Glasgow, Glasgow G12 8QQ, UK; ^kUniv. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur Lille, U1019 – UMR 9017 – Center for Infection and Immunity of Lille, F-59000 Lille, France; ^lDivision of History and Politics, University of Stirling, Stirling FK9 4LJ, UK; ^mCollege of Natural Resources and Environment, Northwest A&F University, Yangling 712100, China; ⁿState Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing 100071, China; ^oVanke School of Public Health, Tsinghua University, Beijing 100084, China; and ^pInstitute of Healthy China, Tsinghua University, Beijing 100084, China

Author contributions: N.C.S. designed research; and N.C.S., B.B., U.B., H.G.F., S.C., F.S., P.S., C.Z., R.Y., and L.X. wrote the paper.

1. G. Alfani, A step forward towards solving the main mysteries in the history of plague? *Proc. Natl. Acad. Sci. U.S.A.* **120**, e2300760119 (2023).
2. N. C. Stenseth *et al.*, No evidence for persistent natural plague reservoirs in historical and modern Europe. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2209816119 (2022).
3. P. Slavin, Out of the west: Formation of a permanent plague reservoir in South-Central Germany (1349–1356) and its Implications. *Past Present* **252**, 3–51 (2021).
4. B. Bramanti, K. R. Dean, L. Walloe, N. C. Stenseth, The third plague pandemic in Europe. *Proc. R. Soc. B Biol. Sci.* **286**, 8 (2019).
5. B. Bramanti, Y. R. Wu, R. F. Yang, Y. J. Cui, N. C. Stenseth, Assessing the origins of the European Plagues following the Black Death: A synthesis of genomic, historical, and ecological information. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2101940118 (2021).
6. K. R. Dean *et al.*, Human ectoparasites and the spread of plague in Europe during the second pandemic. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 1304–1309 (2018).
7. N. C. Stenseth, Katharine R. Dean, B. Bramanti, The end of plague in Europe. *Centaurus* **64**, 61–72 (2022).
8. P. Slavin, Reply: Out of the West – and neither East, nor North, nor South. *Past Present* **256**, 325–360 (2022).
9. J. Klunk *et al.*, Evolution of immune genes is associated with the Black Death. *Nature* **611**, 312–319 (2022).
10. A. Miarinjara, D. M. Bland, J. R. Belthoff, B. J. Hinnebusch, Poor vector competence of the human flea, *Pulex irritans*, to transmit *Yersinia pestis*. *Parasit. Vectors* **14**, 317 (2021).
11. K. R. Dean, F. Krauer, B. V. Schmid, Epidemiology of a bubonic plague outbreak in Glasgow, Scotland in 1900. *R. Soc. Open Sci.* **6**, 181695 (2019).