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Impact of Infectious Disease on Humans and Our Origins

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Abstract: On May 16, 2020, the Center for Academic Research and Training in Anthropogeny organized the symposium "Impact of Infectious Disease on Humans and Our Origins". The symposium aimed to gather experts on infectious diseases in one place and discuss the interrelationship between different pathogens and humans in an evolutionary context. The talks discussed topics including SARS-CoV-2, dengue and Zika, the notion of human-specific diseases, streptococci, microbiome in the human reproductive tract, *Salmonella enterica*, malaria, and human immunological memory.

Key words: human evolution, paleogenetics, immune system, anthropogeny, SARS-CoV-2, dengue, Zika, streptococcus, *Salmonella*, malaria

The symposium, "Impact of Infectious Disease on Humans and Our Origins" was held virtually on May 16, 2020. The symposium was organized by the Center for Academic Research and Training in Anthropogeny (CARTA) of UC San Diego, a virtual organization promoting transdisciplinary research into human origins. The symposium aimed to gather experts on infectious diseases in one place and discuss the interrelationship between different pathogens and humans from an evolutionary context. The gathering was organized as a response to the ongoing COVID-19 pandemic. As of June 1, 2020, the videos from the symposium are available in digital format on CARTA's official website (https://carta.anthropogeny.org). A highly informative glossary for non-experts on infectious diseases is available on the event's page. While all speakers managed to be, in a general way, understandable for non-experts on infectious diseases, readers interested in evolutionary anthropology are especially encouraged to check out the talks by Nissi Varki, Amanda Lewis, and Elizabeth Winzeler.

The symposium was opened by Pascal Gagneux, associate director of CARTA,

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who briefly introduced the concept of anthropogeny and its transdisciplinary character (cf. Gagneux 2021). Gagneux also remarked that eventual paleoepidemics in human evolutionary history would have yielded "surviving populations" and would have, thus, presumably shaped human evolutionary trajectories. In the Q&A section, Susan Kaech similarly noted that such events would have produced founder effects.

Robert Schooley described the new coronavirus SARS-CoV-2 from biological and clinical perspectives, in many regards repeating the information already available to the general public via media. Schooley further gave a historical and epidemiological overview of the previous SARS and MERS outbreaks. Schooley emphasized the role of non-human animals in the transmission of these pathogens to humans, differentiating between (putative) hosts (different bat species) and intermediate species (e.g., the dromedary camel in the case of MERS). The role of bats was particularly highlighted in this context as they can harbor viruses that can infect other mammals and cause diseases in them, and simultaneously remain, at least relatively, unaffected by the virus, partly as they have no bone marrow, and therefore, no B cells. Interestingly, Schooley noted that there exists archaeogenetic evidence that at least three coronavirus species were extant in association with human populations in the last 1,000 years: HCoV-NL63 (~ 500–800 years ago), HCoV-229E (~ 200–300 years ago), and HCoV-OC43 (~ 120 years ago) (Pyrc et al. 2006). Finally, although, Schooley welcomed the search for a COVID-19 vaccine, he found that research on antiviral treatments should receive more attention.

Sujan Shresta described the flaviviruses dengue and Zika from biological and clinical perspectives. These viruses are transmitted to humans by *Aedes* mosquitos. Infections with the viruses lead to dengue fever and Zika fever, respectively. Possible complications include congenital disorders such as congenital Zika syndrome and microcephaly. Crucially, after some 70 years of research, there are no effective treatments or vaccines for these two diseases. The usual antibody vaccine approach is not applicable for the dengue fever as there are four dengue virus serotypes that can infect the host independently of whether the same host was previously infected by another serotype. Indeed, secondary dengue infections are associated with more severe symptoms. Shresta and her team found in their investigations with mouse models that prior infections by the dengue virus provide cross-protection against Zika infections in the short run (Elong Ngono et al. 2017; cf. Mugabe et al. 2021; Pedroso et al. 2019). However, the Zika virus can 'evolve' to become so virulent that the pre-existing dengue immunity no longer affords protection against Zika. Curiously, Shresta noted in the Q&A section that the African genetic variation might be protective against dengue and Zika. Still, not much is known, and, problematically, the true prevalence and incidence of these diseases remain unknown due to the qualities of the health systems in areas affected by the epidemics.

Nissi Varki introduced the concepts of "definite", "probable", and "possible" candidates for human-specific diseases. Most putatively human-specific diseases are limited to infectious diseases. Varki compared causes of death in humans (historically vs. contemporarily) and chimpanzees and further empha-

sized the evolutionary importance of sialic acids in the differences between humans and other primates (and mammals) in the susceptibility to different pathogens. More precisely, several evolutionary changes in 2–6-linked sialic acid expression have occurred since the split from the last common ancestor of humans and the great apes, suggesting evolutionary conservatism of this phenomenon in non-human great apes and relatively sudden major changes in the human lineage (Gagneux et al. 2003). Furthermore, there is evidence that the human-specific loss of CMAH (cytidine monophospho-N-acetylneuraminic acid hydroxylase) is associated with some human-specific infectious diseases, including cholera (Alisson-Silva et al. 2018) and typhoid fever (Deng et al. 2014) (cf. Okerblom et al. 2017a).

Victor Nizet described the Group A streptococcus and Group B streptococcus from biological and clinical perspectives. Although these bacteria have been detected in other animal species (e.g., GAS: wild chimpanzees, GBS: some fish, cows), Nizet noted that non-human animal GBS infections highly differ from those described in humans. Nizet yet again emphasized the role of sialic acids and "molecular mimicry" in human infections by these bacteria. Namely, these bacteria contain sugar molecules resembling sugars found in humans (the so-called mechanism of "wolf in sheep's clothing disguise"), thus increasing bacterial disease potential (cf. Carlin et al. 2009).

Amanda Lewis discussed the microbiome in the human reproductive tract, which has been understudied. Notably, the vaginal microbiome can influence reproductive success, and thus, has the potential to be involved in selective mechanisms. Lewis introduced two general macro-types of the human vaginal microbiome: the *Lactobacillus*-dominant microbiome and the "diverse" microbiome, which often consists of many bacterial types, with *Gardnerella vaginalis* displaying higher proportions compared to other bacteria (cf. Miller et al. 2016). Approximately 30% of women with the latter type also have bacterial vaginosis associated with limited reproductive success due to various mechanisms, including an overgrowth of anaerobic bacteria and a relatively high vaginal pH. Thus, the presence of *G. vaginalis* might be considered disadvantageous compared to the dominant presence of *Lactobacilli*. Interestingly, based on studies of non-human primates (Yildirim et al. 2014) and other empirical arguments, Lewis postulates that the "*Gardnerella*" microbiome type might be the "ancestral state" (cf. Gilbert et al. 2021; Tortelli et al. 2021). E.g., the lactobacilli dominance is not found in other primates, while women with bacterial vaginosis show similar microbiome compositions to healthy baboons and macaques, but the pH-values still tend to be lower in women with bacterial vaginosis compared to non-human primates (Miller et al. 2016). Furthermore, there is evidence that women with bacterial vaginosis display sialic acid depletion from epithelial glycans. On a side note, Lewis discouraged women from using vaginal "hygiene" products, stressing that "the vagina is a self-cleaning oven".

Manuela Raffatellu described *Salmonella enterica* from biological and clinical perspectives. While *S. enterica* comprises over 2,000 serovars that can colonize a variety of hosts, a few of these serovars infect only humans and are categorized as typhoidal *Salmonella*, as they cause the human-specific disease

typhoid fever (cf. Behnsen et al. 2015). Intriguingly, Raffatellu pointed out in the Q&A section that *Salmonella* has been isolated in human remains dated to approx. 6,500 years BP and that there are indications that the human-adapted *Salmonella* emerged with neolithization (Key et al. 2020). Furthermore, Raffatellu noted that *Salmonella* has been isolated in pig remains dated to approx. 4,000 years BP, yet it is suggested that it was, in this case, transmitted from humans to pigs.

Elizabeth Winzeler described malaria from biological and clinical perspectives. Malaria is associated with high mortality in pre-reproductive children. Indeed, it is estimated that approx. 20% of children in the affected areas would have died due to malaria had antimalarial treatments not been discovered, thus, highly influencing the gene pools of these populations. Winzeler added that in some parts of Africa, it is frequently the case that the same individuals experience multiple infections in a given year. It is known that specific genetic variations protect against severe forms of malaria (and therefore, from malaria-caused death), suggesting the role of selective mechanisms in the evolutionary past. The most famous example is the sickle-cell allele. However, Winzeler emphasized that the exact mechanisms underlying this protection against malaria were not well understood and that this was not the only protective phenomenon, adding, e.g., the Duffy blood group antigen to the list. Furthermore, Winzeler discussed whether the evolutionary loss of CMAH in humans provides protection against severe malaria (cf. Rabinovich et al. 2017; Winzeler 2008; Okerblom et al. 2017b).

Susan Kaech described the mechanisms of human immunological memory, a phenomenon in which the immune system recognizes an antigen of a pathogen it has already encountered and successfully eliminated in the past, thereby enabling the system a relatively quick and efficient immune response. Kaech explained the process of the development of memory T cells, which, together with memory B cells, generally comprise the immunological memory. During infection, naïve T cells become effector T cells, indicating they are involved in the immune response during primary infection. Approximately 5% to 10% of effector T cells survive in the system as memory T cells after the infection has passed. Research has further shown that not all effector T cells have the same potential to become memory T cells. While research is limited, studies show that this potential depends on both genetic and environmental factors. Specifically, recent research has related memory T cell long-term survival with Interleukin-7 receptor (IL7R) expression (Kaech et al. 2003; Joshi et al. 2007).

The talks presented at the symposium offered a comprehensive overview of specific infectious diseases and/or infection-related phenomena for attendees interested in anthropogeny. This is incredibly valuable, given that these aspects have been at best understudied in the context of human evolution. Nevertheless, most of the talks were strictly focused on the biomedical aspects of these infection-related phenomena, while their relations to specific anthropological and/or archaeological data were only seldom established. This relative one-sidedness is perhaps somewhat unexpected given that topics merging human evolution and history, and infectiology are not unknown in the

scientific literature: e.g., the presence of herpes simplex virus 1 in the hominin lineage as early as the split from the last common ancestor of humans and chimpanzees (Wertheim et al. 2014), the evolutionary association between humans and gorillas in the context of specific *Pthirus* species (sucking lice; Reed et al. 2007), the introduction of syphilis and other pathogen-caused diseases via Columbian migrations (Harper et al. 2011; Majander et al. 2020), etc. Still, a large amount of the presented data might bear implications for human evolution, highlighting the need for further integration of knowledge between infectologists and human evolution experts and future symposia of this type. In this regard, CARTA's general initiative is to be applauded and encouraged without qualification.

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