

Coronavirus pandemic

CHANGING PROFILE
OF A POTENTIAL KILLER

The detectives of the microbial world are still learning more about the coronavirus

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Many things have changed in the five months since the world came to know of SARS-CoV-2, the long name for the tiny virus that has had an outsized impact on economies and societies.

And there may be more surprises – or shocks – to come.

Scientists – the detectives of the microbial world – are still learning more about the virus, so that tests, drugs and vaccines can be developed to identify and treat those who are infected, and inoculate those who are not.

But as they peel back the layers of the unknown, it may seem that the virus is one that is ever-changing, leading to U-turns in public health policy.

At first, it seemed unlikely that those without symptoms could spread the virus, so only those who were unwell were asked to wear a mask in Singapore. By April, it became clear that asymptomatic persons with Covid-19 were more common than previously thought – and could go out and infect others. Now anyone caught with public without a mask faces a \$300 fine.

Several other questions about the virus still remain.

For instance, even though this virus is in the same family as the one that caused the severe acute respiratory syndrome (Sars) outbreak in 2003, why is it so much more contagious?

And why do some Covid-19 patients develop a severe form of the disease while others do not?

Safe distancing measures can buy us some time while the wait for a vaccine goes on.

As the Health Ministry's chief health scientist, Professor Tan Chorh Chuan, said in the early days of the outbreak: "To fight a war, you must know your enemy, and the virus is the enemy."

The *Straits Times* highlights what we know of the virus, and the gaps that remain.

PICTURE OF A KILLER

Piecing together a profile of a killer requires, first and foremost, knowledge about its identity.

It is once that identity has been nailed down, the next step is to counter it.

The virus first surfaced in Wuhan, China, late last December, infecting workers at a wildlife market in China and causing them to exhibit pneumonia-like symptoms.

In its early stages, it was referred to simply as the 2019 novel coronavirus, or 2019-nCoV – a nod to how new and unknown this virus was.

But on Jan 12, scientists around the world were handed an important clue when Chinese scientists uploaded the genome of the coronavirus on a public database.

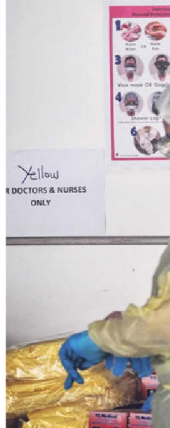
An organism's genome is unique to it, and helps scientists distinguish it from others.

The genome of this coronavirus is made up of a single-stranded genetic material known as RNA, which is made up of an "alphabet" of molecules known as nucleotides.

There are four different nucleotide bases that function as the basic building blocks for all RNA viruses – adenine (a), cytosine (c), guanine (g) and uracil (u). The way in which these four nucleotide bases are arranged is unique to each virus.

From this, scientists could tell that the virus was closely related to the one that caused Sars in 2003. The virus' official name, SARS-CoV-2, which was announced in February by the World Health Organisation (WHO) about a month after the release of the genome – reflects this relationship.

Scientists are still trying to find out why. And its genome may yield important clues.



Healthcare workers donning their protective gear at the community isolation facility at Singapore Expo. Unlike Sars, which caused about 800 deaths, Covid-19 has caused a far higher death toll, with nearly 300,000 dead around the world so far. Scientists are still trying to find out why. ST PHOTO: KEVIN LIM

Said Nanyang Technological University's (NTU) infectious diseases expert Julien Lescar. "The availability of the genome is a very important step and this information is used constantly."

Genes refer to a specific sequence of nucleotides along the genome.

In humans, genes determine how we look and how we behave, as genes direct the type of protein – an important building block of cells, tissue and organs – being produced.

This is the same for viruses.

For instance, specific genes in the viral genome direct the production of proteins that are used to hijack a human cell.

Under a microscope, the virus that causes Covid-19 is spherical.

In the centre is its genome, which is surrounded by an oily membrane that has a "crown" of sugar-coated spike proteins protruding from it – hence the name "corona", or crown.

It is these spike proteins, or S-proteins, that help the virus infect its host, by latching onto receptors on the human cell, the way a key fits into a lock.

This could have real-world implications.

"Some candidate vaccines target this part of the virus to elicit a protective immune response," said Associate Professor Lescar.

In principle, antibodies against the S-protein should be sufficient to prevent infection.

Antibodies are elements of the human immune system.

By "capturing" the S-proteins before they latch onto the receptors on the human cell, these antibodies can prevent an invasion, said Prof Lescar.

But viruses are prone to mutation, which occur when the virus makes imperfect copies of itself, introducing variations along the way.

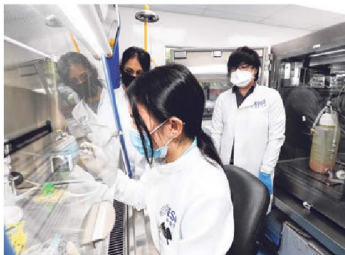
So far, the mutations in the coronavirus have made little difference in its ability to infect humans, said Dr Sebastian Maurer-Stroh, deputy executive director for research at the Agency for Science, Technology and Research's (A*Star) Bioinformatics Institute, who is involved in the surveillance of the viral genome.

Instead, the various "types" of the coronavirus observed so far were like similar vehicles carrying different licence plates, he added.

MODUS OPERANDI

So when does a coronavirus invasion begin?

Does it begin when virus-laden respiratory droplets enter the mouth, nose or eyes? Or can one get the disease from breathing in virus particles in the air? If the virus can be found in stool samples, can it spread via the faecal-oral route?



(Clockwise from foreground) Esco Aster research officer Micaela Goh, senior bioscience scientist Nandini Prabhakar and CEO Lin Xiangling in the firm's lab. On the right is the bioreactor used to culture the vaccine. ST PHOTO: KEVIN CHING



Passengers leaving Wuhan's Hankou railway station having their health codes checked before taking a taxi on Tuesday. PHOTO: AGENCE FRANCE-PRESSE

Scientists have raised all these possibilities.

But the WHO is clear.

"According to current evidence, the Covid-19 virus is primarily transmitted between people through respiratory droplets and contact routes," it said on its website.

And in an analysis of 75,465 Covid-19 cases in China, airborne transmission was not reported, the global health body added, saying there have also been no reports of faecal-oral transmission of the virus to date.

But once in the human body, the virus can cause disease, and scientists are now trying to find out how exactly.

The virus begins its invasion by using its S-proteins to latch onto the receptors on the human cell. The ACE2 receptor on the surface of the human cell is a likely entry point. Once in, the virus releases its RNA into the human cell, and uses its

host's cellular machinery to replicate. Once the replication is complete, new viral particles are released from the host cell. The active replication and release of viral particles cause the host cell to die.

"Assuming that there is no immune response, the virus would invade cells in the lungs and multiply exponentially, killing cells as it infects them. This would cause great damage to the lungs," said Dr Poh Chek Meng, research fellow at A*Star's Singapore Immunology Network.

This is why people who have compromised immune systems can get severe bacterial and viral infections easily.

In the case of most people, however, the immune system responds to fight off the virus, said Dr Poh. "Unfortunately, sometimes the immune system itself can cause damage to the lungs," he added.

When a human host cell dies from

COLLECTIVE FAILURE

It has been 17 years since the outbreak of Sars, and while there has been scattered research on coronaviruses since then, there was little coordination between research groups, and no useful drug or vaccine from that... That was where we collectively failed. It's great now that everyone is working on this, and the pandemic illustrates the need for real, international collaboration going forward.



PROFESSOR JULIEN LESCAR

Nanyang Technological University's infectious diseases expert

The vaccine works by first injecting part of the virus' genetic material into the patient's body.

This kick-starts a series of molecular processes, including the manufacture of viral parts that the human immune system remembers.

This allows the immune system to recognise the virus, causing the production of antibodies without actually exposing the patient to the risk of infection.

But NTU's Prof Lescar said it could be a year or more before a vaccine can be developed and rolled out, due to the need for rigorous checks to ensure that it is safe for use on people.

While rapid diagnostic tests and antiviral drugs could be achieved sooner, he stressed that scientific inquiry is a marathon, not a race.

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But sometimes, the immune system goes into overdrive, causing

the overproduction of cytokines that could eventually damage the lung infrastructure.

This cytokine storm may also circulate to other organs, leading to multi-organ damage, or muscle and joint pain and fatigue, as well as abdominal pain, vomiting and diarrhoea.

While cytokines are first produced at the site of infection, they may spill over to other sites in the body, explained Dr Tay.

"This could occur when the virus multiplies too much, or the host's immune response towards the infection becomes dysfunctional, causing the production of cytokines to become uncontrollably high," he said.

Both Dr Poh and Dr Tay are part of a team of scientists that last month published a paper in the journal *Nature Reviews Immunology* on how Sars-CoV-2 causes disease in the body, and possible ways of treating it.

One strategy proposed in the paper was to deliver high concentrations of a soluble form of ACE2 – the receptor found on the surface of the human cell – which could potentially reduce virus entry into target host cells.

Dr Poh said such decoy strategies are already being used against other diseases, such as rheumatoid arthritis. "This decoy strategy may work against Covid-19, especially if the soluble ACE2 receptors get to meet the virus when injected into the body, and if they are injected at a sufficiently early point in the infection, before inflammation gets out of control."

But more work needs to be done, he said, as the stability of the soluble ACE2 receptor in the human body is unclear at this moment.

FIGHTING BACK

But humanity has more than one sword in its arsenal to fight the virus.

Antibody therapy, which involves injecting laboratory-produced antibodies into a patient as a substitute for those generated by the immune system, is one promising area.

When antibodies detect the presence of a virus, they latch on to the infected cell, flagging the presence of the pathogen so other elements of the immune system can kick in to destroy it.

A*Star, for example, is working with Japanese pharmaceutical company Chugai Pharmaceutical Research on a therapeutic antibody for Covid-19. This antibody targets the S-protein of the virus, preventing it from attaching onto a human host cell.

But in the long run, vaccines are also being developed to help inoculate the population before they get infected. They work by injecting a small amount of a less- or non-infectious strain of the virus into a person, awakening the body's protective response to it.

Home-grown biomedical company Esco Aster, for example, is working on a "chimeric vaccine" in collaboration with American biotechnology company Vivaldi Biosciences.

This vaccine is produced by joining antigens – the part of the virus that antibodies detect – from the coronavirus, with proteins from the influenza virus. The hope is that the vaccine, if rolled out successfully within the next year or so, could confer immunity against both Covid-19 and influenza.

The Duke-NUS Medical School is also working on a vaccine in collaboration with American firm Arcutis Therapeutics.

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