COVID-19 THE FIRST 100 DAYS

THE SCIENCE

Medical, tech investments pay off in Covid-19 war

Singapore able to respond to crisis effectively and quickly due to capability built up over time

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The world is fighting a war against a virus and Singapore scientists are pulling their weight when it comes to building up an arsenal of knowledge that can be used to vanquish the enemy.

But their expertise did not spring up overnight. It is the fruit of the continuing investment in the health and biomedical sciences that Singapore started decades ago – an investment that, during this crisis, is paying off handsomely.

For instance, in the early stages of the coronavirus outbreak, scientists here developed a diagnostic test that allowed clinicians to identify and quickly isolate infected patients.

Since then, a multitude of inventions and discoveries have been rolled out.

Disinfection robots, armed with ultraviolet ray "swords", will soon rove some public places to get rid of viruses lingering on surfaces.

Swabbing booths have also been designed to provide extra protection for healthcare workers doing large-scale Covid-19 tests.

But as Mr Frederick Chew, chief executive of the Agency for Science, Technology and Research (A*Star), points out, these products do not just appear overnight. They are founded on a strong capability base built up and nurtured painstakingly over time, he tells Insight.

"In terms of peacetime dividends, Singapore is starting to reap tangible health and economic outcomes from investments made into the health and biomedical sciences," he says.

"In this Covid-19 wartime period, the same peacetime capability sets are being strung together to swiftly address Singapore's public health emergency needs."

BUILDING AN ARSENAL

Today, Singapore's biomedical manufacturing cluster makes up more than 4 per cent of the nation's gross domestic product and employs more than 24,000 people, many of whom are in high-skilled jobs.

It also supports the development of healthcare solutions and products that benefit Singaporeans, given the focus of research on diseases prevalent among Asian populations, says a spokesman for Singapore's National Research Foundation (NRF).

Many of the scientists have been working behind the scenes for years. But it was perhaps not until the Covid-19 crisis that the importance of their work has been highlighted.

Singapore has been building up the nation's capabilities in the health and biomedical sciences over the past two decades, notes the NRF spokesman.

This started with the formation of A*Star and its Biomedical Research Council research institutes, which preceded the outbreak of the severe acute respiratory syndrome (Sars) in 2003. A*Star was formed in 2002, taking over from what was known as the National Science and Technology Board.

It was this long-term investment that allowed the country to respond quickly and effectively to the Covid-19 outbreak, adds the NRF spokesman.

For example, NRF supported scientists such as Professor Wang Linfa of the Duke-NUS Medical School to pursue basic research on bat-borne viruses, which include coronaviruses. This allowed Prof Wang and his team to achieve significant breakthroughs in Covid-19 when called upon.

Preliminary research has indicated that the coronavirus-causing Covid-19 originated in bats.

It took Prof Wang's team just one week to successfully culture the virus from an infected person's sample after Singapore reported its first case on Jan 23, making it the third country in the world outside China to do so.

The ability to grow the virus in a laboratory during the early stages of the outbreak was a crucial starting point for scientists here, in terms of helping them develop new diagnostic methods or a potential vaccine, for instance.

The Sars outbreak had also spurred action, prompting an emphasis on infectious diseases as a focus area, says the NRF spokesman. This led to the formation of the National Centre for Infectious Diseases (NCID), which developed state-of-the-art facilities and created a national focal point for work around infectious diseases, she adds.

The experience with infectious diseases over the years, including Sars and the swine and avian influenza, also helped to hone the radars of researchers here.

The moment a series of pneumonia-like cases was reported in Wuhan, China, last December, scientists and clinicians at A*Star and Tan Tock Seng Hospital were already on high alert.

After China shared the genome sequence of the coronavirus in the second week of January, they – scientists and doctors – worked together to develop and roll out a diagnostic test kit in less than a month. This was a record, considering that a similar one for Sars had taken months.

Today, the Fortitude Kit has been deployed in 13 public and private hospitals and laboratories in Singapore, as well as in more than 20 other places, including Hong Kong, New Zealand and the United States, says A*Star.

Microbiologist Julien Lescar, an associate professor at Nanyang Technological University's School of Biological Sciences, came to Singapore from France in 2002, just before the outbreak of Sars.

And since then, the scientific landscape in Singapore has progressed tremendously, says Prof Lescar, who studies the molecular structure of RNA viruses, including coronaviruses, and the ways they infect humans.

"I am amazed by the number of excellent dedicated scientists and superb facilities that are now in place here," he says.

"We should pay tribute to the vision of the leaders who supported this and the great dedication of the staff and managers running facilities such as NCID and the hospitals."

DEALING WITH UNKNOWNS

Singapore has, over the past 100 days or so, achieved a number of key scientific milestones.

But the work continues, as scientists move to peel back the remaining layers of unknowns about the virus. And many mysteries still remain, says Prof Lescar.

For instance, even though this virus is in the same family as the one that caused Sars, it is still not known why this one is so much more contagious, he says.

It is also unclear why some Covid-19 patients develop severe disease while others do not.

"The good news is that there is a huge international effort to address these issues, which hopefully will lead to vaccines and cures in the form of specific anti-viral drugs," Prof Lescar says.

Preliminary studies have pointed to possible answers, and some important clues may lie in the structure of the virus.

Under a microscope, the coronavirus – called Sars-CoV-2 – appears spherical. In its centre, encased by an oily membrane, is a single-stranded genetic material called RNA. Protruding from the membrane is a crown of spikes made of protein, or S-proteins, Prof Lescar explains.

One possible explanation for the higher infectivity of the virus at the centre of the current outbreak, he says, is that compared with the virus that caused Sars, the spikes of this virus may have a higher affinity for the ACE-2 receptor on the human cell.

Scientists think this receptor, located on the surface of the human cell, could be used by the coronavirus as an entry route.

These spike proteins are what helps the virus "hijack" human cells, the first step of an infection. The S-proteins of the virus latch on to the receptors on the human cell, much like how pieces of a jigsaw puzzle fit together.

This enables the virus to inject its RNA into the human cell, and use the resources of its host to make new copies of the virus.

Prof Lescar says: "It seems like just a few mutations at the surface of the spike protein of the virus are enough to affect how infectious the virus is and also its pathogenicity – the way it harms an infected person."

Viruses are not static but are prone to mutation. This could change the behaviour of a virus, and also affect the sensitivity of a test kit.

Scientists such as Dr Sebastian Maurer-Stroh, deputy executive director of research at A*Star's Bioinformatics Institute, are keeping an eye out on it in case it does.

The active surveillance of the viral genome is key to ensuring that the diagnostic test kits remain sensitive in detecting the virus in Covid-19 patients, says an A*Star spokesman.

A virus' unique genome serves as a "fingerprint" to distinguish it from other viruses. By comparing the genome of the virus causing Covid-19 with that of other viruses, scientists were able to identify parts of the genetic code that were unique to Sars-CoV-2.

These differences allowed scientists to develop diagnostic tests, such as those in the Fortitude Kit. These tests work by flagging the unique parts of the viral genome in a person's respiratory secretions through a process known as polymerase chain reaction (PCR).

Professor Tan Chorh Chuan, chief health scientist at the Ministry of Health, says new tools – including a new serology test developed by Prof Wang – to combat Covid-19 will soon be unveiled.

A serology test, or antibody test, is different from a PCR test.

PCR tests look for the presence of viral genetic material in a sample, but a serology test detects markers of the human immune system.

Specifically, serology tests flag the presence of antibodies, which are proteins developed by the immune system to fight off bacteria or viruses in the body.

"This can be used to assess if a patient had been recently infected, and will be also very helpful in assessing the extent of community exposure to Covid-19 infections," says Prof Tan.

Associate Professor Hsu Li Yang, programme leader for infectious diseases at the National University of Singapore's (NUS) Saw Swee Hock School of Public Health, says the test will not pick up an infection in someone who has just been infected, because antibodies are produced only between days 10 and 14 of the illness.

Antibody testing is also not foolproof, as some 5 per cent of the people who have been infected with the coronavirus disease do not develop antibodies, he says, adding that serological tests are being evaluated here.

While the presence of antibodies may be indicative that a person has recovered from Covid-19, it is not clear if they protect against the disease for sure.

For instance, there have been reports that South Korea is seeing a growing number of recovered Covid-19 patients who relapsed.

VACCINES, DRUGS AND THE WAY FORWARD

A successful coronavirus vaccine, on the other hand, would confer immunity, and developing this is the subject of research worldwide.

Billionaire Bill Gates, whose Bill and Melinda Gates Foundation is funding seven Covid-19 vaccine candidates, recently said a coronavirus vaccine could be manufactured at scale in just a year.

There are now at least 76 vaccine candidates and, in Singapore, the Duke-NUS Medical School has tied up with Arcturus Therapeutics in the United States to develop one, based on a new way of making a vaccine. Clinical trials are expected to start by August.

In the meantime, groups of scientists are studying how infected patients could be better treated. This includes efforts across the local research ecosystem to look at the use of repurposed drugs and explore various drug combinations that might prove to be an effective cure, says A*Star.

Professor Dean Ho, director of the N.1 Institute for Health and the Institute for Digital Medicine at NUS, is working with a collaborator to leverage artificial intelligence in the search for the best combination of drugs in the best doses to treat Covid-19 patients.

Because there are so many parameters to consider – from the type of drug to the ways the drugs can be combined and in varying doses – it is a task that can sometimes feel like searching for a nail in 10 galaxies, he says.

Enter IDentif.AI (pronounced Identify), a platform that can rapidly optimise drug regimens for infectious diseases.

The platform uses a pool of 12 carefully selected drugs – including the ritonavir and lopinavir combination used to treat HIV patients – to figure out the optimal dosage of drugs that can be used in combination for the treatment of Covid-19 patients.

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There are multiple ways that drugs can work, Prof Ho explains.

One, the drug could have a direct effect on the virus. For example, it could stop a virus from replicating in the body. But there may be limits on how high a dose can be administered to a patient, because of factors such as how toxic the drug is, for example.

Two, in a cocktail of medicine taken by a patient, a drug could also help by reducing the side effects caused by another drug in the mix. Or, it could work by reinforcing the positive effects of another drug.

Prof Ho, who is also head of the NUS Department of Biomedical Engineering, says: "Biology is complex and drug interactions can be unpredictable. But AI allows us to interrogate and study huge parameters in a short span of time."

IDentif.AI could soon be used to rank the best drug combinations and dosing for Covid-19 patients, he says.

"And with the results, we will follow up with potential clinical collaborators in Singapore to potentially roll out a drug trial involving an AI-optimised combination of drugs, which may be a world's first."

Singapore's ability to respond rapidly with technology-driven solutions to the Covid-19 pandemic was possible only because of consistent investment in the nation's research, innovation and enterprise ecosystem, says NRF.

"Without the investments we made years ago, we would not have these capabilities today," says the spokesman.

"It is thus important that we continue to invest in building new capabilities today, so that we will also have the capacity to deal with the emergencies of tomorrow."

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Key scientific terms

Antibodies

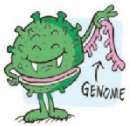
- An important element of the immune system. Antibodies, which are found in the blood, detect the presence of a virus and latch on to the infected cell, flagging it so other elements of the immune system can kick in to destroy it.

Serology tests

- These detect the presence of virus-fighting antibodies in the body.

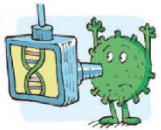
Genome

- A virus' unique genome serves as a "fingerprint" to distinguish it from other viruses. The genome of Sars-CoV-2 – the virus which causes Covid-19 – comprises a single-strand of genetic material called RNA, which is made up of an "alphabet" of molecules known as nucleotides.



Polymerase chain reaction

- This refers to a molecular biology process which can help to determine if a sample contains any detectable genetic material of the coronavirus.



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