COMMENTARY

A real-time competition between humans and SARS-CoV-2*

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Antagonistic interactions among species are an important facet of population ecology and evolutionary biology. Competitive interactions among host and parasite, predator and prey, and plant and pathogen seem like an 'arms race' between competitors, wherein one is trying to overtake the other with new gameplans and counteradaptations. We have witnessed one such competitive interaction between humans and SARS-CoV-2. Perhaps for the first time, with a wealth of openly available data on a global scale, an evolutionary process is being followed in real-time. The available data on the COVID-19 pandemic constitute an excellent material for analysis from an evolutionary perspective, and may provide real-time evidence for a number of theories and concepts. An evolutionary approach to the pandemic may help us understand the strategies of the pathogen, i.e. the virus, and of the host, i.e. humans. The race between pathogens and their hosts is a major evolutionary driver, where both reshuffle their genomes to overcome and reorganize the defences for infection respectively[1]. However, during the competition between humans and SARS-CoV-2, two contrasting strategies are witnessed. The armoury of the virus reflects the strategy of competing and evolving in an evolutionary mode with mutations and recombinations along with consequent changes in its traits. The human host is responding with natural and vaccine-induced immune response, societal measures taken to prevent infection and spread, the rapid development of drugs and vaccines, and other actions mediated by technology with international collaboration to deal with the pandemic, which are not host genomic responses. Overall, this asymmetric interspecies competition epitomizes the very essence of competition and struggle, as enunciated in Darwin's theory of evolution by natural selection.

*Based on the INSA Sunder Lal Hora Medal Lecture delivered at Azim Premji University, Bengaluru, on 8 April 2022. I dedicate this note to the memory of my Teachers Prof. M. R. Rajasekarasetty and Prof. L. Siddaveere Gowda, who introduced me to the field of evolutionary biology.

Information available on the COVID-19 pandemic in the public domain is the source of this note.

Particularly during this pandemic, to start with, the most important breakthrough was the quick identification of the causative agent, namely SARS-CoV-2. This was followed by a detailed understanding of its structure and the steps involved in infection and follow-up processes, i.e. replication of the virus and spread of infection. The interaction between humans and the virus commences with the virus docking on the human host cell. This is followed by the cleavage of the spike protein envelope of the virus by host cell proteases, one of which is the enzyme furin. SARS-CoV-2 seems to have a unique and more efficiently cleavable furin site compared to other coronaviruses. From an evolutionary point of view, this difference in the furin cleavage site among related coronavirus species raised the question of the origin of SARS-CoV-2. Two possibilities, namely the evolution of the genome of SARS-CoV-2 via natural genetic processes and genetic manipulation, are being discussed[2]. As it stands, the question of the origin of SARS-CoV-2 is still unresolved.

The entire human host response revolves around overcoming infection and dealing with the harmful effects of SARS-CoV-2. It may be mentioned that the human response is 'non-random', meaning it is target-oriented. The invader, the virus, 'responds' via the random processes of genetic mutation and recombination, seemingly to explore ways not only to overcome the immune response of the host, but also to pose new challenges to the host.

In case of the COVID-19 pandemic, evolution of the virus can be witnessed in terms of its changing antigenic traits. During the first wave of COVID-19 infection, since the host had not previously been exposed to the virus, natural immunity against it was weak or absent; also, vaccines were not yet available. Therefore, there was no need for the virus to have an antigenic escape 'trait'. Hence, it may be inferred that, during this period, natural selection for antigenic escape mutations was weak. On the other hand, during the second and subsequent waves of the pandemic, a fraction of the human population had natural as well as vaccine-induced immunity. In this changed situation, variants of SARS-CoV-2, which can escape the immune response of the host and replicate within the host, have better fitness and are preferred by selection over others. The virus with this altered fitness prevails till the host develops the ability to recognize new features of SARS-CoV-2 and neutralizes it. Again, the gene pool of the virus may acquire new variations (mutations) that confer the ability to overcome immunological response of the host. The oscillations in virus infection and host response (resistance/neutralization), that is, the evolution of fitness, is what we have seen during this pandemic.

Evolutionary ecology is the study of the evolutionary histories of species and the interactions among them. An important domain of evolutionary ecology is the life-history traits of players involved in the competition. Life-history theory explains general features of a life cycle, i.e. how fast an organism grows, at what age it matures, how long it lives and how often it reproduces. For a virus, changing life-history traits that affect its ability to infect its host contribute to its evolution. With reference to SARS-CoV-2, the relevant life-history traits are the appearance and spread of genotypes that cause different disease characteristics, such as transmission rates, asymptomatic infections, disease progression and disease virulence. These features, individually or in combination, may influence the overall fitness of the virus on which natural selection acts and thus decide the fate of the variants.

Gene mutation is one of the important means of generating genetic variability, which provides the raw material for evolution. Viruses constantly change through mutation. A 'variant' has one or more mutations that differentiate it from other variants in circulation. During this pandemic, globally, multiple variants of SARS-CoV-2 have been identified, and on the basis of their genomic differences, different lineages of SARS-CoV-2 variants have been recognized.

The evolution of SARS-CoV-2 is driven by mutation. The SARS-CoV-2 Interagency Group (SIG) used a SARS-CoV-2 mutation tracker and Monte Carlo simulations to estimate the number of mutations per infected human. For instance, it has been estimated that more than 820 million people had been infected by 5 October 2021, producing up to 10^{21} copies of the virus, with 12 new effective receptor binding domain (RBD)

variants appearing, on average, daily[1]. Doubling the number of RBD variants every 89 days, followed by the selection of the most infective variants, challenges our defences and calls for a shift to an anticipatory approach. This reflects the immense potential of the armoury of SARS-CoV-2. As long as the virus survives and replicates within the host, more mutations can occur, which may change or influence antigenic features as well as the life-history traits of the virus. Such an evolutionary diversification of the virus has occurred during this pandemic.

On the basis of palaeontological and other historical evidences during the evolution of different lineages of animals and plants, Darwin defined evolution as 'descent with modification'. Different forms have descended with modifications of certain recognizable features of the ancestral forms. At that time, the evolutionary mechanisms underlying this process were not understood. Subsequently, with progress in the knowledge of genetics and allied subjects, the likely mechanisms influencing Darwinian evolution were uncovered. Such an evolutionary process is being witnessed in real-time in the populations of SARS-CoV-2. This virus was first detected in Wuhan city, China, in 2019 ('wu', strain). Since then, the virus has spread across the globe, and COVID-19 has acquired the status of a pandemic. During this spread, the virus has undergone many mutations which make the new virus populations different from the 'wu' strain not only in genomic sequence, but also in disease characteristics. These new populations are referred to as variants. The World Health Organization, Geneva, is coordinating the collection and curation of a wealth of information emerging globally and is naming these variants with advisories to address the challenges of the evolving pandemic. By taking cognizance of their differences, the variants have been classified and their phylogenetic relationships in real-time have been understood.

Rapid genome sequencing technology has enabled the identification of many variants[1,3]. The lineages of SARS-CoV-2 variants are now recognized and named. They are alpha, beta, gamma, delta, epsilon, eta, iota, kappa, mu, zeta and omicron. Some of the key properties of the variants which have been considered for comparisons are genome sequence, transmissibility, response to treatments and earlier generated antibodies in infected people, receptor binding, the efficacy of detection and diagnostic tools, and disease severity. For instance, the new omicron sub-lineages discovered by South African scientists are likely able to evade protection provided by vaccines and natural immunity acquired after earlier infections. The variants contributing to the diversity of SARS-CoV-2 did not appear simultaneously. Studies have revealed that, during this pandemic, the new variants (descendants) appeared one after another, with modifications in genomic sequence and also in one or more of a set of diagnostic features compared to the forms from which they arose (ancestors). The Darwinian concept of 'descent with modification' is evidenced in the 'evolution of SARS-CoV-2 in real time'.

Recombination is another genetic mechanism which is capable of generating new variants by mixing parts of genomes of different strains. In addition to mutation, recombination between variants also adds to the rapid diversification and evolution of SARS-CoV-2. This is facilitated by co-infection of an individual or cell by different variants. Horizontal transfer of genes occurs by exchange of genomic segments resulting in recombination, also called 'reassortment', between genomes of two different variants. For instance, to start with, three recombinant lineages of omicron have been reported: (i) XD, (ii) XF and (iii) XE. A recent article indicates that so far, 21 recombinant strains have been recorded in the database[4]. Since these recombinants have features of two different ancestral variants, they are referred to as 'super mutants' and are also called 'stealth variants' because it is harder to track them.

The frequencies of these variants of SARS-CoV-2 in different populations reflect yet another facet of evolution, like competition, fitness and selection. Variants that replicate better and those that can evade or overcome some of the immune response of the host enjoy better fitness, and natural selection favours such variants. For instance, the variants B.1.1.7, B.1.351 and P.1, which appear to be more infectious than the original strain, have persisted in the population. Another example is the delta variant, which has higher infection potential and shorter serial transfer time, and has virtually replaced the original Wuhan strain. Some variants, such as B.1.1.7 (alpha), which were in low frequency, might have escaped the scrutiny of natural selection and increased in frequency in populations. This is a case of rare genotype advantage as well as frequency-dependent selection. During the COVID-19 pandemic, inter-variant competition between earlier and new variants and differential dominance of variants have been routinely recorded.

Evolutionary epidemiology deals with the incidence, distribution and control of diseases in human populations. Evolutionary epidemiologists seek to explain the factors that contribute to the evolution of pathogens and virulence. Some of the epidemiological factors are incidences of new infections, patient responses and outcomes such as susceptibility of different individuals, asymptomatic and symptomatic infections, different levels of disease severity in different age groups, immune response, recovery and mortality and the extent of virulence, transmissibility and incubation period of the virus. The COVID-19 pandemic with robust information on these aspects, has enriched the discipline of epidemiology. Also, epidemiology is expanding, with the involvement of researchers from other fields such as physics, mathematics, computer science and network science, who have contributed their ideas and expertise[5].

The incidence of infections at the population level during this pandemic presents an interesting picture. Globally, in different geographic regions, periodically, a wave-like pattern with rising and declining trends of infections has been recorded. The epidemiological factors influencing the wavy pattern, particularly during the lull period, are new virus mutations that result in altered life-history traits, varying virus transmission rates, waning immunity of the host, sub-group isolation, relaxed human behaviour and others.

The response from the human species during the pandemic was the imposition of 'COVID disciplines', followed by extensive genetic and antibody/antigen testing, disease and genomic surveillance, etc. The remarkable success, within 16 months, was the development and deployment of vaccines, which is a triumph of science. As the virus has evolved and variants have emerged, it is also becoming clear that there will be differential efficacy of the first versions of the vaccines against some new variants. This reflects a facet of the 'arms race' between the virus and humans.

The SARS-CoV-2 virus, endowed with a short life cycle, reproduces within the host multiple times and aided by mutation and recombination, is rapidly evolving, posing new challenges. This cannot happen with humans. The pandemic challenge promoted international collaboration, facilitating the sharing of huge amounts of information on different facets of pandemic biology

and also exceptionally large genomic data. The outcome of this analysis by supercomputers may facilitate modelling to predict and anticipate future possible evolutionary pathways for SARS-CoV-2. Big-data analysis and simulations of the possible new variants may allow emergence of new ammunition such as universal consensus vaccines or new cocktails of vaccines. Such armament may accelerate the development of 'population immunity' against SARS-CoV-2. The UK Government's Scientific Advisory Group for Emergencies, which explored the scenarios for the long-term evolution of the virus, has predicted 'antigenic drift' and 'antigenic shift' of the virus, and a realistic possibility of 'reverse zoonosis'. In view of these, as expressed in the Red Queen hypothesis, we need to run faster to keep pace with the virus, and even faster if we have to overcome it.

The SARS-CoV-2 virus is alive because it has a host. Within the host, it not only survives but also evolves. During December 2022, there was a surge in the COVID-19 pandemic in China due to the evolution of a new Variant of SARS-CoV-2. The new variant's ancestor is Omicron and this sub-lineage is called BF.7, also known as BA.5.2.1.7. The new Omicron sub-variant is more infectious than previous variants and possesses more immune escape capacity than earlier variants. It is a better competitor than its ancestors. It reflects the Darwinian definition of 'descent with modification' and the evolution of fitness in real-time. The BF.7 has been detected in several other countries around the world including India, the US, the UK and several European countries such as Belgium, Germany, France and Denmark. The SARS-CoV-2 virus journey continues, with new characteristics of the virus facilitated by mutation and recombination. What will be the outcome of this competition? It looks like a nip-and-tuck battle between the competitors. COVID-19 could become a seasonal problem like influenza or mild and endemic like the common cold and coexist with us.

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