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Zoonoses and their traces in ancient genomes – a possible indicator for ancient life-style changes?

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ABSTRACT

Humans are constantly exposed to health risks inherent to the environment in which they live, thereby including non-human fauna. Zoonoses are infectious diseases caused by agents such as bacteria, parasites, or viruses being transmitted to humans from wild animals and livestock. The close proximity of animals and humans facilitate the spread of zoonoses, so it is intriguing to hypothesize that populations accustomed to different lifestyles will also vary in the prevalence of zoonotic agents. The Neolithic era in human history is characterised by a dramatic transition in lifestyle, from hunting and gathering to farming. Thus, with the changes in the reservoir of animal species humans were exposed to zoonotic agents potentially penetrating human populations. Due to the rapid development of sequencing technologies and methodology in ancient DNA research, it is now possible to generate complete genomes of ancient specimens and pinpoint those genomic regions or epigenetic signatures that might be influenced by past zoonotic transmissions. Unravelling such traces, particularly on a population-scale, will help to overcome the lack of generalisation that hampered previous research focusing exclusively on the model fossils in human evolution, and facilitate a better understanding of the aetiology of diseases, including those caused by zoonotic agents.

Humans are constantly exposed to health risks inherent to their environment or facilitated by direct interactions with members of our species or other organisms. Zoonoses are infectious diseases that pose a severe risk to health and while being manifested in human populations, they have their origin in non-human fauna [1]. Bacteria, parasites, viruses or other agents are transmitted to humans from wild animals and livestock, thereby causing serious illnesses like Ebola and SARS [2, 3]. Zoonoses are tightly linked to human-animal interactions and contemporary exposure can directly be assessed via stool or blood screens, and whenever a genetic marker

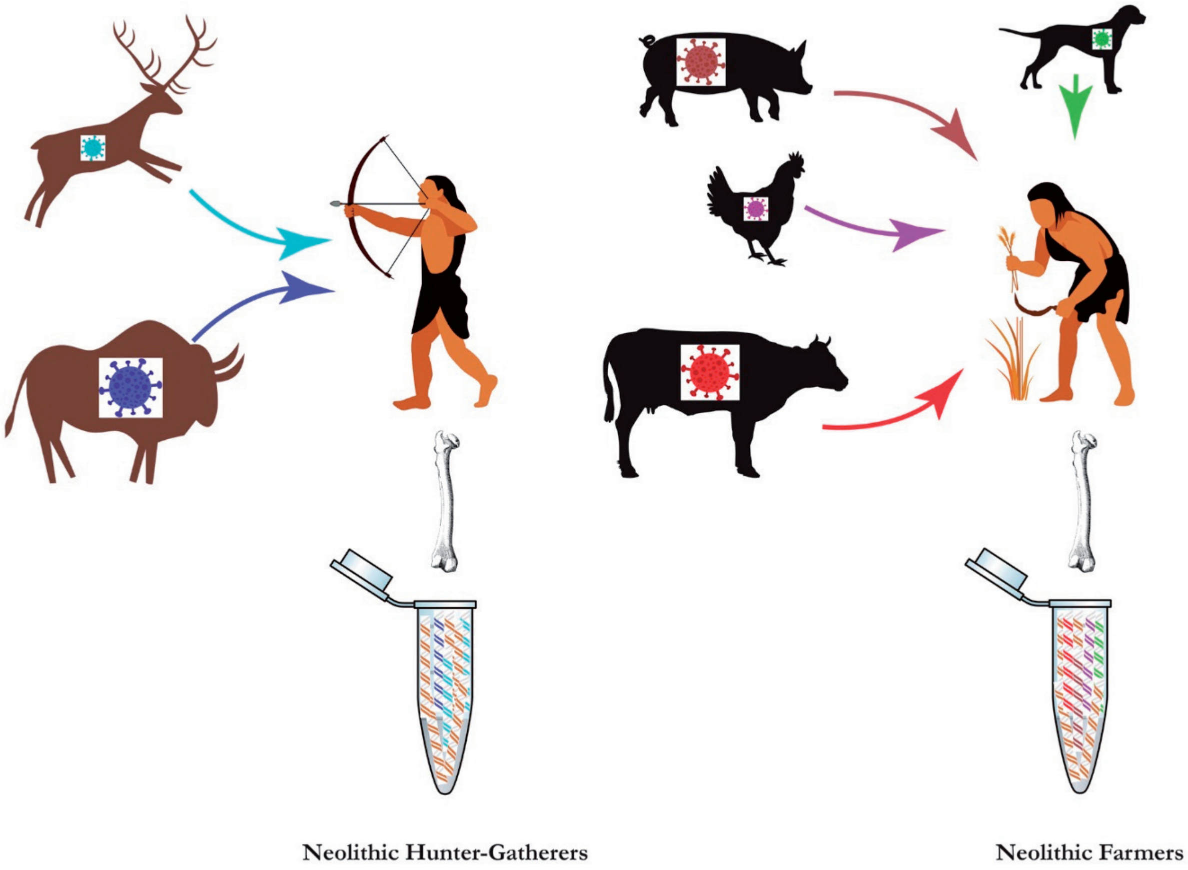

Figure 1. Graphical depiction of the hypothesis of population differences in zoonoses exposure and detection in Neolithic humans

of the agent becomes available, it can be traced through space and time. A classical example is the emergence and trajectory of various Ebola outbreaks [4], however, while Ebola is most likely associated with recent exposure to the virus, other zoonotic agents entered human populations a long time ago.

It is now intriguing to speculate that various human lifestyles or the transition between them might have facilitated the emergence of zoonoses. One such crucial periods in human history was the Neolithic, in which the shift from hunting-gathering to farming occurred. During this era, the agricultural revolution sustainably altered our diet and how communities were organised, thereby allowing cultures to thrive. Most importantly, humans started to interact with animals that ultimately became our domesticates (5). Archaeological evidence and simulation data support the idea of increased zoonotic prevalence due to lifestyle transitions [6, 7], however, to explicitly test this hypothesis and evaluate the zoonotic burden of our Neolithic ancestors, we must exploit their respective ancient genomes. First attempts to detect disease agents in ancient genomes have provided encouraging results, suggesting an onset of tuberculosis and plaque as early as 5000 years ago or identifying the trajectory of HBV transmission and its origin 100,000 years ago [8, 9]. We believe that incorporating population-wide genomic data generated from actual Neolithic human samples would greatly expand current knowledge with respect to zoonoses, possibly providing new evidence regarding the health implications of the Neolithic Revolution. Herein, we discuss the prospects of novel Paleogenomic and Paleoepigenomic approaches in light of the evolution of zoonoses [10].

One major hurdle that needs to be addressed relates to the characteristics of ancient DNA, namely its fragmentation, various damage patterns and low endogenous DNA content [11]. Recent developments in sequencing technologies [12] have enabled us to not only account for these patterns but also to make use of them. It has long been accepted that ancient DNA extracts are a mixture of endogenous DNA, environmental, microbiological and modern contaminants [13]. Generating billions of DNA snippets facilitates the investigation of the origin of literally every single DNA fragment obtained from an ancient sample. The prospects are unlimited, and the recent drop in per-base sequencing costs render the 1,000 $ genome rather science than fiction. The length of the molecules sequenced from ancient materials can be indicative of the age of the specimen with shorter fragments representing older material [14], which further helps to differentiate endogenous from contaminant DNA. A comparison of these fragments with genetic databases allows a taxonomic classification of those not mapping to the respective reference genome (i.e. the human genome). Intriguingly, this approach might readily uncover disease agents the specimen was exposed to in the past [15, 16]. However, the quality of the genome is further determined by its coverage, a measure of how often a single nucleotide has been sequenced from a sample. This is crucial, as the higher the coverage in a particular genomic region, the better the chances of identifying rare variants, including those with health relevance (e.g. encoding viral/pathogen interacting proteins [17]). Despite a qualitative difference in the genes affected by such variances, we would further predict a difference in frequencies observed in populations differentially exposed to zoonotic agents. Alternatively, by screening the endogenous genome, we could detect genetic material potentially incorporated from actual zoonotic agents. Parasites infecting livestock and wild animals can act as media species for horizontal gene transfer [18-20], an often underappreciated but widespread phenomenon [20]. If so, we can hypothesise that two populations accustomed to different diets and ways in which they interact with animals will differ in terms of parasitic infections and horizontally transferred DNA fragments. The methodical approach has been established on modern genomes [18] and its application for ancient DNA should pose no major obstacles. Despite the merits of investigating endogenous DNA, assessing the metagenomic composition of, for instance, dental plaque will further help to not only highlight dietary components but also to evaluate the oral fauna, thereby assess host-pathogen interactions and provide a direct health indicator from the past [21].

A highly covered, high-quality ancient genome is the basis of Paleoepigenomic analyses [12, 22]. It has been suggested that populations with low genetic variation might exhibit higher epigenetic variation leading to the hypothesis that epigenetic mechanisms might act as a fast compensatory mechanism for the adaptation to novel environments [23, 24]. If these patterns are now translated into the Neolithic, it is tempting to speculate that changes in the methylation landscape, the only means to detect epigenetic changes in the past [12], and in particular, those affecting immunological responses might have been triggered by a decreased vicinity and a prolonged exposure to livestock in novel farming communities. Prior to the emergence of next-generation sequencing technologies [25], we simply lacked the means to address Paleoepigenomics questions, but high-quality ancient genomes have now produced intriguing results alluding to epigenetic changes in our archaic human ancestors. Gokhman and colleagues provided a first ancient methylation map [22] and were able to identify thousands of differentially methylated sites in the genomes of Denisovan, Neanderthals and modern humans, and by using these maps they proposed a detailed morphological profile of Denisovans [26].

As these studies solely focused on the charismatic models in human evolution, they can merely present an individual assessment, thereby lack generalisation. Consequently, the investigation of population-wide patterns of genomic variation prevalent in the past will help to circumvent such singularity and address patterns of broader relevance for the emergence and prevalence of zoonotic agents during the lifestyle transition in the Neolithic. Such elaborate investigations will not only elevate ancient DNA research to a next level but also allow the evaluation of the effects of lifestyle changes in the past on the aetiology of modern diseases, and our knowledge of the variety and severity of zoonotic agents.

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Conflict of interest statement
The authors declare no conflict of interest.

Author contribution
All authors have discussed the ideas and contributed to the manuscript.

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