BIZCOMMUNITY

How the coronavirus mutates and what this means for the future of Covid-19

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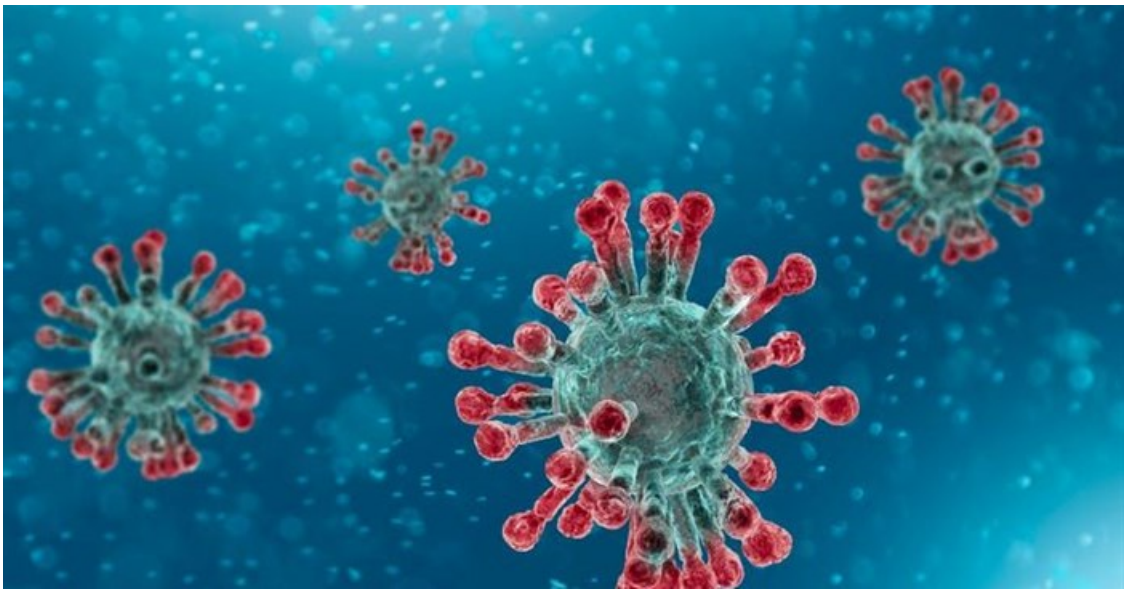
The recent appearance of new variants of SARS-CoV-2 (the coronavirus causing Covid-19 infections), that may be associated with increased transmission of the virus and disease severity, has raised questions about the nature and rates of mutations in viruses. The answers to these questions will potentially guide public health decisions. However, it is also important for individuals to understand them so as to prevent potential panic.



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Here are some of the basics.

Mutations 101

All organisms, including viruses, have genomes: these are their genetic inheritance. All cells have genomes made of strands of deoxyribonucleic acid (DNA). Viruses, on the other hand, may have genomes made of strings of DNA or ribonucleic acid (RNA) nucleotides.

Mutations in virus and cell genomes (substitutions, additions or deletions in the cellular DNA and viral DNA or RNA sequences) occur continually. This can happen as a result of replication errors – where copying of the genome by the molecular replication machinery inadvertently introduces changes – or because of the effects of chemicals or radiation.

The rates of mutation (how often one of these changes occurs) vary between the different types of viruses, and between viruses and cells. Viruses in general mutate faster than host genomes, and RNA viruses generally mutate faster than DNA viruses.

This is largely because RNA virus replication machinery generally does not have an error correction ability, as all other cells and most DNA viruses do. For example, influenza viruses causing seasonal flu have an error rate of 0.5 nucleotide positions per genome per cell infection. This means mutations accumulate rapidly as the virus multiplies in one person.

But SARS-CoV-2 and other coronaviruses are an exception to the rule. They mutate at least four times more slowly than influenza.

Many mutations in viral genomes are silent: they do not alter the function of the virus in any way, and they don't result in changes in disease severity or immune responses. Of those that are not silent, many are damaging to virus functions and result in non-viable viruses, and therefore do not do survive into a new generation of viruses.

Occasionally, a mutation will give the virus a better chance of surviving and reproducing itself, and will result in a new population (known as a new lineage). It is noteworthy that there were only 4-10 mutations accumulated for SARS-CoV-2 viruses that infected people in the US in mid-2020, compared to the original virus found in Wuhan months earlier: thus, only a small proportion of the 24 possible mutations in this sequence have produced a viable mutant.

An accumulation of mutations that significantly alter the properties of a virus lineage would be a new variant. The SARS-CoV-2 variants found in the UK, South Africa and Brazil – more properly referred to as the B.1.1.7, B.1.135 and P.1 variants – are examples. All are reported to have significantly higher transmission rates than earlier lineages.

The infection pathology of SARS-CoV-2

When the SARS-CoV-2 virus enters the human host, usually in liquid droplets or aerosols from a cough or sneeze, the virus attaches via its surface S protein to the human ACE2 on cell surfaces, like a key fitting into a lock. ACE2 "receptors" are present on virtually all human cell types. But they are especially common on cells of the human nose and throat.

The viral genome then enters the cell and hijacks it to make multiple copies of itself, and then spreads. Mutations causing two amino acid changes in the S protein of the B.1.135 variant (E484K and N501Y), cause the virus to bind significantly more effectively to the human ACE2 receptors. This means that this and similar variants can spread more rapidly and efficiently within the human host population.

Initial infection of humans is in the upper respiratory tract, and early symptoms are generally of a respiratory infection. However, it is increasingly obvious that SARS-CoV-2 is a systemic virus. This means it can also infect and damage intestinal and urogenital tissues, cells of the central nervous system, and the endothelial cells of minor blood vessels, leading to clotting complaints and even strokes.

The consequences of mutations

Two issues about the new variants are causing global concern: will they cause more severe disease; will they be more resistant to the anti-Covid-19 vaccines coming on to the market.

The British government and others claim the B.1.1.7 variant "may be more deadly". The B1.135 variant found first in South Africa is apparently not more severe.

The question of immunity is complex. Natural infections lead to broad antibody and cellular immune responses that target many parts of the virus. But most SARS-CoV-2 vaccines stimulate responses that target only the S protein: this has led to concern that new variants may escape these "narrow" immune responses.

Apparent proof of this is the revelation that the AstraZeneca vaccine that is the first to reach South Africa, and was scheduled to be used in front-line healthcare workers, has little efficacy in preventing mild or moderate Covid-19 caused by the B.1.135 variant.

Reassuringly there is little evidence that any of the changes so far catalogued in the S protein affect the efficacy of most of the other current vaccines – despite hype generated by in vitro work with laboratory-made monoclonal antibodies.

There is in fact evidence that the efficacy of the Pfizer/BioNTech and Moderna mRNA and Johnson & Johnson adenovirus vaccines – are not significantly affected. This is because there are still many epitopes – or binding sites – for antibodies in the S protein or RBD that are not affected by known mutations.

It is also possible to quickly re-engineer the mRNA vaccines to counter any threat. An encouraging recent recommendation was that Johnson & Johnson's single-shot adenovirus-based vaccine would be good for controlling outbreaks, while Novavax's protein-based vaccine could give better overall protection.

What about future mutations?

It's highly likely that there will be new variants of SARS-CoV-2 in the near future. In fact, it is very likely that new variants are already circulating in the human population, but have yet to be detected by genomic surveillance. Surveillance is strong in some countries – such as the UK and South Africa – but is very limited in others, including most countries in Africa.

What is concerning is that we now know that the S proteins of seasonal common cold-causing coronaviruses evolve to avoid host immune responses, just as influenza viruses do, which results in people catching these individual viruses every three years or so. This means that SARS-CoV-2 vaccines may have to be changed regularly, just as flu vaccines are.

Is it likely that other functional mutations will occur; for example, mutations that may increase the pathogenicity of the virus, as they have already increased its transmissibility?

The answer is that we simply don't know whether new mutations will make the virus more dangerous or easily transmitted. But evidence from the history of some well-known human common cold viruses may be informative. Colds are caused by several different viruses, the most common of which are the numerous rhinoviruses. These have been permanent residents in the human population for many centuries, and re-emerge annually as seasonal epidemics. Despite this, however, there is no evidence for any worsening pathology. In fact, the four coronaviruses that also cause the common cold may originally have caused much more severe disease, before becoming endemic and seasonal.

It is sincerely hoped that Covid-19 follows the same route.

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