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Viewpoint

A focus on the spread of the delta variant of SARS-CoV-2 in India

It has been a little over one year, since SARS-CoV-2 appeared in the human population through a probable zoonotic origin. However, despite the discovery of animal coronaviruses related to SARS-CoV-2, the evolutionary origins of this virus are elusive[1]. There has been a debate about the origin of SARS-CoV-2, with scrutiny and investigations[2]. Though the World Health Organization (WHO) has set up a panel of scientists to investigate the virus origin and the initial response to the COVID-19, no significant results have emerged yet[3]. It is important to define and elaborate protocols of action[4], especially in emerging and/or developing countries. Thoughtful assistance will be needed to deal with health crisis of the same magnitude that could also recur in the future, in the light of the fact that the virus family of SARS-CoV-2 is composed of numerous members capable of infecting different species and jumping from one to another[5].

During the ongoing pandemic, the appearance of variants as a natural result of the evolutive process of the virus raised public concern. SARS-CoV-2, as well as other RNA viruses, have a high mutation rate ($\sim 0.8\times10^{-4}$ expected substitutions per site per year), despite having proofreading activity during viral replication[6,7]. While some mutations are deleterious for viral replication or infection, others are positively selected to persist in the population: these may result in higher transmissibility, infectivity or empowered virulence that correlate with rising rate of the disease severity[8].

Over one million SARS-CoV-2 genomic sequences, heterogeneously distributed in different geographic areas, have been filed in GISAID (Global Initiative on Sharing all Influenza Data)[9]. The predominant form of SARS-CoV-2 is the D614G variant in the spike (S) protein[10]. Several mutations within the receptor-binding domain (RBD) of the S protein have been independently selected (N501Y, N501T and N501S)[11]. The variant N501Y, B.1.1.7 (known as Alpha variant, as per the latest WHO nomenclature of SARS-CoV-2 variants)[12], is rapidly spreading. Mutations affecting this residue, which plays a major role in the angiotensin-converting enzyme 2 (ACE2) binding and antibody recognition, are associated with enhanced transmission and infectivity[4]. Similar variants include B.1.351 (known as Beta variant), B.1.525 (Eta variant), MB61[13], P.1 (Gamma variant), B.1.429 (Epsilon variant) and B.1.617[14]. A highly infectious variant, B.1.617.2, also known as Delta variant, has been found to represent the primary cause behind the second COVID-19 wave in India. The sub-lineage B.1.617.1 is identified as the Kappa variant[15-17].

Viruses mutate, it is in their nature, but this should only concern us if the variants lead to infection of individuals who have already had COVID-19 (as it seems for the Gamma and Beta variants) or coronavirus variants which could evade immune responses triggered by the vaccines and previous infections[18]. These two possibilities must always be confirmed by accurate laboratory and epidemiological data. We need to be alert and monitor the appearance and distribution of variants. The available vaccines have been developed against the current prevalent viral variants and respond well in neutralizing these variants, with some differences such as for the Beta variants for the Vaxzevria vaccine (ChAdOx1 nCoV-19)[19].

The appearance of the Delta variant is of great concern[14]. This variant has 13 different mutations, seven of which are in the S protein. The Delta variant has been shown to be very infectious (50% more contagious than Alpha) and able to 'escape' some neutralizing antibodies[20]. On the other hand,

initial data show that this variant appears to respond to currently available vaccines and is sensitive to antibodies generated by cured individuals[21]. This suggests that an aggressive vaccination campaign should be instituted in India as soon as possible and in other countries with low vaccination rates.

Although the variants in the UK, Brazil and Italy took several months to be identified and fully characterized, the magnitude of their outbreaks was contained because of relatively lower virulence and population densities in these countries. The Delta variant has been spreading rapidly in India as shown by the country submissions on GISAID (it accounts for the 96.3% of the submissions over the past four weeks, as of May 31, 2021)[9]. Currently, the Delta variant is the dominant variant in the UK[22] and is now gaining ground in the US, posing a particular threat to people who are not vaccinated or who have not completed their vaccination course and risking an increase in cases. The Delta variant has been reported in 80 countries worldwide and, recently, a new Delta variant (K417N), named Delta Plus (also known as AY.1), has been found in nine countries, other than in three States in India (Maharashtra, Kerala and Madhya Pradesh)[23]. Evidences suggest that it is resistant to monoclonal antibody therapy[24]. In December 2020, 271 million people (about one-fifth of India's population) were already infected with COVID-19[25]. Furthermore, it has been suggested that India may have already reached herd immunity through natural infection[26].

At present, it is difficult to determine whether the surge in COVID-19 cases in India could be attributable to the emergence of this variant, to population density[27], to social behavioural phenomena such as participation in large gatherings and/or the lack of preventive measures such as quarantine and rigorous isolation. The mutation was initially found in Maharashtra and West Bengal, and it has now been identified in several other countries[28]. In India, there has been an ongoing acceleration of COVID-19 with more than 400,000 new cases registered in 24h and more than 3500 deaths in a single day in May & June 2021[29]. It is difficult to reconcile these numbers with specific practices of the Indian society[30], which until the beginning of January 2021 was studied precisely due to the low number of deaths (the so-called Indian paradox) attributed to a young population (45% of the population under 19 yr old and only 4% over 65)[31]. Some scientists have suggested that genetics may also play a role in this context, but Indians living in the USA or in the UK showed similar rates of infection and disease severity to the local population, confirming the environment pivotal role[31]. To combat the Delta variant, it is mandatory to implement two important strategies: vaccination and tracking. Finding the positives, identifying the contacts and isolating them quickly allow to interrupt the transmission chains of SARS-CoV-2, preventing the Delta variant from becoming dominant before having secured the majority of the population with the complete vaccination cycle.

The total number of infections ascertained on May 31, 2021 in India was 30 million, with a case fatality rate of 1.3 per cent[32]. While India is one of the world's leading producers of vaccines, fewer than 10 per cent of Indians received a dose[33]. More than 20 world leaders came together to call for a Global Pandemic Preparedness Treaty and said: 'Nobody is safe until everyone is safe'[34].

More infections mean more mutations, and more mutations mean more infections and this is a vicious circle that is not predictable. Though a mutant that is both more contagious and more virulent will be a rare event, when there are 400,000 new cases[35], it is possible for new mutants to emerge. Mutation analysis and monitoring of the evolutionary capacity of the virus is important for the design and development of therapeutic targets.

The scientific progress achieved this year must also inspire optimism on the possibility of effectively intervening with the vaccines already available and with others that will arrive (currently 90 vaccines are being tested in various clinical studies and at least 27 of these have reached the final stages of the experimentation)[36]. Everyone should continue to receive the vaccination unless specifically advised otherwise. It is clear that vaccines and all drugs must be monitored continuously to report any possible adverse event. We are all different, we must not forget it: each one of us has our own genetic profile that allows us to respond differently to each therapy[37].

From a preventive medicine point of view, the vaccination approach is promising and will allow limiting the genetic drift of the virus, if properly implemented. It is also necessary to increase the production of vaccines and other drugs, to assist in the fight against coronavirus and relative emerging variants. For example, vaccines can be combined in the future with synthetic monoclonal antibodies

capable of neutralizing the virus. Monoclonal antibodies can be synthesized quickly in laboratory and can be designed and optimized to block the fearful emerging variants. These are already widely used with good efficacy and if administered at the onset of the first symptoms, these allow to keep the course of the disease under control and to avoid the most serious form[37]. Despite the success of vaccines and the promising data on blocking antibodies, no antiviral drug treatment is available to date for COVID-19 patients.

The understanding of the virus entry and egress mechanisms could open the door to promising therapeutic perspectives[38]. The identification of key proteins in pathways involved in the viral replication process represents another example of targeted therapy, capable not only of drastically reducing side effects in COVID-19 patients but also of reducing hospitalization[39]. The combined use of multiple therapeutic agents could, therefore, lead to a better clinical outcome and a faster recovery. Drug repositioning also appears to be a promising strategy. As an example, we recently evaluated the ability of indole-3-carbinol (I3C) to inhibit the activity of HECT proteins, enzymes required for the cellular egress of SARS-CoV-2 and other RNA viruses, and I3C was shown to reduce the output and diffusion of SARS-CoV-2 from infected cells[40]. Moreover, unconventional tools, such as the Cas13a-crRNA complex, have been shown to reduce viral replication and symptoms in animal models[41,42].

On this premise, a search for new drugs is underway, with at least 500 different molecules in laboratory studies and clinical trials[43]. Furthermore, innovative SARS-CoV-2 genome analyses may represent a key point to identify the progenitor genome, thus leading to a deeper knowledge about the virus spatiotemporal evolution, which is of great importance to drive therapeutics development[44]. Only the combination of vaccines and effective antiviral therapies will definitively defeat this pandemic and the next ones we will face.

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