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Emergence of New Variants of SARS-CoV-2: Current Scenario, Potential Consequences and Future Direction

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ABSTRACT

Amidst the second wave of the pandemic across the globe, three (3) new variants of SARS-CoV-2 have been detected in recent weeks in the United Kingdom (SARS-CoV-2 VOC 202012/01), South Africa (SARS-CoV-2 501.V2) and Nigeria (SARS-CoV-2 P681H). The SARS-CoV-2 VOC 202012/01 variant in particular, has been implicated in more than 1,000 cases especially in South-East of England, purportedly accounting for 60% of new infections in London. It has so far spread to at least 17 countries, causing rising global concerns. Twenty-three (23) separate mutations particularly in the S gene of the variant have been detected at a time, 17 of which were linked to the building blocks of proteins that form the virus. One of the most important is an N501Y mutation in the spike protein that the virus uses to bind to the human angiotensin converting enzyme Type-2 (ACE2) receptor. Experts opined that changes in this portion of the spike protein is responsible for the increased transmissibility. The potential implications of this observed mutations in terms of diagnostics, therapeutics and vaccine development is still being studied. Enhanced genomic and epidemiological surveillances is important to stay one step ahead of the virus in the molecular-arm-race. At the moment, Research efforts are ongoing to learn more about the variants to better understand how easily they might be transmitted and whether currently authorized vaccines will protect people against it. Information regarding the virologic, epidemiologic, and clinical characteristics of the variants are rapidly emerging. This review seeks to examine the current scenario, potential Consequences and future direction for the emerging new variants.

Keywords: *COVID-19; SARS-CoV-2; Emerging variants; Consequences, Future Direction*

INTRODUCTION

A year ago, cases of patients presenting with pneumonia of unknown origin were reported to the World Health Organization (WHO) in late December, 2019 from the Wuhan City in the Republic of China (Enitan et al., 2020a). Specimens were collected and laboratory test conducted. A novel coronavirus, the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), with very high propensity for spread was discovered. Since then, infection has spread to other Chinese cities and internationally, resulting in the current pandemic (Lau et al., 2020). The World Health Organization (WHO) officially declared the novel Coronavirus outbreak a pandemic on the 11th of March, 2020 (Live Science, (2020) and international flights from high-risk countries have been identified as a key driver of the current pandemic (Enitan et al., 2020b). As of 28th of December, 2020, more than 81.1 million confirmed cases and over 1.7 million deaths have been recorded in 220 countries and territories of the world (JHU-CSSE, 2020). Currently, the Africa continent has recorded over 1.8 million confirmed cases with a cumulative fatality of 40,456 as of December28th, 2020 (WHO-Africa Region, 2020). So far, South Africa has been far hit by the deadly virus with a cumulative confirmed cases of 1,004,413 and 26,735 deaths, followed by Algeria (98,249 and 2,728, respectively) and

Nigeria (84,414 and 1,254, respectively). Amidst the second wave of the pandemic across the globe, three (3) new variants of SARS-CoV-2 with rising concerns have been detected in recent weeks in the United Kingdom, South Africa and Nigeria. The potential implications of this observed mutations in terms of diagnostics, therapeutics and vaccine development is still being studied. This review seeks to examine the current scenario, potential consequences and future direction for the emerging new variants.

CURRENT SCENARIO

On 14th of December, 2020, a new coronavirus variant (SARS-CoV-2 VOC 202012/01) of the B.1.1.7 lineage with series of mutations, thought to have first appeared in mid-September was first reported in the United Kingdom (Rambaut et al., 2020). The new variant has been implicated in more than 1,000 cases amidst the second wave of the pandemic in different parts of the country, especially in South-East of England, reportedly accounting for 60% of recent infections in London and has been spreading very rapidly both locally and internationally (Jacqui, 2020). Mutation in RNA viruses, including the Coronaviruses is a common natural phenomenon as they replicate and there are many variants already circulating in the UK before now. The emergence of the new variant (VUI-202012/01- B.1.1.7 lineage) triggered alarm because it involved 23 separate mutations particularly in the S gene, 17 of which were linked to the building blocks of proteins that form the virus (Schraer, 2020**)**. One of the most important is an N501Y mutation (*i.e.*, replacement of amino acid asparagine (N) with tyrosine (Y) at position 501) in the spike protein that the virus uses to bind to the human angiotensin converting enzyme Type-2 (ACE2) receptor. Experts opined that changes in this portion of the spike protein (Receptor-Binding Domain) is responsible for the increased transmissibility. This variant, however carries many other mutations, including a double deletion at positions 69 and 70 (Jacqui, 2020). Although, zoonotic transmission of SARS-CoV-2 between humans and animals have been reported (Enitan et al., 2020a), so far, the VOC 202012/01 variant has no known association with animals or animal contact.

On December 21st, 2020, the new variant was reported to have been exported to Australia by two travelers from the UK. On the same day, South Africa reported another new variant (501.V2) completely different from that of the UK variant. The new variant has been detected in more than 8,500 people (younger patients inclusive) currently hospitalized with COVID-19 in South Africa. A 40% increase in cases has so far been reported (Africa News, 2020; Magome and Meldrum, 2020). And very worrisome is that the said variant has been exported to quite a few countries including the United Kingdom (Aljazeera and News Agencies, 2020), prompting Britain on December 24th, 2020 to place immediate travel ban on travelers from South Africa, including those transiting. However, the ban excludes British nationals and permanent residents arriving from South Africa (BBC, 2020).

Furthermore; on 22nd of December, 2020, the Dutch Health Minister (Hugo de Jonge) announced two cases of COVID-19 in Netherlands (Amsterdam) found to be associated with the new variant identified in the UK. On December 23, 2020, Italy registered the second case of the new SARS-CoV-2 variant, but the affected patient had no travel history to UK. Singapore reported its first case of the UK variant on December 24th, 2020.

On December 24, the Director-General of the Africa Centre for Disease control (Africa CDC), Dr. John Nkengasong, announced that a new variant known as the P681H was identified in Nigeria, Africa's most populous country with more than 200 million populations.According to him, the variant is of a separate lineage from the other mutants, but with reduced transmissibility when compared to the other two new variants. The P681H spike protein mutation has been earlier noted to be directly adjacent to the furin cleavage site, which may have biological significance (Rambaut et al., 2020). The P681H variant was earlier detected in two patient samples collected on 3rd of August and 9th of October in Osun state, South-West, Nigeria. The variant shares one non-synonymous SNP in the spike protein in common with the B.1.1.7 lineage, but none of the 22 other unique lineage-defining mutations. The non-synonymous SNP, S: P681H, has been observed in global data outside of the B.1.1.7 lineage, and likely represents an independent, homoplasic occurrence of this substitution from the UK. Currently, only about 1% of the SARS-CoV-2 genomes from Nigeria share any of the 17 protein-altering variants from the B.1.1.7 lineage (Oluniyi, 2020a,2020b). At the moment, Nigeria have reported a 52% increase in cases. Researchers at the moment are trying to establish if the increase in cases were due to the emergence of the new variant having the P681H spike protein mutation or as a result of relaxation in non-pharmaceutical measures among the populace.

Japan, on December 25th, 2020, reported its first five cases of the fast-spreading new variant in passengers arriving from the UK. On the same day, Lebanon also reported a case of the new variant detected among passengers on a flight arriving from London. On 26th of December, 2020, the French, Spanish, Swedish and Canadian authorities announced the country's first cases of the new variant earlier reported in the United Kingdom. The French, Spanish and Swedish cases had travel history to UK (Reuters, 2020; Medical Express, 2020; Bhaduri, 2020); while the Canadian cases had no known travel history, exposure or high-risk contacts (Parkhill and Jones, 2020). Meanwhile, South Korea reported its new cases of the new variant on December 28th, 2020. It involved a family with recent travel history to the United Kingdom. Accordingly, the Korea Disease Control and Prevention Agency (KDCA) has announced its intention to suspend all flights coming from the United Kingdom (Yan, 2020).

The United States of America has been far hit by the pandemic, with over 19.4 million cumulative cases and over 350,000 deaths recorded. Although, a specific variant (the D614G variant) has previously been detected in the United States of America (CDC, 2020); the country officially announced its first case of the VOC 202012/01 variant on the 29th of December, 2020 (Singh, 2020). Although the new variant had not been found in the US until now, the Centers for Disease Control and Prevention (CDC, 2020) noted that the variant could already be in the United States waiting to be identified given the small portion of US infections that have been sequenced (about 52,000 of the 19 million US cases). High traffic between the United Kingdom and the United States, as well as the high prevalence of this variant among current UK infections has been linked to the importation of the variant into the country (Singh, 2020).

Denmark like other European countries have also reported the arrival of the UK variant. Earlier in June, 2020, the World Health Organization (WHO, 2020) alerted the global scientific community about the occurrences of 214 human cases of COVID-19 caused by SARS-CoV-2 variants found in farmed minks in Denmark. Twelve (12) cases with a distinctive variant, was reported on the 5th of November, 2020. Eight (8) out of the 12 cases had a link to the mink farming industry and four cases were from the local community. This new variant, designated as the "*Cluster 5*" variant, had a combination of genetic changes that have not been previously observed. SARS-CoV-2 can acquire unique changes while infecting minks. It has been observed that these mink variants are able to jump back into humans. Preliminary results suggest that the mink variants infecting humans appear to have the same properties as other variants of the SARS-CoV-2 virus. Further research is needed to better understand whether these mink variants will be able to provide sustained transmission among humans and could have a negative impact on countermeasures, such as vaccines (WHO, 2020a).

Furthermore, early in September, 2020, Researchers in Bangladesh reported a new mutation (NSP2_V480I) in three (3) strains of SARS-CoV-2 (Akter et al., 2020). The mutation rate (12.6 per cent) of Bangladesh variant has been reported to be higher than the global average of 7.23 per cent (Sujan, 2020). The potential implications of this observed mutations in terms of diagnostics, therapeutics and vaccine development is still being studied. The new variants have been reported to be 50-70 percent more infectious than the original virus. In anticipation of the potential importation of the new variants, many countries have taken stringent new lockdown measures, including travel restrictions and cancellation of flights from the UK and South Africa, in efforts to curb further spread of the new variants.

POTENTIAL CONSEQUENCES

An understanding of viral replication is paramount to appreciate the potential consequences of the mutations. Normally, when a virus replicates, it sometimes under goes some changes in its genetic make-up. These changes are called “mutations”. The virus with the new mutation(s) is called a “variant” of the original virus (WHO, 2020b). The virus exists as a cloud of variants known as quasispecies and individual viruses are selected at the time of infection (Koyama et al., 2020). Most changes have little to no impact on the virus’s properties. Occasionally, they result in a virus variant that is better adapted to its environment compared to the original virus. In that case, it can become dominant in a specific environment. This process of selection of successful variants is called "viral evolution" and this is a natural process all viruses go through. If a virus changes so much that it is different from the one that vaccines are designed to combat, or tests to detect, it may influence how well vaccines and diagnostic tests work. While some viruses change fast, SARS-CoV-2, has been reported to change more slowly than others viruses such as influenza viruses. This is in part due to the fact that SARS-CoV-2 has an internal "proofreading mechanism" which corrects mistakes during replication (WHO, 2020b).

Furthermore; SARS-CoV-2 acquires at least one new mutation in its genome every two weeks (Koyama et al., 2020). Many mutations are silent (*i.e.*, cause no change in the structure of the proteins they encode) because they produce a three-letter codon that translates to the same amino acid (*i.e.*, they are "synonymous"). Other mutations may change the codon in a way that leads to an amino acid change (*i.e.*, they are "non-synonymous"), but this amino acid substitution does not impact the proteins function. VOC 202012/01 has 14 non-synonymous (amino acid [AA] altering) mutations, 6 synonymous (non-AA altering), and 3 deletions, notably including 69/70 deletion: this double deletion has occurred spontaneously many times, and likely leads to a conformational change in the spike protein (CDC, 2020).

Potential consequences of these mutations include: 1) Ability to spread more quickly in humans, 2) Ability to cause either milder or more severe disease in humans, 3) Ability to evade detection by specific diagnostic tests, 4) Decreased susceptibility to therapeutic agents such as monoclonal antibodies, 5) Ability to escape vaccine-induced immunity. Among these possibilities mentioned above, the last—the ability to escape vaccine-induced immunity—would likely be the most worrisome because once a large proportion of the population is vaccinated, there will be immune pressure that could favor and accelerate emergence of such variants by selecting for "escape mutants." However, currently, there is no evidence that this is occurring, and most experts opined that escape mutants are unlikely to emerge because of the nature of the virus (CDC, 2020; Magome andMeldrum, 2020).

FUTURE DIRECTION

Mutations in SARS-CoV-2 is expected and must be kept under genomic surveillance (Urhan and Abeel, 2020). This calls for a robust up scaling of genomic sequencing efforts globally (da Silva et al., 2020). Even though Coronaviruses tend to mutate more slowly than some other viruses like the influenza viruses, this does not mean that they would not change over time. A new strain cannot come to predominate unless it provides some advantage to the virus and none has so far been reported. An adventitious variant is most likely to arise in other parts of the world where infection is rampant. The previous reports of emerging variants, D614G, N439K and the "mink" virus have not translated into a new "strain" so it is unlikely that the VOC 202012/01 variant will behave differently, Cumulative mutation may result in the emergence of more virulent variants in the future (Thomson et al., 2020). But so far, the genome of SARS-CoV-2 has changed very little having no impact on available diagnostics, therapeutics and vaccines that are in development. At the moment, no evidence of greater virulence, severe illness, increased fatality or evasion of cure and vaccine is available (Achenbach, 2020). The FDA-authorized vaccines are polyclonal in nature, producing antibodies against many regions in the spike protein it is very unlikely a single change would make the vaccine less effective. The virus would likely need to accumulate multiple mutations in the spike protein to evade immunity induced by vaccines or by natural infection. Emergence of vaccine escape mutants should be expected, rapidly identified and isolated. Multi-variants (Conjugate) vaccine may be needed to stay protected against emerging variants. Interestingly, most commercial polymerase chain reaction (PCR) tests have multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other PCR targets will still work. Hence, experts opined that there is no cause for alarm, but the world must be alert. Epidemiological preparedness is key to prevention of spread. The emergence of new variants of SARS-CoV-2 amidst the second wave of the pandemic across the globe calls for an urgent need to scale up genomic surveillance globally (Science Media Centre, 2020; Urhan and Abeel, 2020).

CONCLUSION

Enhanced genomic and epidemiological surveillances is important to stay one step ahead of the virus in the molecular-arm-race. At the moment, Researchers are working to learn more about the variants to betterunderstand how easily they might be transmitted and whether currently authorized vaccines will protect people against it. Information regarding the virologic, epidemiologic, and clinical characteristics of the variants are rapidly emerging. Research groups from all over the world have sequenced SARS-CoV-2 and shared the data on public databases, including the Global Initiative on Sharing All Influenza Data (GISAID). This global collaboration allows scientists to better track the evolution of the virus. It is a good thing that in November, 2020, the CDC officially launched the National SARS-CoV-2 Strain Surveillance (NS3) program to increase the number and representativeness of viruses undergoing characterization. In addition, CDC's COVID-19 response is actively seeking samples of interest, such as samples associated with animal infection and, in the future, samples from vaccine-breakthrough infections. Data from these efforts will be very helpful to the scientific community, researchers, public health agencies, and industry globally. Also, since the start of the outbreak, WHO has been working with a global network of expert laboratories around the world to support testing and better understanding of the SARS-CoV-2 virus. The SARS-CoV-2 Evolution Working Group in particular is working to detect new mutations early and assess their possible impact on the virus itself and on diagnostics, therapeutics and vaccines. The pace of the research efforts in the past year has been unprecedented, allowing us to make significant progress on the diagnostics, cure and vaccines needed to end the pandemic. However; there is still so much to learn about the novel coronavirus and therefore, there is no room for complacency. Since the pandemic is not over, a lot of surprises regarding the evolution of the virus and the trajectory of the pandemic should still be expected in the coming year.

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