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The coronavirus evolves

Several new viral variants pose added threats – how worried should we be?

Graham Lawton

THE rise and spread of new variants of the coronavirus are seen as ushering in a dangerous new phase of the covid-19 pandemic. But from the virus’s perspective, nothing has changed. It is just doing what comes naturally to viruses: evolving.

It is now well-established that SARS-CoV-2 is a coronavirus with a large and unusually stable RNA genome, but that doesn’t mean it doesn’t change at all. Unlike most other RNA viruses, which are among the most mutation-prone biological entities in the world, SARS-CoV-2’s genome changes very slowly. This is largely because it has a proofreading function that is efficient at eliminating errors during replication, a major source of the genetic variation that we call evolution.

“There’s not masses of evolution occurring, this is a very slow-evolving virus,” says David Robertson at the MRC-University of Glasgow Centre for Virus Research in the UK.

A project called Nextstrain, based at the Fred Hutchinson Cancer Research Center in Seattle, compiles all published viral genome sequences and plots them on a family tree. This shows the original virus, called Wuhan-Hu-1, diverging steadily as it spread around the world.

The virus’s average mutation rate remains low and steady at about two mutations per lineage per month, but over time this has given rise to thousands of different lineages. For example, there are more than 4000 different versions of the spike protein that the virus uses to break into host cells and which is the target of most vaccines.

Intriguingly, most of the mutations seem to be induced by the human immune system rather than by RNA replication errors.

One arm of our innate immune system is a generalised antiviral weapon that introduces random errors into viral genomes in a bid to neutralise them. It doesn’t always succeed.

Most of the surviving mutations are of no medical significance. Up until now, the virus has been circulating unhindered in a large host population with little immunity, and hence has encountered minimal resistance, or selection pressure as evolutionary biologists call it. The evolution that has occurred is therefore mostly just random genetic drift rather than being the virus adapting.

But not entirely. In May 2020, a new variant with a mutation called D614G started circulating. It seems to be slightly more transmissible than the original virus because of an alteration to its spike protein. About 90 per cent of the viruses now circulating worldwide carry this mutation.

More recently, three other mutants, known as the UK, South African and Brazilian variants, have also started spreading rapidly. All are also thought to have mutations that make them more transmissible, and some might be able to outsmart parts of the immune system, although they don’t seem to be more deadly.

The sudden appearance of these three new variants doesn’t suggest that the virus has upped its mutation rate, says Sudhir Kumar at Temple University in Pennsylvania. They are an inevitable product of time and lots of transmission events between people. Under such circumstances, new variants are bound to arise by chance. Highly transmissible ones have a biological advantage and so will outcompete their more sluggish rivals.

More variants are inevitable. “As the virus mutates, this story will keep repeating itself,” says Sharon Peacock, head of the COVID-19 Genomics UK Consortium. The big worry is the emergence of “escape mutations” that enable the virus to dodge the immune system or render vaccines or drugs useless (see page 10).

Such an escape becomes even more likely as we begin to exert selection pressure on the virus in the form of vaccines, natural immunity and drugs. Mutants that can evade these interventions could slip through the net and start circulating wildly, potentially pushing us back towards square one in our efforts to beat the pandemic.

“We are rolling out vaccines to high-risk groups. We may well see a rapid rise in mutations as a result”

ILLUSTRATION OF THE B.1.1.7 CORONAVIRUS VARIANT’S SPIKE PROTEIN (RED)
"We are now rolling out vaccination to high-risk groups and this is going to provide a very strong selection pressure," says Emma Thomson at the University of Glasgow. "We may well see a rapid rise in mutations as a result."

We will also have to keep an eye out for viruses that can evade natural immunity, she says. Virologists have already discovered variants that are able to partially evade antibodies.

These are a wake-up call. Even though the UK variant, known as B.1.1.7, doesn’t seem to have an escape mutation, the fact that its spike protein is 17 mutations away from the original is "a little bit terrifying", says Robertson. "It is a concern that a large number of spike mutations are found in the same strain," says Kumar.

One potential danger that we can probably stop worrying about is recombination, which occurs when two related coronaviruses mash their genomes together to create a hybrid. Two studies scouring thousands of viral genomes have found no evidence that this has occurred.

But escape mutation is a real and present danger. A recent case study highlights what could happen once we put the virus under heavy selection pressure. In May 2020, an immunocompromised patient was admitted to a UK hospital with covid-19. He died of the disease in August. Over the 101-day course of his illness, a team led by Ravindra Gupta at the University of Cambridge repeatedly sampled and sequenced viruses from the patient’s respiratory tract.

The virus strikes back

The patient was given infusions of an antiviral therapy called convalescent plasma – an antibody-rich blood extract from another person infected with the virus. Days later, Gupta’s team saw a dramatic rise in a mutant version of the coronavirus and later confirmed that it had partially escaped the therapeutic effects of the plasma. This mutant virus eventually killed the patient.

We mustn’t draw too many conclusions from this single case, says Gupta. The patient was also being treated for cancer and couldn’t mount an effective immune response of his own. But the study shows how quickly and viciously the virus can mutate and escape under selection pressure.

The answer to these threats is surveillance, to flag up and isolate escape mutants before they spiral out of control. The UK’s world-class surveillance system relies on a combination of monitoring and sequencing. Red flags are raised if something unusual happens clinically or epidemiologically, and then geneticists search for mutant viruses that could be responsible.

The new UK variant, for example, was spotted because lockdown restrictions were reducing viral spread everywhere but Kent. Surveillance would also be triggered if vaccinated people or those who had recovered started falling ill, says Kumar.

About 10,000 genomes a week are sequenced in the UK and there are plans to up that to 20,000 by March. The country also has a new body called the G2P-UK National Virology Consortium to keep track of new mutations and warn about potentially dangerous ones.

"Even though this virus is evolving slowly, we have to take surveillance very, very seriously"