EDITORIAL

Oman Medical Journal [2021], Vol. 36, No. 2: e235

Implications of the Emerging SARS-CoV-2 Variant: Caution is the Key

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ARTICLE INFO
Article history:
Received: 17 January 2021
Accepted: 30 January 2021

Online:
DOI 10.5001/omj.2021.107

Viruses undergo continuous evolution due to natural selection.[1] Specifically, RNA viruses mutate at exponentially high levels when compared to DNA viruses.[2,3] The more opportunities a virus is offered to spread, the more likely we will see new mutations. While most mutations are either deleterious or neutral, some might result in the emergence of a better-fit virus.[4] Some mutations might make the virus more infective, more transmissible, or more virulent – a case in point is the increased infectivity of Ebola virus during the 2013–2016 outbreak.[5]

The current COVID-19 pandemic is thought to have spread faster than any other disease outbreak in the last 100 years. It has already infected over 95 million people and caused the deaths of over 2 million people.[6] This pandemic is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is similar to SARS-CoV but with key genomic differences. Both viruses are believed to have originated in bats.[4] Since the start of COVID-19 pandemic, SARS-CoV-2 showed heterogeneity.[7]

Shortly after its emergence, researchers were closely monitoring the SARS-CoV-2 genetic diversity in real-time, unlike any other virus in history. Numerous mutations have already been detected, but the majority are neutral in effect or have no significant impact on the virus.[8] One of the notable substitutions that emerged early during the pandemic is the spike D614G.[9] Another mutation in the spike protein is Y453F, which has spread more widely in minks and humans in the Netherlands and Denmark.[10] These mutations raised interest and concerns regarding their potential impact on the virus and the course of the pandemic.[11]

On 14 December 2020, authorities of the UK reported a new variant strain of SARS-CoV-2 labeled as a variant of concern (VOC) 202012/01 and later named B.1.1.7.[12] It has become highly prevalent in London and Southeast England, as reported by the COVID-19 Genomics UK consortium. The new B.1.1.7 lineage carries larger than usual number of virus genetic changes and differs by 29 nucleotide substitutions from the original SARS-CoV-2 Wuhan strain, which is higher than current molecular clock estimates of two nucleotide substitutions/genome/month.[13] The two earliest sampled genomes that belong to this lineage were collected during the last week of September 2020 in Kent and Greater London. Infections with B.1.1.7 quickly increased in frequency in the UK through early December 2020 and replaced the other viral lineages in this geographical region.[14]

The B.1.1.7 lineage contains 14 non-synonymous (amino acid (AA) altering) mutations, six synonymous (non-AA altering), and three deletions. It is also phylogenetically different from the SARS-CoV-2 virus circulating in the UK when the variant was detected.[15] This genetic variation includes multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H) as well as mutations in other genomic regions.[16] The N501Y substitution in the spike protein lies in the receptor-binding region that the virus uses to fuse with the human angiotensin-converting enzyme 2 to invade host

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cells. Meanwhile, the 69/70del is reported to affect the performance of some diagnostic polymerase chain reaction assays with an S gene target (known as S-gene drop-out), which can be used as a proxy to detect the B.1.1.7 lineage in the absence of genome sequence capability.[17]

Preliminary epidemiologic modeling, phylogenetic, and clinical findings suggest that B.1.1.7 lineage has increased transmissibility compared to other strains. Nonetheless, these reports suggest no significant change in disease severity or risk of reinfection with the new variant compared to other SARS-CoV-2 viruses circulating in the UK.[18] The effect of spike protein variants, particularly those harboring surface exposed substitutions such as S501Y, on the efficacy of vaccines is a matter of concern. However, assuring data showed that sera from recipients of the BNT162b2 possessed similar neutralizing antibody titers against both S501 and Y501 isogenic SARS-CoV-2.[19] Therefore, it would potentially require the virus multiple mutations to collate in the spike protein to evade vaccine-induced immunity. However, despite the likelihood of vaccine efficacy against new variants, vaccines may need to be updated as more mutations occur with time. As of 30 December 2020, the B.1.1.7 lineage has been reported in 31 other countries/territories/areas in five of the six World Health Organization regions.[12]

Continued surveillance and genetic monitoring of an emerging pandemic virus, such as SARS-CoV-2, is of paramount public health significance to enable rapid containment and ensures the efficacy of vaccines and antivirals in light of evolving variants. However, for this tool to be effective and useful, data needs to be representative and timely. As of 1 January 2021, SARS-CoV-2 high-coverage sequences counted 3341 from the Eastern Mediterranean Region (EMR) in the global initiative on sharing of avian influenza data (GISAID) database,[20] representing more than a two-fold increase in the number of sequences available on 12 November 2020.[18] Overall, the number of sequenced specimens does not echo the increase in reporting confirmed cases with time in the EMR countries. Indeed, only 19.1% of the sequences were collected from October through December, which originated exclusively from five EMR countries, mainly Jordan, Bahrain, and Morocco.

More concerning, the majority (72.2%) of newly submitted sequences after 12 November were from earlier months, such that a significant delay in sequence submission for most EMR countries is notable. The three EMR countries with most sequenced viruses (i.e., UAE, Saudi Arabia, and Jordan) had an average delay of two-to-four months between virus sampling and sequence data becoming publicly available, with Jordan having the shortest delay in sequence publication. There was also no difference in the average delays in sequence publication in these three countries during the early and late phase of the pandemic (first and last collected sequences). Sequencing in remaining EMR countries was sporadic throughout the pandemic and therefore not very informative for public health in an apt manner. This highlights the challenge of timely and open sharing of SARS-CoV-2 data and subsequently detecting new variants in the EMR, thereby hampering efficient regional responses.

In a recent analysis of 1414 SARS-CoV-2 high-coverage sequences available from EMR countries, we identified 10 substitutions that were common in the region. Two of these mutations, spike D614G and NSP12 P323L, had co-evolved and were highly represented in these countries. A lot of speculations have circulated in the media and among the public concerning the emergence of more transmissible or more lethal strains in the region. However, the lack of timely data availability made it difficult to address such an overabundance of information in an evidence-based manner. Our analysis demonstrated no association between the monthly case fatality rates and any of the commonly detected substitutions in the EMR, including spike D614G and NSP12 P323L. We also emphasized the inconsistent and suboptimal sequencing efforts in most EMR countries, especially in war conflict zones such as Syria and Libya.[21]

With new variants of SARS-CoV-2 emerging globally, the real concern is the potential emergence of vaccine escape strains that outpace the global vaccination efforts. For instance, the South African variant 501Y.V2 possesses an E484K substitution that evades neutralization by COVID-19 convalescent plasma.[22] However, the way by which more infectious variants are appearing in different geographical regions mandates that the major focus should be to control the ongoing pandemic with good public health methods. Relying solely on vaccines for pandemic control is a long process and will take much longer to protect the world's seven

billion population. Even if viral virulence is unaltered, a 70% increase in infectivity could seriously affect populations by raising levels of hospitalizations and deaths. Indeed, this is thought to be the case with the UK variant, where exponential growth of cases has been seen as the variant is replacing the older strain.[23]

With the emergence of multiple variants, there is a dire need for global investment in basic public health infrastructure, as those measures serve not only one pathogen and its variants but other known and future infectious microbes. Efforts in disease surveillance, outbreak detection and response, risk communication, health education as well as implementing non-pharmaceutical interventions will prepare the world to face current and other pathogens of pandemic potential. In a raging pandemic with unprecedented monitoring capacities of viral transmission, scientists and public health experts should also use sequencing and surveillance tools to simultaneously identify new viral variants and their effects on transmission or virulence. This enables rapid containment of potentially more infectious or vaccine/drug-resistant viral species.

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