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SARS-COV-2 and biomimetics: What saves the planet will save our health

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Introduction

The underdeveloped opportunity to use the broad awareness of the diversity of animal life and comparative physiology (i.e. biomimetics) as nature´s own road map to provide novel insights and solutions from burden of lifestyle diseases has recently been discussed [1-5]. Since human health, environmental changes and animal welfare are closely related (i.e. the 'one health' or 'planetary health' approach), such studies require close interdisciplinary requires multidiscipline collaboration including medical doctors, veterinarians, zoologists, climate researchers, ecologists, biologists and anthropologists [6]. The ongoing coronavirus 2019 (COVID-19) pandemic is a sobering example of the urgent need for global interdisciplinary collaboration, integrating human and animal health with environmental sustainability and ecosystem health. To begin with, it is worth noting that there is simply nothing uniquely Chinese about the COVID-19 outbreak. The explanations for why so many epidemics seem to arise in China may not only be cultural, but also a matter of its current economic geography paired with the close interface between wildlife, livestock and humans [7]. This is abundantly clear if we compare China to the United States, or Europe, when the latter were hubs of global production and mass industrial employment. The geography of blame, naming a germ after a country or ethnic group, has often been a symbol of helplessness during previous pandemics, detracting from the global aspect and unfairly labelling a country or ethnic group as being solely responsible. Ironically, the 'Spanish flu' pandemic of 1918 likely originated from a farm community in south-western Kansas [8]. Whilst previous pandemics were mainly linked to crises resulting from wars, the COVID-19 pandemic is linked to a crisis based on environmental pollution, exploitation of the natural world, wildlife abuse and subsequent cumulative consequences on human health.

The transformative impacts of the COVID-19 pandemic on human welfare, socio-economic and political structures are enormous. The planet is already experiencing an extraordinary loss of biodiversity (an ongoing sixth mass extinction) linked to human activity: illegal wildlife trade, habitat destruction, pollution, global warming and overconsumption of a sugar-rich high-protein diet, superimposed on population growth [9]. As gut microbiota regulate immune defences against respiratory tract influenza A infection [10], the role of the foodome in the severity of respiratory involvement during COVID-19 infection requires attention. Furthermore, a 'normal' food supply system has developed as factory farming, with massive numbers of livestock and poultry kept at high density, creating an environment ripe for the genesis of new viral diseases [11]. Climate change can impact both vector-borne diseases, and even the evolution and progression of viruses, such as influenza A [12], whilst atmospheric pollution, due to small airborne particles, may also enhance spread of SARS-CoV-2 [13]. Thus, anthropogenic environmental changes are redefining the nature of 21st century pathologies [9], and pandemics, such as COVID-19, may not be an exception in years to come.

It is estimated that in the United States alone, three out of four new infectious diseases have emerged from human–animal contact [14] and zoonoses are responsible for >2 billion cases of human illness and >2 million human deaths each year [15]. Whilst the origin of the SARS-CoV-2 virus is still

not certain, most studies suggest it originated in bats and infected people were exposed via the sale of wild meat at a wet market in Wuhan, China [16]. Indeed, bats are believed to be one of the more common wildlife species that carry zoonotic disease potential for domestic animals and humans. Their special flight physiology, with high body temperatures, may have perfectly adapted viruses [17,18] to survive a febrile status in SARS-CoV-2-infected human patients. Over the last century, human activity has destroyed natural habitats and wildlife to develop more anthropocentric landscapes [7], providing the basis for emerging disease 'hotspots' and the spillover of new viral zoonoses [9]. Exploitation of wildlife through hunting and trade facilitates close contact between wildlife and humans and has increased opportunities for animal–human interactions and facilitated zoonotic disease transmission [19]. In bats stressed by entrapment, habitat destruction, infections and climate change, spillover of the virus to other species is more likely to occur. Indeed, intestines of virus-infected bats that were also co-infected with fungus contained on average 60-fold more coronavirus RNA than bats with virus alone [20]. Since SARS-CoV-2 recently was shown to infect intestinal cells of bats and the virus replicate in human intestinal organoids [21], there is a possibility of transmission to humans by contact with bat faeces, without need for an intermediate vector.

We contend that lessons from nature (biomimetics) provide solutions for understanding, treating and preventing emergent diseases. Biomimetic solutions, generated from insights from the natural world, may provide ingenious natural solutions not only for chronic noncommunicable lifestyle-related diseases [1] but also for zoonotic diseases. It seems likely that the major therapeutic dilemma in severe COVID-19 infection is the combination of an inappropriate inflammatory response (cytokine storm) with reduced innate antiviral defence mechanisms [22]. The increased susceptibility to severe disease observed in the elderly and individuals with burden of lifestyle disease, such as obesity, cardiovascular disease and diabetes, argues for impaired interferon (IFN) antiviral host defence mechanisms.

Although there is a relatively large diversity of zoonotic viruses in bats, viral diseases in bats are mild [18]. Since bats have developed unique mechanisms to control both excessive inflammation and having robust interferon antiviral responses [23], they may provide a biomimetic solution for the COVID-19 pandemic. SARS-CoV-2 infection is characterized by a lack of robust type I/III IFN signatures from infected cell lines [22] and patients with severe COVID-19 demonstrate a profoundly impaired IFN-I response as compared to mild or moderate cases [24]. In COVID-19 infection, ORF3b – one of the viral proteins which is dominantly expressed – is a potent INF antagonist [25]. Coronaviruses are known to have multiple other mechanisms for evasion of the host immune response. Bats share many of the immunological features of other mammals but an understanding of the unique host–viral interaction in bats may help understand the pathogenesis of emerging zoonoses in humans. The long co-evolutionary history of bats and viruses has led to immunological adaptation of bats and the resident viruses allowing for apathogenic infection. Some of these unique immunological differences in bats that have been studied include constitutive expression of INF-signalling molecules, impaired formation of inflammasomes, absence of a number of NK-cell receptors, lack of somatic hypermutation in immunoglobulin heavy chain genes and an altered INF-stimulated gene profile, which is not associated with an acute inflammatory response [26]. The links between 'trained immunity' after live vaccinations, such as Bacillus Calmette–Guérin (BCG), and reduced severity of SARS-CoV-2 infection [27] as well recent positive results in an open-label randomized trial of COVID-19-infected patients with a triple regimen including INF beta-1b [28], support observations made in bats that a robust INF system plays a key role in protection against SARS-CoV-2. Further understanding of evolutionary adaptation of both host and symbiont/pathogen may provide insights into both pathophysiology and potential therapeutic pathways.

The current SARS-CoV-2 pandemic is the best proof of the necessity for recreation of sustainable human and ecosystem health [29], and for an increased protection of wildlife in its natural and undisturbed habitat, away from close human contact. A biomimetic approach would allow us to learn from animals that through evolution have managed to regulate viral persistence, and to develop novel antiviral drugs based on the planet's own botanical medicine cabinet. A biomimetic initiative needs prompt action as loss of species diversity, habitat destruction and pollution will prevent this opportunity to learn from the biochemical wonders of nature.

Conflict of interest

None of the authors have any conflict of interest related to the content of this perspective.

Author Contribution

Peter Stenvinkel: Conceptualization and Writing of review. **Johanna Painer:** Writing-review & editing (supporting). **Paul Shiels:** Writing-review & editing (supporting). **Anip Bansal:** Writing-review & editing (supporting). **Sasan Fereidouni:** Writing-review & editing (supporting). **Barbara Natterson-Horowitz:** Writing-review & editing (supporting). **Rick Johnson:** Writing-review & editing (supporting). **Jaime Miranda:** Conceptualization (supporting); Writing-review & editing (supporting).P

References

1 Stenvinkel P, Painer J, Johnson RJ, Natterson-Horowitz B. Biomimetics - nature's roadmap to insights and solutions for burden of lifestyle diseases. *J Intern Med* 2020; **287:** 238–51.
2 Johnson RJ, Stenvinkel P, Andrews P *et al.* Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts. *J Intern Med* 2020; **287:** 252–62.
3 Fröbert O, Frøbert AM, Kindberg J, Arnemo JM, Overgaard MT. The brown bear as a translational model for sedentary lifestyle-related diseases. *J Intern Med* 2020; **287:** 263–70.
4 O'Toole PW, Shiels PG. The role of the microbiota in sedentary life style disorders and ageing: Lessons from the animal kingdom. *J Intern Med* 2020; **287:** 271–82.
5 Andrews P, Johnson RJ. Evolutionary basis for the human diet: consequences for human health. *J Intern Med* 2020; **287:** 226–37.
6 Stenvinkel P, Painer J, Kuro-O M *et al.* Novel treatment strategies for chronic kidney disease: insights from the animal kingdom. *Nat Rev Nephrol* 2018; **14:** 265–84.
7 Jones KE, Patel NG, Levy MA *et al.* Global trends in emerging infectious diseases. *Nature* 2008; **451:** 990–3.
8 Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. *J Transl Med* 2004; **2:** 3.
9 Ceballos G, Ehrlich PR, Dirzo R. Biological annihilation via the ongoing sixth mass extinction signaled by vertebrate population losses and declines. *Proc Natl Acad Sci U S A* 2017; **114:** E6089–E96.
10 Ichinohe T, Pang IK, Kumamoto Y *et al.* Microbiota regulates immune defense against respiratory tract influenza A virus infection. *Proc Natl Acad Sci U S A* 2011; **108:** 5354–9.
11 Wallace R. *Big Farms Make Big Flu: Dispatches on Infectious Disease, Agribusiness, and the Nature of Science*. New York: NYU Press; 2016.
12 Yan S, Wu G. Possible impact of global warming on the evolution of hemagglutinins from influenza A virus. *Biomed Environ Sci* 2011; **24:** 62–7.
13 Conticini E, Frediani B, Caro D. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy? *Envir Pollut* 2020; **261:** 114465.
14 Pavlin BI, Schloegel LM, Daszak P. Risk of importing zoonotic diseases through wildlife trade, United States. *Emerg Infect Dis* 2009; **15:** 1721–6.
15 Kreuder Johnson C, Hitchens PL, Smiley Evans T *et al.* Spillover and pandemic properties of zoonotic viruses with high host plasticity. *Sci Rep* 2015; **5:** 14830.
16 Rothan HA, Byareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020; **109:** 102433.
17 Plowright RK, Eby P, Hudson PJ *et al.* Ecological dynamics of emerging bat virus spillover. *Proc Biol Sci* 2015; **282:** 20142124.
18 O'Shea TJ, Cryan PM, Cunningham AA *et al.* Bat flight and zoonotic viruses. *Emerg Infect Dis* 2014; **20:** 741–45.
19 Johnson CK, Hitchens PL, Pandit PS *et al.* Global Shifts in mammalian population trends reveal key predictors of virus spillover. *Risk. Proc Biol Sci* 2020; **287:** 20192736.
20 Davy CM, Donaldson ME, Subudhi S *et al.* White-nose syndrome is associated with increased replication of a naturally persisting coronaviruses in Bats. *Sci Rep* 2018; **8:** 15508.
21 Zhou J, Li C, Liu X *et al.* Infection of bat and human intestinal organoids by SARS-CoV-2. *Nat Med* 2020. https://doi.org/10.1038/s41591-020-0912-6.
22 Blanco-Melo D, Nilsson-Payant BE, Liu WC *et al.* Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020; **181:** 1036–45.e9.
23 Subudhi S, Rapin N, Misra V. Immune system modulation and viral persistence in bats: understanding viral spillover. *Viruses* 2019; **11:** E192.
24 Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Pere H*et al.* Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. medRxiv. 2020: 2020.04.19.20068015.
25 Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y*et al.* SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is further increased by a naturally occurring elongation variant. bioRxiv. 2020: 2020.05.11.088179.
26 Baker ML, Schountz T. Mammalia: Chiroptera: Immunology of Bats. In: Cooper EL, ed. *Advances in Comparative Immunology*. Cham: Springer International Publishing, 2018; 839–62.
27 O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nature Rev Immunol* 2020; **20:** 335–7.
28 Hung IF, Lung KC, Tso EY *et al.* Triple combination of interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in the treatment of patients admitted to hospital with COVID-19: An open-label, randomised, Phase 2 Trial. *Lancet Infect Dis* 2020; **395:** 1695–704.
29 Ji W, Wang W, Zhao X, Zai J, Li X. Cross-species transmission of the newly identified coronavirus 2019-nCoV. *J Med Virol* 2020; **92:** 433–40.

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