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Virology

The evolving coronavirus

The coronavirus has mutated very little, but as more people are treated or vaccinated it could face pressure to evolve, finds **Graham Lawton**

“FORTUNATE” isn’t a word that often comes up in relation to the coronavirus pandemic, but in one respect it is true. In the nine months that the virus behind covid-19 has been circulating widely, it has hardly mutated at all.

“We are fortunate that the virus is not mutating fast,” says Sudhir Kumar at Temple University in Pennsylvania. A rapidly mutating virus could evolve into different, possibly more virulent, strains. “So it’s good to have a low diversity” among the viruses

“As we start to get standardised drug deployment, resistant mutations will likely arise”

currently circulating, he says. However, this could be the calm before the storm.

A recent analysis of more than 18,000 genomes of the new coronavirus, formally called SARS-CoV-2, sampled from around the world found very low levels of genetic diversity. The study, led by Morgane Rolland at the Walter Reed Army Institute of Research in Maryland, concluded that these viruses are so similar that a single vaccine should protect against them all (*PNAS*, doi.org/fdkz).

There are three main reasons for this. First, even though SARS-CoV-2 is an RNA virus, which generally have the fastest mutation rate of any biological entity, coronaviruses change relatively slowly because their genome-copying machinery has a proofreading function.

Second, when mutations have appeared, they are almost all biologically harmful or neutral to the virus, and so haven’t persisted.

And third, the virus hasn’t needed to evolve in order to be successful. Not yet, anyway. This is what makes some virologists



A person with covid-19 connected to a ventilator in Tver Regional Clinical Hospital, Russia

2 Known covid-19 reinfections from genetically distinct viruses

nervous as we move into the next phase of the pandemic.

As a rule, evolutionary adaptation happens due to “selection pressure”, which is when an organism’s environment changes to favour certain variants over others.

Right now, SARS-CoV-2 is under very weak selection pressure. There are still plenty of humans to infect who have no “immune memory” to fight the virus; there are very few drugs to evade; and there is no vaccine. But as these benign conditions become harsher for the virus, selection pressure will ramp up and we can expect to see it evolve in response, perhaps in ways that

make it even more dangerous.

According to an epidemiological model developed by a team led by Chadi Saad-Roy at Princeton University, the evolution of the virus will have a substantial effect on how the pandemic pans out over the next five years, ranging from sustained outbreaks to near-elimination (*Science*, doi.org/fdqc).

Change is coming

Predicting what will actually happen is impossible. “I don’t think anyone can do that,” says Oscar MacLean at the University of Glasgow in the UK.

“There is no strong evidence that the virus is evolving



adaptively,” says Sergei Pond, also at Temple University. “It is boring genetically, with relatively little diversity and divergence, and we haven’t exposed it to much selective pressure.”

One thing we can be sure about is that the virus will change. “It is changing at a slow pace compared to many other viruses, but at a brisk pace compared to the human genome,” says Kumar.

“There will be more interesting mutations as time goes by, especially as vaccines and treatments are introduced,” says Rolland, who continues to monitor the virus’s evolution.

Successful therapies could cause the virus to evolve resistance, for example. “As we start to get standardised drug deployment applied to every infection, then resistant mutations will quite likely arise,” says MacLean. The same applies to the spread of natural immunity and vaccines, he says.

The selection pressure doesn’t force the virus to mutate. But if a mutation conferring resistance to a drug happens to arise in a virus that is inside somebody being treated with that drug, then the mutant could proliferate and go on to infect another person, and then spread far and wide. This is known as “escape”.

While this scenario is unlikely to happen in any one person, there are so many cases of covid-19 around the world that it isn’t an impossibility.

Because of this danger, it may be wise to hold back some drugs to use as a last resort, says MacLean, or to administer two different drugs at once to exploit the fact that two resistance mutations are extremely unlikely to arise simultaneously.

SARS-CoV-2 also has another mutational trick up its sleeve:

recombination. If a cell is simultaneously infected by two SARS-CoV-2 viruses with slightly different genomes, the RNA-copying enzyme can mash them together to make a hybrid. In this way, mutations can be brought together, which is another source of genetic variation that selection pressure could act on.

“We do expect them to recombine,” says MacLean. “Coronaviruses recombine so often in bats.”

Viral surveillance

There are already signs of new strains of the virus emerging. There have been several confirmed cases of reinfection, and in at least two of these, the second infection was with a genetically distinct virus. But whether these genetic differences enabled the viruses to dodge the host’s immune memory hasn’t been established, says Rolland.

Selection pressure and subsequent escape due to a vaccine is unlikely, she says. It has never been observed before. There is a case of an experimental HIV vaccine inducing genetic changes in that virus, says Rolland, but HIV has a much higher

mutation rate than SARS-CoV-2.

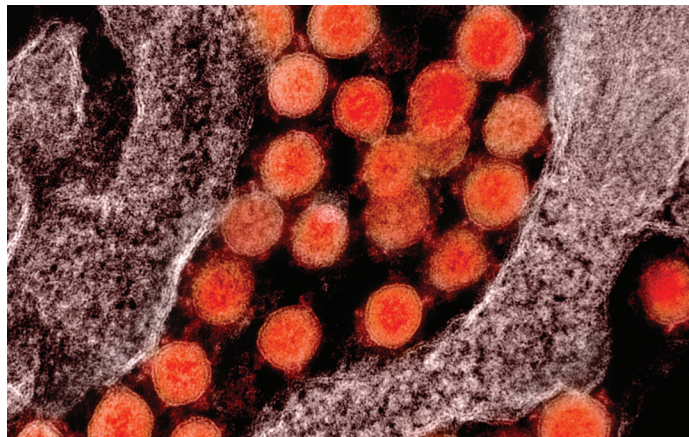
Related viruses can also be a guide. The original SARS virus that caused the 2002-2003 epidemic acquired two big genetic changes early on in the outbreak. These mutants came to dominate, suggesting they were adaptations.

“Could SARS-CoV-2 adapt in the same way? Yes,” says Nathan Grubaugh at Yale School of Medicine. However, he emphasises that mutation doesn’t necessarily mean a virus will become more virulent or deadly. Mutations often do the opposite.

But we can’t rely on this happening with SARS-CoV-2, says MacLean. “I think people are jumping the gun assuming that mutations will reduce the severity of infection. I really don’t think that is a valid assumption,” he says.

Viral diseases do become less virulent over time in a population, but that is partly due to people becoming immune. While killing hosts is bad for a virus’s survival, being aggressive could be a useful trait, says MacLean, and therefore selection pressure can

SARS-CoV-2 particles (orange) isolated from a person with covid-19



stop it becoming less aggressive.

What we must do, says Kumar, is limit opportunities for the virus to acquire mutations that could be advantageous to it when selection pressure is applied.

New mutations can arise during an infection, but evolution mainly acts on genetic differences already existing in the virus population. Right now, there are few of those says Kumar, and we can keep it that way by limiting transmission.

The virus can only evolve if it infects another person. If it isn’t being transmitted as frequently as it used to be, any potential evolution of new strains will decrease.

“If everybody wears a mask and everybody gets vaccinated, the virus can’t evolve”

But just in case, virologists are keeping the virus under surveillance to watch for mutations of interest. One project at Temple University monitors newly sequenced viral genomes. If it spots a mutation that has arisen independently twice, it assumes it may be being selected for and flags it up for other labs to check for enhanced virulence.

Another emerging approach is to grow the virus in cell culture, challenge it with drugs or an immune response and observe how it reacts at the genetic level. A project to do that is getting under way, but its leaders told *New Scientist* that it was too early to share any details.

For Kumar, the message from evolutionary biology is clear: “The future is hard to predict, but if everybody wears a mask, and if everybody gets vaccinated, the virus can’t evolve. Then the chance of escape is less. That is what we are hoping for.” ■