MOLECULAR BIOLOGY & GENETICS

Was Wuhan the early epicenter of the COVID-19 pandemic?— A critique

Yanan Cao 10, Lingling Chen², Hua Chen 10, Yupeng Cun⁴, Xiaofeng Dai 10, Hongli Du⁶, Feng Gao 10, Fengbiao Guo⁸, Yalong Guo 10, Pei Hao¹⁰, Shunmin He 11, Shunping He¹², XiongLei He 10, Zheng Hu¹⁴, Boon-Peng Hoh¹⁵, Xin Jin¹⁶, Qian Jiang¹⁷, Qinghua Jiang 10, Asifullah Khan¹⁹, Hong-Zhi Kong⁹, Jinchen Li 10, Shuai Cheng Li²¹, Ying Li²², Qiang Lin²³, Jianquan Liu²⁴, Qi Liu²⁵, Jian Lu 10, Xuemei Lu²⁷, Shujin Luo²⁶, Qinghua Nie²⁸, Zilong Qiu²⁹, Tieliu Shi 10, Xiaofeng Song 10, Jianzhong Su 10, Sheng-ce Tao³³, Chaolong Wang 10, Chuan-Chao Wang³⁵, Guo-Dong Wang²⁷, Jiguang Wang 10, Qi Wu³⁷, Shaoyuan Wu³⁸, Shuhua Xu 10, Yu Xue 10, Wenjun Yang⁴¹, Zhaohui Yang⁴², Kai Ye⁴³, Yuan-Nong Ye⁴⁴, Li Yu⁴⁵, Fangqing Zhao 10, Yiqiang Zhao⁴⁷, Weiwei Zhai⁴⁸, Dandan Zhang⁴⁹, Liye Zhang 10, Houfeng Zheng 10, Tianqi Zhu⁵³ and Ya-ping Zhang 10, Liye Zhang 10, Tianqi Zhu⁵³, Tianqi Zhu⁵³ and Ya-ping Zhang 10, Xiaofeng Zhang 11, Xiaofeng Zhang 11

Recently, Worobey et al. (2022) published a report entitled 'The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic' that succinctly summarizes their study [1]. A pre-print version of this study had earlier elicited a series of high-profile media coverages [2,3]. All these reports deliver a social-political message that the Huanan market is the epicenter of COVID-19.

At the outset, we shall clarify the meaning of 'epicenter' in the context of the pandemic. Epicenter, narrowly defined, is the point on the earth's surface directly above an earthquake. Hence, in this context, epicenter should be the place from which the pathogen spread globally to cause the pandemic. By this definition, what Worobey et al. identified is not the epicenter of the global pandemic for the obvious reason that the conclusion is based entirely on SARS-CoV-2 samples collected in Wuhan. Where else could they have pinpointed the epicenter with their samples? Had they used only virus data from the

Antarctica, they would have concluded that some place on that continent is the epicenter. A relevant example is the island province across the Taiwan Strait. Studies that analyzed the virus data entirely from the island have also shown that the Taoyuan International Airport south of the city of Taipei is the 'epicenter'. In short, what Worobey *et al.* (2022) show is that the early epidemic in Wuhan centered around its seafood market, analogous to the Taoyuan Airport 'epicenter' of Taiwan.

In a technical sense, Worobey *et al.*'s title is vague. Did they simply mean that the Huanan Market is the 'epicenter' of the early *local* epidemic in Wuhan? Nevertheless, the juxtaposition of 'epicenter' and 'pandemic' in their title must have meant the global epicenter. Indeed, the global media has read Worobey *et al.* to mean Wuhan, with its seafood market, as the epicenter of the entire pandemic [2–6].

Worobey *et al.* have failed to follow the standard practice of presenting a scientific report in the context of previous publications on the same subject. This is particularly important when the conclusion is diametrically opposed to those of previous publications. Worobey *et al.* should have compared their conclusions with studies that have more extensive geographic data. Furthermore, although the interest is in the early phase of the pandemic, it has been shown that samples from subsequent periods can be informative about the early phase by interpolation. After all, later samples are far more abundant and better organized when human societies became aware of the onset of epidemics.

We have compiled a set of reports on viral samples from wild animals [7–16] which, collectively, are far more global by geography than the report we critique here. Another set of diverse studies provides evidence that SARS-CoV-2 may have been spreading worldwide for weeks or even months prior to the epidemic in Wuhan in December 2019 [17–24]. Such reports have been brushed aside due to a mis-conception on the onset of epidemics.

The misconception is most explicitly stated in a recent news report [25] as follows: 'the idea of a pandemic origin outside China is preposterous to many scientists, because there's simply no way SARS-CoV-2 could have come from some foreign place to Wuhan and triggered an explosive outbreak there without first racing through humans at the site of its origin'. In the absence of an evolutionary perspective, that human and chimpanzee could have a common ancestor would be equally 'preposterous'. Cohen's other points including the integrity of Chinese scientists is not worthy of a response.

Using the branching process to model the evolution of epidemics, Ruan et al. [26,27] and Kucharski et al. [28] have shown that invasions into a new population could trigger local epidemics only sporadically in the early phase. Local epidemics may even reach an alarming level of infections before fading out on its own. In this sense, there may be many earlier local epidemics (or endemics) that rise and fall before the eventual success of global spread from the true epicenter of the pandemic. The many reports of local infections prior to the global pandemic could be such a manifestation [17-24].

Ruan et al.'s [29] title 'The twinbeginnings of COVID-19 in Asia and Europe—one prevails quickly' may be a most explicit analysis of multiple early events. Their analysis has corroborated the earlier sampling results from the Lombardy region of Italy [20,21]. All these studies have concluded that Wuhan is not likely to be the epicenter of the COVID-19 pandemic. Finally, however the critiques and debates in the scientific community may resolve the issue, it is unfortunate that the pre-print version of Worobey et al. has attained unwarranted publicity on a subject of enormous social and political implication. The pre-print platform should be used by the scientific community to speed up exchanges, rather than by investigators to influence the societies at large before being debated among scientists.

Conflict of interest statement. None declared.

Yanan Cao 1, Lingling Chen, Hua Chen 1, Yupeng Cun⁴, Xiaofeng Dai D⁵, Hongli Du⁶, Feng Gao D7, Fengbiao Guo⁸, Yalong Guo D9, Pei Hao¹⁰, Shunmin He 11, Shunping He¹², XionaLei He 13. Zhena Hu¹⁴. Boon-Pena Hoh¹⁵. Xin Jin¹⁶, Qian Jiang¹⁷, Qinghua Jiang D¹⁸, Asifullah Khan¹⁹, Hong-Zhi Kong⁹, Jinchen Li 1020, Shuai Cheng Li21, Ying Li22, Qiang Lin²³, Jianquan Liu²⁴, Qi Liu²⁵. Jian Lu 126, Xuemei Lu27, Shujin Luo26, Qinghua Nie²⁸, Zilong Qiu²⁹, Tieliu Shi 10³⁰, Xiaofeng Song D31, Jianzhong Su D32, Sheng-ce Tao³³, Chaolong Wang D³⁴, Chuan-Chao Wang³⁵, Guo-Dong Wang²⁷, Jiguang Wang 1036, Qi Wu³⁷, Shaoyuan Wu³⁸, Shuhua Xu 1039, Yu Xue 1040, Wenjun Yanq41. Zhaohui Yang⁴², Kai Ye⁴³, Yuan-Nong Ye⁴⁴, Li Yu⁴⁵, Fangging Zhao 1046, Yigiang Zhao⁴⁷, Weiwei Zhai⁴⁸, Dandan Zhang⁴⁹, Liye Zhang 1050, Houfeng Zheng 1051, Qi Zhou 1052, Tiangi Zhu53 and Ya-ping Zhang D27,* ¹Ruijin Hospital, Shanghai Jiao Tong University, China; ²College of Life Science and Technology, Guangxi University, China; ³Beijing Institute of Genomics, Chinese Academy of Sciences, China; ⁴Children's Hospital of Chongging Medical University, China; ⁵Wuxi School of Medicine, Jiangnan University, China; ⁶School of Biology and Biological Engineering, South China University of Technology, China; ⁷Department of Physics, School of Science, Tianjin University, China; 8 School of Pharmaceutical Sciences, Wuhan University, China; ⁹Institute of Botany, Chinese Academy of Sciences, China; 10 Institut Pasteur of Shanghai, Chinese Academy of Sciences, China; 11 Institute of Biophysics, Chinese Academy of Sciences, China; 12 Institute of Hydrobiology, Chinese Academy of Sciences, China; 13 School of Life Sciences, Sun Yat-sen University, China; 14 Institute of Synthetic Biology, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, China; 15 Faculty of Medicine and Health Sciences, University College Sedaya International, Malaysia; 16 School of Medicine, South China University of Technology, China; 17 Department of Medical Genetics, Capital Institute of Pediatrics, China; ¹⁸School of Life Science and Technology, Harbin Institute of Technology, China; 19 Department of Biochemistry, Abdul Wali Khan University, Pakistan; 20 Xiangya Hospital, Central South University, China; ²¹Department of Computer Science, City University

of Hong Kong, China; ²²College of Life Science and Technology, Foshan University, China; ²³South China Sea Institute of Oceanology, Chinese Academy of Sciences, China; ²⁴College of Ecology, Lanzhou University, China: ²⁵School of Life Sciences and Technology, Tongji University, China; ²⁶School of Life Sciences, Peking University, China; 27 Kunming Institute of Zoology, Chinese Academy of Sciences, China; ²⁸College of Animal Science, South China Agricultural University, China; 29 Institute of Neuroscience, Chinese Academy of Sciences, China; 30 School of Life Sciences, East China Normal University, China; 31 Nanjing University of Aeronautics and Astronautics, China; 32 Wenzhou Institute, University of Chinese Academy of Sciences, China; 33 Institute of Systems Biomedicine, Shanghai Jiao Tong University, China; 34 Tongji Medical College, Huazhong University of Science and Technology, China; 35 School of Life Sciences, Xiamen University, China; 36 Division of Life Science and Department of Chemical and Biological Engineering, The Hong Kong University of Science and Technology, China; 37 Institute of Microbiology, Chinese Academy of Sciences, China; 38 School of Life Sciences, Jiangsu Normal University, China; ³⁹School of Life Sciences, Fudan University, China; ⁴⁰College of Life Science and Technology, Huazhong University of Science and Technology, China; ⁴¹International Center for Aging and Cancer, Hainan Medical University, China; 42 Academy of Medical Science, Zhengzhou University, China; 43 Faculty of Electronic and Information Engineering, Xi'an Jiaotong University, China; 44 Bioinformatics and BioMedical Bigdata Mining Laboratory, School of Big Health, Guizhou Medical University, China; 45School of Life Sciences, Yunnan University, China; 46 Beijing Institutes of Life Science, Chinese Academy of Sciences, China; 47 College of Biological Sciences, China Agricultural University, China; 48 Institute of Zoology, Chinese Academy of Sciences, China; ⁴⁹Department of Pathology, and Department of Medical Oncology of the Second Affiliated Hospital, Zhejiang University School of Medicine, China; ⁵⁰School of Life Science and Technology, ShanghaiTech University, China; 51 School of Life Sciences, Westlake University, China; 52Life Sciences Institute, Zhejiang University, China and 53 Academy of Mathematics and Systems Science, Chinese Academy of Sciences, China *Corresponding author. E-mail:

zhangyp@mail.kiz.ac.cn

REFERENCES

1. Worobey M, Levy JI and Serrano LM et al. Science 2022; **377**: 951-9.

- 2. Maxmen A. Nature 2022; 603: 15-6.
- Zimmer C and Mueller B. NY Times 2022; 26. https://www.nytimes.com/interactive/2022/02/26/ science/covid-virus-wuhan-origins.html Advance access publication 25 August 2022
- 4. Cohen J. Science 2022; 375: 946-7.
- Gill V. BBC News 2022. https://www.bbc.com/ news/science-environment-62307383 Advance access publication 25 August 2022
- Mathur N. News-Medical 2022. https://www. news-medical.net/news/20220728/Evidence-thatthe-Huanan-market-in-Wuhan-China-was-theepicenter-of-the-COVID-19-pandemic.aspx Advance access publication 25 August 2022
- 7. Wu Z, Han Y and Wang Y *et al. Natl Sci Rev.* 2023; **10**: nwac213.
- 8. Zhao S, Hou Y and Zhang X *et al. J Genet Genomics* 2022; **49**: 900–2.
- 9. Wu Z, Jin Q and Wu G *et al. Lancet North Am Ed* 2021; **398**: 1299–303.

- Temmam S, Vongphayloth K and Baquero E et al. Nature 2022; 604: 330–6.
- 11. Zhou H, Chen X and Hu T *et al. Curr Biol* 2020; **30**: 2196–203.
- 12. Zhou H, Ji J and Chen X *et al. Cell* 2021; **184**: 4380–91.
- 13. Zhang T, Wu Q and Zhang Z. *Curr Biol* 2020; **30**: 1346–51.
- Lam TT, Jia N and Zhang YW et al. Nature 2020;
 583: 282–5.
- Xiao K, Zhai J and Feng Y et al. Nature 2020; 583: 286–9.
- 16. Peng MS, Li JB and Cai ZF *et al. Zool Res* 2021; **42**: 834–44.
- 17. Montomoli E, Apolone G and Manenti A *et al. Viruses* 2022; **14**: 61.
- 18. Lai A, Tambuzzi S and Bergna A *et al. Front Microbiol* 2022; **13**: 886317.
- Apolone G, Montomoli E and Manenti A *et al. Tumori* 2021; **107**: 446–51.

- 20. Amendola A, Canuti M and Bianchi S *et al. Envi*ron Res 2022: **115**: 113979.
- 21. Amendola A, Bianchi S and Gori M *et al. Emerg Infect Dis* 2021; **27**: 648–50.
- Deslandes A, Berti V and Tandjaoui-Lambotte Y et al. Int J Antimicrob Agents 2020; 55: 106006.
- 23. La Rosa G, Mancini P and Bonanno Ferraro G *et al. Sci Total Environ* 2021; **750**: 141711.
- 24. Canuti M, Bianchi S and Kolbl O *et al. BMJ Glob Health* 2022; **7**: e008386.
- 25. Cohen J. *Science* 2022; **377**: 805–9.
- 26. Ruan Y, Wen H and He X *et al. Sci Bull* 2021; **66**: 1022–9.
- 27. Ruan Y, Luo Z and Tang X *et al. Natl Sci Rev* 2021; **8**: nwaa246.
- 28. Kucharski AJ, Russell TW and Diamond C *et al. Lancet Infect Dis* 2020; **20**: 553–8.
- 29. Ruan Y, Wen H and Hou M *et al. Natl Sci Rev* 2022; **9**: nwab223.