



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Evolution

Threats from new variants

Mutated forms of the coronavirus from the UK and South Africa are providing fresh challenges for controlling the pandemic, reports **Michael Le Page**

SINCE the start of the pandemic, there have been concerns that the coronavirus could evolve to become more dangerous. Now, hospitals in the UK are at risk of being overwhelmed by surging numbers of covid-19 cases and there is growing evidence that this is partly due to a new variant of the virus that spreads more readily. This variant has already reached many other countries.

Hospitals in South Africa are also being overrun, due to a resurgence of covid-19 being blamed on another variant of SARS-CoV-2, the virus responsible.

It isn't yet clear how much faster this variant, called B.1.351, spreads. Yet initial studies of the variant from the UK, known as B.1.1.7, estimate that it is around 40 to 74 per cent more transmissible. This may be because people infected with it shed more of the virus.

In response to these initial studies and high UK transmission rates, England and Scotland this week joined Wales and Northern Ireland in another period of strict lockdown, during which most schools and universities will use remote learning.

"No matter how the virus changes, it needs us to be close enough to each other and to have interactions to let it jump between us," says Emma Hodcroft at the University of Basel in Switzerland. "If we don't give the virus those opportunities, it simply can't spread no matter what variant it is."

Neither new variant appears any deadlier. But there is concern that current vaccines could be less effective against B.1.351.

The new variants were discovered by sequencing the entire genome of the virus, which is around 30,000 RNA letters long. Researchers around the world routinely sequence samples to track the spread of the coronavirus



TOLGA KEMENAFI/PA VIA GETTY IMAGES

and see how it is evolving.

Such efforts have found there are already tens of thousands of "mutant" viruses that differ from each other by at least one mutation. This is unsurprising as viruses constantly mutate.

In fact, the coronavirus changes less than many other viruses. Any two SARS-CoV-2 viruses from

"There is concern that vaccines could be less effective against the variant from South Africa"

anywhere in the world will usually differ by fewer than 30 mutations, and they are regarded as all belonging to the same strain. Researchers instead talk about different lineages or variants.

B.1.1.7 was first sequenced in the UK on 20 September. It caught

the attention of scientists on 8 December, when they were looking for reasons for the surge of cases in south-east England.

B.1.1.7 has 23 mutations compared with the original SARS-CoV-2 virus first discovered in Wuhan, China. Seventeen lead to changes in viral proteins. Many of these mutations have been found before and their overall number isn't unusual, but this combination is unique.

In particular, eight of the mutations in B.1.1.7 change the shape of the outer spike protein. One of these mutations, called N501Y, is in the part of the spike protein that binds to receptors protruding from human cells and helps the virus infect them – the receptor binding domain.

The N501Y mutation might help make the virus more infectious by

binding more tightly to the human receptors. However, this can't be the whole story, as this mutation has been around for a while. It was first seen in Brazil in April and has since been detected in several other countries with no apparent effect on transmission.

So if B.1.1.7 is more infectious, it must be due to a combination of mutations. Lab studies are under way to try to understand the effects of its mutations, but, for now, the main evidence of higher transmissibility comes from the fact that it is spreading faster than other, older variants.

Normally, the only way to truly tell if one particular variant is spreading faster than others is to sequence entire viruses. But in one way, health authorities in the UK got lucky. The standard test for the coronavirus involves looking for

Guy's Hospital in London. UK health services are at risk of being overrun

any of three small parts of the viral genome. By chance, in some tests used in the UK, one of these parts is the region where one of the mutations in B.1.1.7 occurs, causing this element of the test to produce a negative result with the variant.

So by looking at standard test results that came back positive for only two of the three parts, called an S gene dropout, we have been able to get a better idea of how fast the variant is spreading in the UK than would be possible from genome sequence data alone.

Based on this, an initial analysis by Neil Ferguson at Imperial College London and his colleagues concludes that B.1.1.7 has “a substantial transmission advantage”, spreading 40 to 70 per cent faster than other variants.

Another analysis, by Nick Davies at the London School of Hygiene & Tropical Medicine and his colleagues, put B.1.1.7's increased transmissibility at 50 to 74 per cent.

Preliminary numbers from Denmark also add to the evidence that B.1.1.7 spreads faster. So far, only 86 cases of the variant have been detected in Denmark. However, the percentage of B.1.1.7 in sequenced samples has risen every week for the past four weeks.

Meanwhile, a study of 600 nose or throat swabs by Michael Kidd at Public Health England's public health laboratory in Birmingham and his colleagues found higher than normal levels of the virus in 35 per cent of S gene-dropout samples – that is, ones from people who probably had B.1.1.7 – compared with 10 per cent of samples without S gene dropout. This suggests that B.1.1.7 is more infectious because people shed more viruses on average, but

this has yet to be confirmed.

All this is bad news because it means tougher measures are needed. “Without effective control policies, rapid surges are predicted and the burden in the first six months of 2021 may be greater than what was seen in 2020,” Davies tweeted before Christmas about the threat posed to England.

Early data suggested that B.1.1.7 might spread especially readily among children. It now appears that this was just an artefact related to schools being open during the second lockdown in England in November, says Davies.

Nonetheless, his analysis suggests that imposing a similar lockdown won't be enough to stop B.1.1.7. It will be necessary to close schools and universities too, as has largely happened in the UK.

The good news is that an initial study by Public Health England found that people infected with B.1.1.7 were no more likely to be hospitalised or to die than those infected with other variants.

The B.1.351 variant in South Africa also seems to cause higher transmission rates. In October, coronavirus cases began rising unusually fast in Nelson Mandela Bay Municipality. They soon started rising fast in surrounding areas too.

This prompted the sequencing of thousands of viral genomes to see if a new variant had arisen. That revealed the B.1.351 lineage, which, when first sequenced on 15 October, had various mutations including six in the spike protein. By the end of November, it had acquired another three in the spike protein. Only one of the mutations, the N501Y one, is the same as in B.1.1.7.

What is worrying some researchers is that B.1.351 has three mutations, including N501Y, in the receptor binding domain of the

40-74%

How much more transmissible the new coronavirus variant from the UK is thought to be

9

Number of mutations on the spike protein of the variant from South Africa

39

Number of countries that have reported cases of the variant from the UK

The resuscitation room of the covid-19 ward, Khayelitsha Hospital, South Africa



RODGER BOSCHIAFF VIA GETTY IMAGES

spike protein. This is an important region for immunity as well as infectivity because many of our antibodies work by attaching themselves to this region.

This might mean that vaccines confer less protection against B.1.351 than they do against other variants, but we just don't know yet. “It's all speculation still,” says Aine O'Toole at the University of Edinburgh, UK. “We have no confirmation.”

Lab studies are now under way to try to find out, for instance by measuring how well antibodies from people who have been vaccinated bind to these variants.

Meanwhile, other countries are trying to avoid importing the new variants, but it may be too late. B.1.351 has reached at least eight countries besides South Africa, including the UK and Australia, although it isn't reported to be spreading locally, says O'Toole, who is part of a team monitoring the variants' spread.

B.1.1.7 has reached at least 39 countries, including the US, China, Australia and New Zealand, and is definitely spreading locally in a few. So far, Denmark has reported the most cases besides the UK, but this is likely to be because it does more sequencing than most other countries.

More people from the UK travel to countries such as Spain and Germany than Denmark, O'Toole points out, so the expectation is that there should be more cases of B.1.1.7 in these places. “The virus moves with people,” she says.

Both O'Toole and Hodcroft think other nations should do all they can to prevent more introductions of this new variant. This will help keep down the number of cases and make them easier to control, says Hodcroft. “The goal here is more to buy time,” she says. ■